Supplementary Information

Total Synthesis of (±)-Cyclopeltain B

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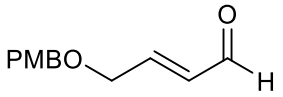
General Remarks:

All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen. Moisture-sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus through rubber septa. Reagents, starting materials, and solvents were received from available commercial suppliers and utilized with no further purification. All reactions were monitored by thin-layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualization was accomplished with the help of either UV light, iodine adsorbed on silica gel or by immersion in an ethanolic solution of phosphomolybdic acid (PMA), p-anisaldehyde, KMnO4, and ninhydrin solution, followed by heating with a heat gun for ~15 sec. Purifications were carried out on column chromatography over silica gel (100-200 or 230-400 mesh size). Commercially received deuterated solvents were used as such for NMR spectroscopic analysis, and ^{1}H NMR, ^{13}C NMR spectra were obtained using a 300 MHz, 400 MHz, 500 MHz or 600 MHz spectrometer. Coupling constants were mentioned in Hertz, and chemical shifts were quoted in ppm, relative to TMS, using the residual solvent peak as a reference standard ($CDCl_3$ = 7.27 ppm).abbreviations below were used to explain the multiplicities: s = singlet, d = doublet, t = triplet,q = quartet, m = multiplet, br = broad. HRMS (ESI) were recorded on an ORBITRAP mass analyzer(Thermo Scientific, Exploris 120). Mass spectra were measured with ESI ionization in an LC-MS (SHIMADZU) mass spectrometer. Infrared (IR) spectra were recorded on a Bruker FT-IR spectrometer as a thin film, and data were integrated by using OPUS (version 17.5) software. The melting points of solids were measured by a melting point apparatus (Buchi 565). Optical rotation values were recorded on the Anton Paar Polarimeter (MCP 200) instrument at 589 nm. Chemical nomenclature was generated using Chembiodraw 23.0.

Experimental procedures:



7

(*E*)-4-((4-methoxybenzyl)oxy)but-2-enal (7):

Compound **7** was prepared following the known protocol.[1]

Yield: 4.2 g, 61% over two steps, yellow liquid.

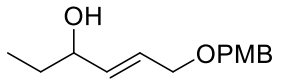
R_f = 0.7 (7:3, hexanes: ethyl acetate).

IR υ_{max}(film): 3003, 2730, 1685, 1611, 1512, 1244, 1175, 1102, 1028, 967, 818 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.57 (d, *J* = 7.9 Hz, 1H), 7.28 – 7.25 (m, 2H), 6.91 – 6.88 (m, 2H), 6.84 (dt, *J* = 15.8, 4.2 Hz, 1H), 6.38 (ddt, *J* = 15.8, 7.9, 1.9 Hz, 1H), 4.52 (s, 2H), 4.26 (dd, *J* = 4.2, 2.0 Hz, 2H), 3.81 (s, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 193.4, 159.5, 153.3, 131.9, 129.6, 129.5, 114.0, 72.8, 68.4, 55.4.

HRMS (ESI) *m/z*: $[M+ Na]^+$ calcd for $C_{12}H_{14}O_3Na$, 229.0840; Found 229.0842.



8

(*E*)-6-((4-methoxybenzyl) oxy) hex-4-en-3-ol (8):

To a stirred solution of (*E*)-4-((4-methoxybenzyl)oxy)but-2-enal (**7**) (4.20 g, 20.36 mmol, 1.0 equiv.) in diethyl ether (100 mL) at 0 °C, ethylmagnesium bromide (1.0 M in Et_2O, 24.44 mL, 24.44 mmol, 1.2 equiv.) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h, and the progress of the reaction was monitored by TLC. The reaction was then quenched with saturated aq. NH_4Cl (20 mL), and the aqueous layer was extracted with ethyl acetate (3 × 75 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography using a gradient of hexanes: ethyl acetate (9:1 to

8:2) to afford compound **8**.

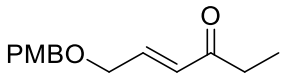
R_f = 0.5 (7:3 hexanes: ethyl acetate). **Yield:** 3.15 g (65%) as a yellow liquid.

IR υ_{max}(film): 3402, 3001, 2962, 2854, 2361, 1611, 1585, 1459, 1244, 1112, 967cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.25 (m, 2H), 6.89 – 6.86 (m, 2H), 5.81 – 5.71 (m, 2H), 4.45 (s, 2H), 4.04 (dd, *J* = 12.3, 6.2 Hz, 1H), 4.00 – 3.99 (m, 2H), 3.80 (s, 3H), 1.77 (s, 1H), 1.60 – 1.50 (m, 2H), 0.92 (t, *J* = 7.5 Hz, 3H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.3, 135.9, 130.4, 129.5, 127.5, 113.9, 73.8, 72.0, 70.0, 55.4, 30.1, 9.8.

HRMS (ESI) *m/z*: calcd for $[M+ Na]^+$ $C_{14}H_{20}O_3Na$, 259.1310; Found 259.1315



9

(*E*)-6-((4-methoxybenzyl) oxy) hex-4-en-3-one (9):

To a stirred solution of oxalyl chloride (1.45 mL, 17.14 mmol, 1.5 equiv.) in CH_2Cl_2 (80 mL), DMSO (2.43 mL, 34.28 mmol, 3.0 equiv.) was added dropwise at −78 °C. After 30 minutes, Compound **8** (2.70 g, 11.43 mmol, 1.0 equiv.) in CH_2Cl_2 (25 mL) was added, and the reaction mixture was stirred at −78 °C for 2 h. At the same temperature, the *N, N*-Diisopropylethylamine (11.94 mL, 68.55 mmol, 6.0 equiv.) was added slowly. The mixture was allowed to warm slowly to room temperature, and the reaction progress was monitored by TLC. After 30 minutes, 1.0 N aq. HCl (50 mL) was added, and the reaction mixture was stirred for an additional 30 minutes. The mixture was then extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic extracts were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using a gradient of hexanes: ethyl acetate (9.5:0.5 to 8:2), yielding compound **9**.

R_f = 0.7 (7:3 hexanes: ethyl acetate). **Yield:** 2g (75 %), light yellow liquid.

IR υ_{max}(film): 2953, 2923, 2863, 1611, 1512, 1462, 1360, 1244, 1174, 1033, 970 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 2H), 6.90 – 6.87 (m, 2H), 6.83 (dt, *J* = 16.0, 4.4 Hz, 1H), 6.37 (dt, *J* = 16.0, 2.0 Hz, 1H), 4.50 (s, 2H), 4.16 (dd, *J* = 4.4, 2.0 Hz,

2H), 3.81 (s, 3H), 2.58 (q, *J* = 7.3 Hz, 2H), 1.10 (t, *J* = 7.3 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 200.8, 159.5, 141.9, 129.8, 129.5, 129.2, 114.0, 72.7, 68.7, 55.4, 33.8, 8.1.

HRMS (ESI) *m/z*: calcd for $[M+ Na]^+$ $C_{14}H_{18}O_3Na$, 257.1153; Found, 257.1164

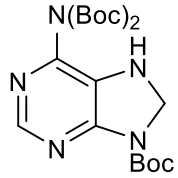
11

Tert-butyl 6-(bis(tert-butoxycarbonyl)amino)-9*H*-purine-9-carboxylate (11):

Compound **11** was prepared from commercially available adenine (8 g, 59.2 mmol) following the known protocol.

Yield: 13.8 g, 53%, white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.50 (s, 1H), 1.70 (s, 9H), 1.42 (s, 18H).



4

tert-butyl 6-(bis(tert-butoxycarbonyl)amino)-7, 8-dihydro-9*H*-purine-9-carboxylate (4):

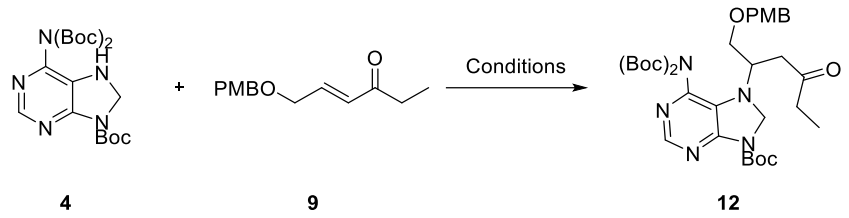
Compound **4** was prepared from compound **11** (13.7 g, 31.5 mmol) following the known protocol.[2]

Yield: 11 g, 80%. white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 5.27 (d, *J* = 4.1 Hz, 2H), 4.16 (t, *J* = 3.8 Hz, 1H), 1.57 (s, 9H), 1.50 (s, 18H).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 156.8, 150.3, 149.9, 148.7, 137.9, 126.6, 84.2, 83.5, 64.7, 28.3, 27.9.

Table 1: Optimization conditions for Aza-Michael reaction



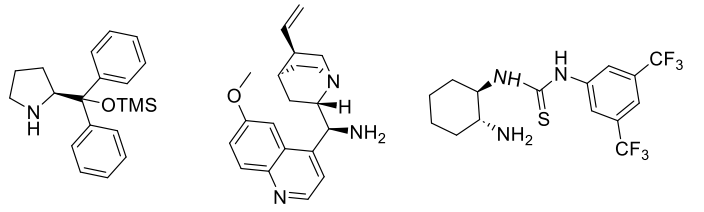
4 9 12

Sr. No.	Conditions	Remarks
1	LiCl, ACN, reflux, 12 h	Compound **12** decomposed
2	Cs_2CO_3, THF, rt, 24 h	Recovered SM
3	DBU, ACN, rt– 50 °C, 24 h	10% desired product
4	DBU, ACN, rt, 16 h	51% desired product
5	KO-*t*-Bu, CH_3CN, 80 °C, 12 h	Compound **12** decomposed
6	BTMAH, DMF, 60–90 °C, 8 h	Compound **12** decomposed

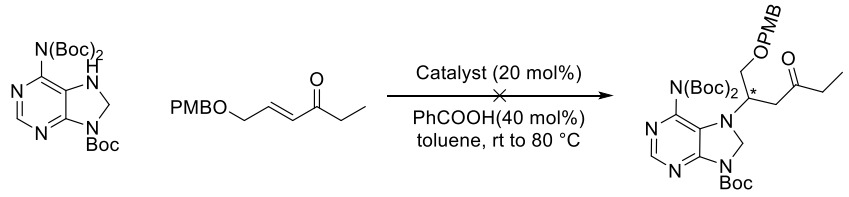
*SM= Starting Materials

Table 1: Optimization conditions for Aza-Michael reaction

Preliminary investigation of chiral organocatalysts in the aza-Michael reaction



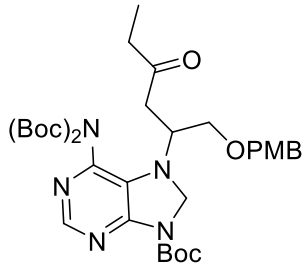
Catalyst I Catalyst II Catalyst III



4 9 12

To a sample vial equipped with a magnetic stirring bar was added **catalyst I-III** (10 mol%), $PhCO_2H$ (30 mol%) and toluene (3.0 mL), and the solution was stirred for 5 min at room temperature. After the addition of *α, β*-unsaturated ketone **9** (200 mol%), the

mixture was stirred for another 10 min. Then compound **4** (100 mol%) was added at room temperature. The reaction was monitored by TLC from rt to 80 °C for 72 h, but no product formation was observed.



12

tert-butyl 6-(bis(tert-butoxycarbonyl)amino)-7-(1-((4-methoxybenzyl)oxy)-4-oxohexan-2-yl)-7,8-dihydro-9*H*-purine-9-carboxylate (12)：

To a stirred solution of compound **4** (1.0 g, 2.29 mmol, 1.0 equiv.) in acetonitrile (30 mL) under a nitrogen atmosphere at room temperature, DBU (0.513 mL, 3.43 mmol, 1.5 equiv.) was added. The solution of the *α, β*-unsaturated ketone **9** (803 mg, 3.43 mmol, 1.5 equiv.) in acetonitrile (20 mL) was then added dropwise over 20 minutes. The reaction mixture was stirred at room temperature for 16 h, and the progress of the reaction was monitored by TLC. The mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexanes: ethyl acetate, 6:4) to afford compound **12** as a yellow liquid.

R_f = 0.38 (7:3 hexanes: ethyl acetate). **Yield:** 521 mg, (34% isolated, 51% brsm)

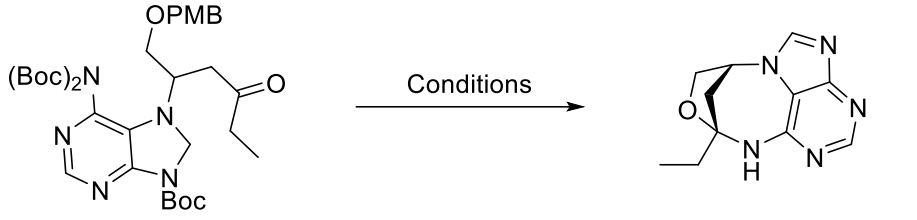
IR υ_{max}(film): 3013, 2864, 1739, 1713, 1604, 1512, 1465, 1364, 1299, 808 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.17 (d, *J* = 8.6 Hz, 2H), 6.87 – 6.83 (m, 2H), 5.28 (d, *J* = 6.0 Hz, 1H), 5.16 (d, *J* = 6.0 Hz, 1H), 4.36 (q, *J* = 11.4 Hz, 2H), 4.30 – 4.22 (m, 1H), 3.80 (s, 3H), 3.64 (d, *J* = 3.6 Hz, 2H), 3.04 (dd, *J* = 16.9, 10.0 Hz, 1H), 2.54 (dd, *J* = 16.9, 3.9 Hz, 1H), 2.44 – 2.30 (m, 2H), 1.56 (s, 9H), 1.44 (s, 18H), 0.99 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 207.8, 159.5, 156.6, 150.7, 148.6, 148.4, 135.0, 129.8, 129.4, 128.5, 114.0, 83.9, 83.6, 73.2, 70.2, 65.9, 55.4, 51.50, 40.1, 36.4, 28.3, 28.0, 7.7

HRMS (ESI) *m/z*: calcd for $[M+H]^+$ $C_{34}H_{50}N_5O_9$, 672.3608; Found 672.3646

Optimization conditions for natural product (±)-Cyclopeltain B (2):

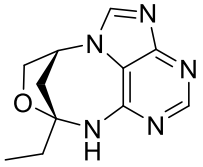


12 ***(±)-Cyclopeltain B, (2)***

Sr. No.	Conditions	Observation
1	DDQ, CH_2Cl_2: H_2O (10: 1), rt, 6 h	Recovered SM
2	DDQ, buffer solution (pH 7), CH_2Cl_2, 0 °C, 4 h	Recovered SM
3	CAN, CH_3CN: H_2O (9: 1), rt, 12 h	Recovered SM
4	TfOH, CH_2Cl_2, rt, 12 h	Decomposed SM
5	TFA: CH_2Cl_2 (5%), rt, 1 h	Decomposed SM
6	$TiCl_4$, CH_2Cl_2, 0 °C- rt, 4 h	56% yield of (**2**)

SM= Starting Materials

Table 2: Optimization conditions for natural product (±)-Cyclopeltain B (**2**)



(±)-Cyclopeltain B (2)

10-ethyl-7,8,10,11-tetrahydro-7,10-methano[1,3,6]oxadiazocino[6,5,4-*gh*]purine (2):

To a stirred solution of compound **12** (200 mg, 0.927 mmol, 1.0 equiv.) in CH_2Cl_2 (12 mL) was added a solution of $TiCl_4$ (0.595 mL, 1M in CH_2Cl_2, 0.595 mmol, 2.0 equiv.) under nitrogen atmosphere and the reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was allowed to warm slowly to room temperature, and stirred at same temperature for another 2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, quenched with saturated aq. $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL), the combined organic phases were washed with brine, dried

over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography using a gradient of CH_2Cl_2: MeOH (9.9:0.1 to 9.4:0.6).

R_f: 0.4 (9:1, CH_2Cl_2: MeOH), **Yield:** 39 mg (56 %), yellow solid.

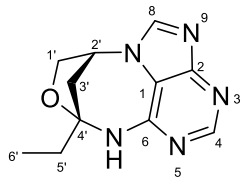
IR υ_{max}(film): 3225, 2973, 2877, 1615, 1569, 1507, 1441, 1397, 1231, 1030 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (s, 2H), 5.38 (dd, *J* = 5.4, 3.3 Hz, 1H), 4.06 (dd, *J* = 9.5, 3.3 Hz, 1H), 3.91 (dd, *J* = 9.5, 1.8 Hz, 1H), 2.80 (dd, *J* = 14.3, 5.6 Hz, 1H), 2.46 (dd, *J* = 14.3, 1.6 Hz, 1H), 2.18 (dq, *J* = 14.9, 7.5 Hz, 1H), 2.01 (dq, *J* = 14.9, 7.5 Hz, 1H), 1.13 (t, *J* = 7.5 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 160.0, 153.8, 152.0, 145.4, 112.3, 96.1, 74.8, 59.9, 49.0, 43.3, 33.8, 8.8.

HRMS (ESI) *m/z*: calcd for $[M+H]^+$ $C_{11}H_{14}N_5O$, 232.1198; Found, 232.1203

NMR comparison table of synthetic and natural (±)-Cyclopeltain B (2)



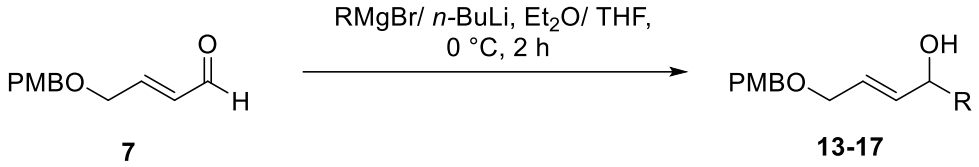
Isolated and Synthesized Natural Product
(±)-Cyclopeltain B (**2**)

(±)-Cyclopeltain B (2)	^{1}H NMR δ ppm		Difference	^{13}C{^{1}H} NMR δ ppm		Difference
	Isolation (J=Hz)	*Synthesis(J=Hz)*		*isolation*	*synthesis*	
1	-	-	-	112.6	112.3	0.3
2	-	-	-	152.2	152.0	0.2
4	8.39 (s, 2H)	8.38 (s, 2H)	0.01	153.7	153.8	0.1
6	-	-	-	159.8	160	0.2

8	8.39 (s, 2H)	8.38 (s, 2H)	0.01	145.5	145.4	0.1
1’	4.06 (dd, 9.6, 3.3, 1H) 3.92 (dd, 9.6, 1.9, 1H)	4.06 (dd, 9.5, 3.3, 1H) 3.91 (dd, 9.5, 1.8 Hz, 1H)	0 0.01	74.9	74.8	0.1
2’	5.38 (dd, 5.5, 3.3, 1H)	5.38 (dd, 5.4, 3.3 Hz, 1H)	0	60.0	59.9	0.1
3’	2.81 (dd, 14.4, 5.5, 1H) 2.47 (dd, 14.4, 1.8, 1H)	2.80 (dd, 14.3, 5.6, 1H) 2.46 (dd, 14.3, 1.6, 1H)	0.01 0.01	43.3	43.3	0
4’	-	-	-	96.1	96.1	0
5’	2.17 (m, 1H) 2.02 (m, 1H) 2.02 (m, 1H)	2.18 (dq, 14.9, 7.5, 1H) 2.01 (dq, 14.9, 7.5, 1H)	0.01	33.9	33.8	0.1
6’	1.14 (t-like, 7.5, 3H)	1.13 (t, 7.5, 3H)	0.01	8.9	8.8	0.1

Table 3: NMR comparison table of synthetic and natural (±)-Cyclopeltain B (**2**)

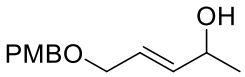
General Procedure A: Synthesis of allylic alcohols from *α, β*-unsaturated aldehyde and alkyl Magnesium bromide/ *n*-BuLi:



7 **13-17**

R= methyl, *n*-butyl, phenethyl, *iso*-butyl and 1-butenyl

To a stirred solution of (*E*)-4-((4-methoxybenzyl)oxy)but-2-enal (**7**) (1.0 equiv.) in diethyl ether(**13**)/ THF(**14-17**) (100 mL) at 0 °C, alkylmagnesium bromide/ *n*-BuLi (1.2 equiv.) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h, and the progress of the reaction was monitored by TLC. The reaction mixture was then quenched with saturated aq. NH_4Cl (20 mL), and the aqueous layer was extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude products were purified by silica gel column chromatography.



13

(*E*)-5-((4-methoxybenzyl)oxy)pent-3-en-2-ol (13) :

Compound **13** was synthesized by following general procedure A and purified by silica gel column chromatography (7:3 hexanes/ethyl acetate).

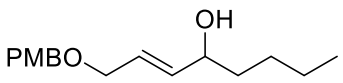
R_f: 0.2 (7:3 hexanes: ethyl acetate), **Yield:** 1.37 g (64%), yellow liquid.

IR υ_{max}(film): 3396, 3004, 2846, 2361, 1611, 1512, 1362, 1244, 1175, 1032, 817 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27– 7.24 (m, 2H), 6.88 – 6.85 (m, 2H), 5.81 – 5.72 (m, 2H), 4.44 (s, 2H), 4.32 – 4.28 (m, 1H), 3.98 – 3.97 (m, 2H), 3.79 (s, 3H), 1.91 (s, 1H), 1.26 (d, *J* = 6.4 Hz, 3H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.3, 137.3, 130.3, 129.5, 126.3, 113.9, 72.0, 69.9, 68.2, 55.3, 23.3.

HRMS (ESI) *m/z*: calcd for $[M+ Na]^+$ $C_{13}H_{18}O_3Na$, 245.1153; Found, 245.1160.



14

(*E*)-1-((4-methoxybenzyl)oxy)oct-2-en-4-ol (14):

Compound **14** was synthesized by following general procedure A and purified by silica gel column chromatography (7:3 petroleum ether/ethyl acetate).

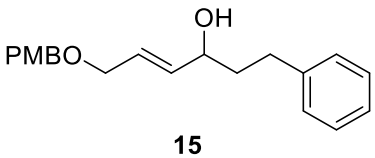
R_f: 0.5 (7:3 hexanes: ethyl acetate), **Yield:** 3.5 g (68%), yellow liquid.

IR υ_{max}(film): 2952, 2928, 2858, 1612, 1512, 1460, 1359, 1244, 1175, 1033cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.25 (m, 2H), 6.89 – 6.87 (m, 2H), 5.81– 5.72 (m, 2H), 4.45 (s, 2H), 4.11 (dd, *J* = 11.8, 6.0 Hz, 1H), 4.00 – 3.99 (m, 2H), 3.80 (s, 3H), 1.65 (s, 1H), 1.55 – 1.52 (m, 2H), 1.37 – 1.29 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.3, 136.3, 130.4, 129.5, 127.2, 113.9, 72.5, 72.0, 70.0, 55.4, 37.00, 27.7, 22.7, 14.2.

HRMS (ESI) *m/z*: calcd for [M+ Na]$^+$ $C_{16}H_{24}O_3Na$, 287.1623; Found 287.1632



15

(*E*)-6-((4-methoxybenzyl)oxy)-1-phenylhex-4-en-3-ol (15):

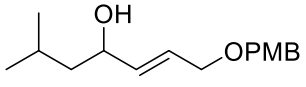
Compound **15** was synthesized by following general procedure A and purified by silica gel column chromatography (8:2 hexanes/ethyl acetate).

R_f: 0.2 (8:2 hexanes: ethyl acetate), **Yield:** 935 mg (31%), yellow liquid.

IR υ_{max}(film): 3411, 3016, 2923, 2361, 1610, 1512, 1455, 1359, 1245, 1175, 1032 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.24 (m, 4H), 7.19 – 7.15 (m, 3H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.78 (dd, *J* = 3.9, 2.4 Hz, 2H), 4.44 (s, 2H), 4.13 (dd, *J* = 10.7, 5.8 Hz, 1H), 3.98 (d, *J* = 3.6 Hz, 2H), 3.78 (s, 3H), 2.77 – 2.63 (m, 2H), 1.89 – 1.79 (m, 2H), 1.71 (s, 1H).
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.3, 141.9, 135.8, 130.3, 129.5, 128.5 (2C), 127.6, 125.9, 113.9, 72.1, 71.7, 69.9, 55.4, 38.7, 31.8.

HRMS (ESI) *m/z*: calcd for [M+ Na]$^+$ $C_{20}H_{24}O_3Na$, 335.1623; Found 335.1631



16

(*E*)-1-((4-methoxybenzyl)oxy)-6-methylhept-2-en-4-ol (16):

Compound **16** was synthesized by following general procedure A and purified by silica gel column chromatography (7:3 hexanes/ethyl acetate).

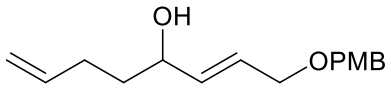
R_f: 0.3 (7:3 hexanes: ethyl acetate), **Yield:** 1.80 g (47%), yellow liquid.

IR υ_{max}(film): 2953, 2923, 2863, 1611, 1512, 1462, 1360, 1300, 1244, 1174, 1033 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.25 (m, 2H), 6.89 – 6.86 (m, 2H), 5.82 – 5.72 (m, 2H), 4.45 (s, 2H), 4.20 – 4.18 (m, 1H), 3.99 (d, *J* = 4.6 Hz, 2H), 3.80 (s, 3H), 1.74 (ddq, *J* = 19.8, 13.2, 6.6 Hz, 1H), 1.53 (s, 1H), 1.50 – 1.44 (m, 1H), 1.35 – 1.25 (m, 1H), 0.93 (d, *J* = 2.4 Hz, 3H), 0.91 (d, *J* = 2.4 Hz, 3H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.3, 136.5, 130.4, 129.5, 127.1, 113.9, 72.0, 70.7, 70.0, 55.4, 46.4, 24.7, 23.2, 22.5.

HRMS (ESI) *m/z*: calcd for $[M+ Na]^+$, $C_{16}H_{24}O_3Na$, 287.1623; found, 287.1634



17

(*E*)-1-((4-methoxybenzyl)oxy)octa-2,7-dien-4-ol (17):

Compound **17** was synthesized by following general procedure A and purified by silica gel column chromatography (8:2 hexanes/ethyl acetate).

R_f: 0.3 (8:2 hexanes: ethyl acetate), **Yield:** 1.2 g (55%), yellow liquid.

IR υ_{max}(film): 3392, 2931, 2853, 1640, 1585, 1454, 1360, 1245, 1059, 1033, 970 cm^{-1}.

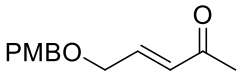
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 2H), 6.90 – 6.85 (m, 2H), 5.90 – 5.71 (m, 3H), 5.08 – 4.95 (m, 2H), 4.45 (s, 2H), 4.15 (dd, *J* = 11.3, 6.0 Hz, 1H), 4.00 (d, *J* = 4.4 Hz, 2H), 3.80 (s, 3H), 2.21 – 2.08 (m, 2H), 1.69 (s, 1H), 1.67 – 1.59 (m, 2H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.3, 138.3, 135.8, 130.4, 129.5, 127.5, 115.0, 113.9, 72.1, 71.9, 69.9, 55.4, 36.2, 29.8.

HRMS (ESI) *m/z*: calcd for $[M+ Na]^+$, $C_{16}H_{22}O_3Na$, 285.1466 found, 285.1463

General Procedure B: Synthesis of *α, β*-unsaturated ketones (18-21) from allylic alcohols (13-16):

To a stirred solution of oxalyl chloride (1.5 equiv.) in CH_2Cl_2 (80 mL), DMSO (3.0 equiv.) was added dropwise at −78 °C. After 30 minutes, allylic alocols **(13-16)** (1.0 equiv.) in CH_2Cl_2 (25 mL) were added, and the reaction mixture was stirred at −78 °C for 2 h. At the same temperature, the *N, N*-Diisopropylethylamine (6.0 equiv.) was added slowly. The mixture was allowed to warm slowly to room temperature, and the reaction progress was monitored by TLC. After 30 minutes, 1.0N aq. HCl (50 mL) was added, and the reaction mixture was stirred for an additional 30 minutes. The mixture was then extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extracts were washed with brine (25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude products were purified by silica gel column chromatography using a gradient of hexanes: ethyl acetate.



18

(*E*)-5-((4-methoxybenzyl)oxy)pent-3-en-2-one (18):

Compound **18** was synthesized by following general procedure B and purified by silica gel column chromatography (7:3 hexanes/ethyl acetate).

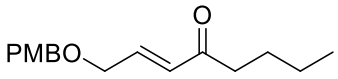
R_f: 0.6 (7:3 hexanes: ethyl acetate), **Yield:** 1.1 g (81%), yellow liquid.

IR υ_{max}(film): 3006, 2924, 1674, 1635, 1512, 1460, 1245, 1174, 1113, 1030, 970 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.26 (m, 2H), 6.91 – 6.87 (m, 2H), 6.79 (dt, *J* = 16.1, 4.5 Hz, 1H), 6.33 (dt, *J* = 16.1, 1.9 Hz, 1H), 4.50 (s, 2H), 4.17 (dd, *J* = 4.5, 1.9 Hz, 2H), 3.80 (s, 3H), 2.26 (s, 3H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.3, 159.5, 143.3, 130.4, 129.7, 129.5, 114.0, 72.7, 68.6, 55.4, 27.4.

HRMS (ESI) *m/z*: calcd for $[M+H]^+$, $C_{13}H_{17}O_3$, 221.1177; Found, 221.1177



19

(*E*)-1-((4-methoxybenzyl)oxy)oct-2-en-4-one (19):

Compound **19** was synthesized by following general procedure B and purified by silica gel column chromatography (7:3 petroleum ether/ethyl acetate).

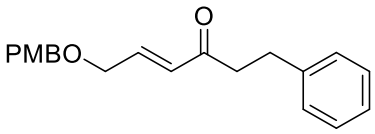
R_f: 0.7 (8:2 hexanes: ethyl acetate), **Yield:** 1.7 g (86%), yellow liquid.

IR υ_{max}(film): 3006, 2956, 1673, 1635, 1512, 1460, 1358, 1245, 1176, 1031 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 2H), 6.90 – 6.87 (m, 2H), 6.82 (dt, *J* = 16.0, 4.5 Hz, 1H), 6.36 (dt, *J* = 16.0, 1.9 Hz, 1H), 4.50 (s, 2H), 4.16 (dd, *J* = 4.4, 1.9 Hz, 2H), 3.81 (s, 3H), 2.56 – 2.53 (m, 2H), 1.60 (dt, *J* = 20.5, 7.5 Hz, 2H) ,1.38– 1.29 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 200.6, 159.5, 142.1, 129.8, 129.5, 114.0, 77.2, 72.7, 68.7, 55.4, 40.4, 26.3, 22.5, 14.0.

HRMS (ESI) *m/z*: calcd for $[M+ Na]^+$, $C_{16}H_{23}O_3$, 263.1647; Found, 263.1650



20

(*E*)-6-((4-methoxybenzyl)oxy)-1-phenylhex-4-en-3-one (20):

Compound **20** was synthesized by following general procedure B and purified by silica gel column chromatography (7:3 hexanes/ethyl acetate).

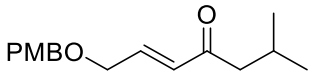
R_f: 0.7 (7:3 hexanes: ethyl acetate), **Yield:** 887 mg (65%), light yellow liquid.

IR υ_{max}(film): 3023, 2924, 2361, 1673, 1635, 1511, 1360, 1245, 1176, 1030 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 4H), 7.18 (dd, *J* = 10.2, 4.1 Hz, 3H), 6.90 – 6.87 (m, 2H), 6.82 (dt, *J* = 16.0, 4.4 Hz, 1H), 6.37 (dt, *J* = 16.0, 1.9 Hz, 1H), 4.48 (s, 2H), 4.15 (dd, *J* = 4.4, 2.0 Hz, 2H), 3.80 (s, 3H), 2.96 – 2.92 (m, 2H), 2.88 (ddd, *J* = 8.8, 5.1, 1.7 Hz, 2H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.2, 159.5, 142.6, 141.2, 129.8, 129.5, 129.3, 128.6, 128.4, 126.2, 114.0, 72.7, 68.6, 55.4, 42.2, 30.0.

HRMS (ESI) *m/z*: calcd for $[M+ H]^+$, $C_{20}H_{23}O_3$, 311.1647; Found 311.1653



21

(*E*)-1-((4-methoxybenzyl)oxy)-6-methylhept-2-en-4-one (21):

Compound **21** was synthesized by following general procedure B and purified by silica gel column chromatography (8:2 hexanes/ethyl acetate).

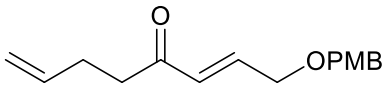
R_f: 0.6 (8:2 hexanes: ethyl acetate), **Yield:** 882 mg (74%), light yellow liquid.

IR υ_{max} (film): 3011, 2957, 2844, 1669, 1633, 1512, 1361, 1245, 1175, 1032 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 2H), 6.91 – 6.87 (m, 2H), 6.81 (dt, *J* = 16.0, 4.4 Hz, 1H), 6.35 (dt, *J* = 16.0, 1.9 Hz, 1H), 4.50 (s, 2H), 4.16 (dd, *J* = 4.4, 2.0 Hz, 2H), 3.81 (s, 3H), 2.42 (d, *J* = 7.0 Hz, 2H), 2.16 (dt, *J* = 13.6, 6.7 Hz, 1H), 0.94 (s, 3H), 0.92 (s, 3H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 200.2, 159.5, 142.2, 129.8, 129.5, 114.0, 72.7, 68.8, 55.4, 49.7, 25.1, 22.8.

HRMS (ESI) *m/z*: calcd for $[M+ H]^+$, $C_{16}H_{23}O_3$, 263.1647; Found 263.1650.



22

(*E*)-1-((4-methoxybenzyl)oxy)octa-2,7-dien-4-one (22):

To a stirred solution of compound **17** (448 mg, 1.71 mmol, 1.0 equiv.) in CH_2Cl_2 (15 mL) was added Dess–Martin periodinane (DMP, 1.09 g, 2.56 mmol, 1.5 equiv.) in one portion at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Upon completion, saturated aq. $Na_2S_2O_3$ (10 mL) and saturated aq. $NaHCO_3$ (10 mL) were added, and the resulting mixture was stirred for an additional 30 min. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (9:1 hexanes/ ethyl acetate).

R_f: 0.6 (9:1 hexanes/ ethyl acetate), **Yield:** 340 mg (76%), yellow liquid.

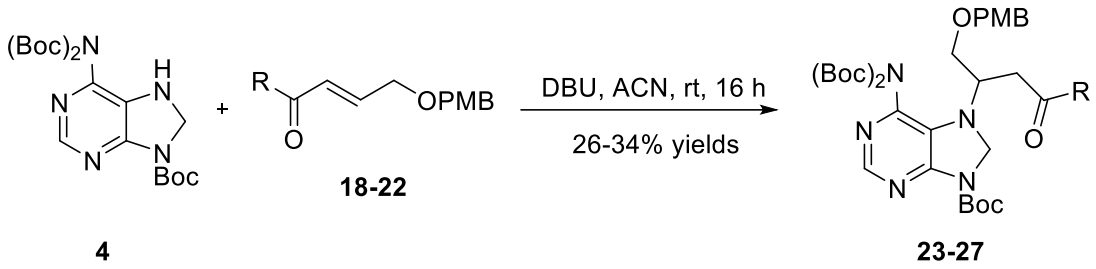
IR υ_{max}(film): 3076, 2912, 1695, 1673, 1636, 1585, 1409, 1301, 1174, 971 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 2H), 6.91 – 6.87 (m, 2H), 6.83 (dt, *J* = 16.0, 4.4 Hz, 1H), 6.37 (dt, *J* = 16.0, 2.0 Hz, 1H), 5.83 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.01 (ddq, *J* = 18.6, 10.2, 1.5 Hz, 2H), 4.50 (s, 2H), 4.17 (dd, *J* = 4.4, 2.0 Hz, 2H), 3.81 (s, 3H), 2.66 (dd, *J* = 8.8, 6.1 Hz, 2H), 2.40 – 2.34 (m, 2H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 199.4, 159.5, 142.4, 137.3, 129.8, 129.5, 129.4, 115.3, 114.0, 72.7, 68.7, 55.4, 39.7, 28.0.

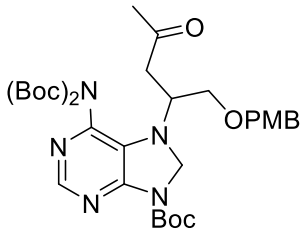
HRMS (ESI) *m/z*: calcd for $[M+H]^+$, $C_{16}H_{23}O_3$, 261.1490; Found 261.1488

General procedure C: Synthesis of Aza-Michael intermediates from *α, β*-unsaturated ketones (18-22) and TriBoc-protected dihydroadenine (4):



R= methyl, *n*-butyl, phenethyl, *iso*-butyl and 1-butenyl

TriBoc-protected dihydroadenine **4** (1.0 equiv.) was dissolved in acetonitrile (30 mL) under N_2 atmosphere was added DBU (1.5 equiv.), and then, *α, β*-unsaturated ketone (**18-22**) (1.5 equiv.) was dissolved in acetonitrile (20 mL) and slowly added to the reaction mixture over 20 min The reaction mixture was kept at room temperature for 16 h, and the reaction progress was monitored by TLC. Concentrated the reaction mixture under reduced pressure, and the crude product was purified by column chromatography using hexanes: ethyl acetate to get the desired Aza-Michael products (**23-27**) in moderate yields.



23

tert-butyl 6-(bis(tert-butoxycarbonyl)amino)-7-(1-((4-methoxybenzyl)oxy)-4-oxopentan-2-yl)-7,8-dihydro-9H-purine-9-carboxylate (23):

Compound **23** was synthesized by following general procedure C and purified by silica gel column chromatography (7:3 hexanes/ethyl acetate).

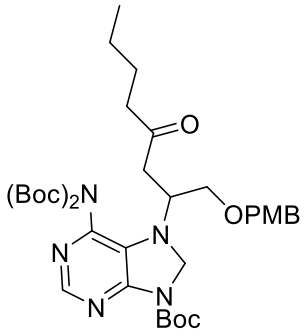
R_f: 0.30 (7:3 hexanes: ethyl acetate), **Yield:** 278 mg (25% isolated, 34% brsm), yellow liquid.

IR υ_{max}(film): 3019, 2962, 2855, 1719, 1609, 1513, 1464, 1252, 1146, 1029 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.19 – 7.16 (m, 2H), 6.87 – 6.84 (m, 2H), 5.28 (d, *J* = 6.0 Hz, 1H), 5.15 (d, *J* = 6.0 Hz, 1H), 4.37 (q, *J* = 11.4 Hz, 2H), 4.28 – 4.21 (m, 1H), 3.80 (s, 3H), 3.64 (d, *J* = 3.8 Hz, 2H), 3.05 (dd, *J* = 17.0, 9.9 Hz, 1H), 2.58 (dd, *J* = 17.0, 4.0 Hz, 1H), 2.11 (s, 3H), 1.56 (s, 9H), 1.45 (s, 18H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 205.2, 159.5, 148.6, 135.0, 129.9, 129.8, 129.4, 128.6, 128.5, 126.3, 114.0, 83.3, 83.6, 73.2, 70.2, 65.9, 55.4, 51.5, 41.5, 30.4, 28.3, 28.0.

HRMS (ESI) *m/z*: calcd for $[M+H]^+$, $C_{33}H_{48}N_5O_9$, 658.3452; Found, 658.3470



24

tert-butyl 6-(bis(tert-butoxycarbonyl)amino)-7-(1-((4-methoxybenzyl)oxy)-4-oxooctan-2-yl)-7,8-dihydro-9H-purine-9-carboxylate (24) :

Compound **24** was synthesized by following general procedure C and purified by silica gel column chromatography (7:3 hexanes/ethyl acetate).

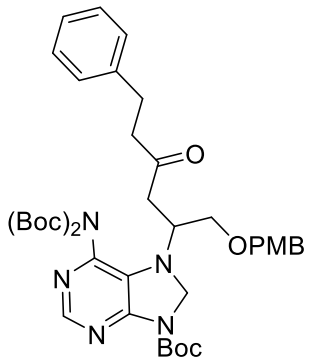
R_f: 0.30 (7:3 hexanes: ethyl acetate), **Yield:** 358 mg (22% isolated, 26% brsm), yellow liquid.

IR υ_{max}(film): 2977, 2868, 1741, 1711, 1604, 1512, 1363, 1298, 1216, 1145, 1034 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.18 – 7.14 (m, 2H), 6.86 – 6.82 (m, 2H), 5.29 (d, *J* = 6.0 Hz, 1H), 5.15 (d, *J* = 6.0 Hz, 1H), 4.35 (dd, *J* = 25.4, 11.4 Hz, 2H), 4.24 (dq, *J* = 10.4, 3.6 Hz, 1H), 3.79 (s, 3H), 3.63 (d, *J* = 3.9 Hz, 2H), 3.05 (dd, *J* = 16.9, 10.1 Hz, 1H), 2.52 (dd, *J* = 16.9, 3.9 Hz, 1H), 2.37 – 2.33 (m, 2H), 1.66 (s, 2H), 1.56 (s, 9H), 1.44 (s, 18H), 1.29 – 1.23 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 207.6, 159.5, 156.6, 150.7, 148.5, 148.4, 135.0, 129.8, 129.4, 128.5, 114.0, 83.8, 83.6, 73.2, 70.2, 65.9, 55.4, 51.4, 43.1, 40.4, 28.3, 28.0, 25.8, 22.4, 14.0.

HRMS (ESI) *m/z*: calcd for $[M+H]^+$, $C_{36}H_{54}N_5O_9$, 700.3921; Found, 700.3940



25

tert-butyl 6-(bis(tert-butoxycarbonyl)amino)-7-(1-((4-methoxybenzyl)oxy)-4-oxo-6-phenylhexan-2-yl)-7,8-dihydro-9H-purine-9-carboxylate (25) :

Compound **25** was synthesized by following general procedure C and purified by silica gel column chromatography (7:3 hexanes/ethyl acetate).

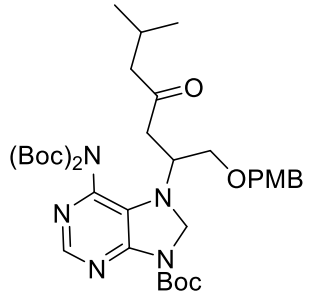
R_f: 0.20 (7:3 hexanes: ethyl acetate), **Yield:** 320 mg (19% isolated, 23% brsm), yellow sticky liquid.

IR υ_{max}(film): 2979, 2928, 2862, 1792, 1741, 1710, 1603, 1461, 1245, 1143 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.27 – 7.23 (m, 2H), 7.19 – 7.11 (m, 5H), 6.89 – 6.82 (m, 2H), 5.26 (d, J = 6.0 Hz, 1H), 5.12 (d, J = 6.0 Hz, 1H), 4.45 – 4.30 (m, 2H), 4.28 – 4.06 (m, 2H), 3.79 (s, 4H), 3.60 (qd, J = 10.0, 3.6 Hz, 2H), 3.01 (dd, J = 16.8, 10.0 Hz, 1H), 2.87 – 2.80 (m, 2H), 2.71 – 2.67 (m, 2H), 2.54 (dd, J = 16.8, 4.0 Hz, 1H), 1.55 (s, 9H), 1.44 (s, 18 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 206.3, 159.5, 156.6, 150.7, 148.6, 148.3, 140.8, 135.0, 129.7, 129.4, 128.6, 128.5, 128.4, 126.3, 114.0, 83.9, 83.6, 73.2, 70.1, 65.8, 55.4, 51.4, 44.7, 40.6, 29.5, 28.3, 28.0.

HRMS (ESI) *m/z*: calcd for $[M+H]^+$, $C_{40}H_{54}N_5O_9$, 748.3921; Found, 748.3958



26

tert-butyl 6-(bis(tert-butoxycarbonyl)amino)-7-(1-((4-methoxybenzyl)oxy)-6-methyl-4-oxoheptan-2-yl)-7,8-dihydro-9H-purine-9-carboxylate (26):

Compound **26** was synthesized by following general procedure C and purified by silica gel column chromatography (7:3 hexanes/ethyl acetate).

R_f: 0.25 (7:3 hexanes: ethyl acetate), **Yield:** 493 mg (26% isolated, 30% brsm), pale yellow liquid.

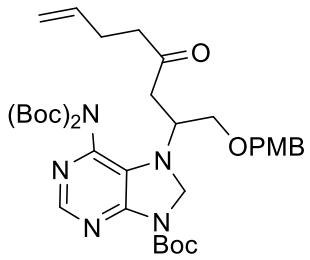
IR υ_{max}(film): 2979, 2873, 1792, 1710, 1603, 1464, 1247, 1143 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.17 – 7.14 (m, 2H), 6.85 – 6.82 (m, 2H), 5.28 (d, *J* = 6.0 Hz, 1H), 5.15 (d, *J* = 6.0 Hz, 1H), 4.34 (q, *J* = 11.3 Hz, 2H), 4.23 (dq, *J* = 10.4, 3.6 Hz, 1H), 3.79 (s, 3H), 3.63 (d, *J* = 3.7 Hz, 2H), 3.04 (dd, *J* = 17.0, 10.1 Hz, 1H), 2.49 (dd, *J* = 17.0, 3.9 Hz, 1H), 2.28 – 2.18 (m, 2H), 2.10 – 2.03 (m, 1H), 1.55 (s, 9H), 1.44 (s, 18H), 0.87 (dd, *J* = 6.6, 3.1 Hz, 6H).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 207.1, 159.4, 156.6, 150.7, 148.5, 148.3, 134.9,

129.7, 129.4, 128.5, 113.9, 83.8, 83.5, 73.2, 70.2, 65.9, 55.4, 52.3, 51.4, 40.8, 28.3, 28.0, 24.6, 22.7, 22.6.

HRMS (ESI) *m/z*: calcd for $[M+H]^+$, $C_{36}H_{54}N_5O_9$, 700.3921; found, 700.3932



27

tert-butyl 6-(bis(tert-butoxycarbonyl)amino)-7-(1-((4-methoxybenzyl)oxy)-4-oxooct-7-en-2-yl)-7,8-dihydro-9H-purine-9-carboxylate (27):

Compound **27** was synthesized by following general procedure C and purified by silica gel column chromatography (7:3 hexanes/ethyl acetate).

R_f: 0.25 (7:3 hexanes: ethyl acetate), **Yield:** 272 mg (17% isolated, 22% brsm), yellow sticky liquid.

IR υ_{max}(film): 2979, 1793, 1742, 1709, 1602, 1463, 1393, 1294, 1144, 907 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.18 – 7.14 (m, 2H), 6.85 – 6.83 (m, 2H), 5.75 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.28 (d, *J* = 6.0 Hz, 1H), 5.15 (d, *J* = 6.0 Hz, 1H), 5.01 – 4.93 (m, 2H), 4.35 (dd, *J* = 25.0, 11.4 Hz, 2H), 4.28 – 4.22 (m, 1H), 3.79 (s, 3H), 3.65 – 3.60 (m, 2H), 3.04 (dd, *J* = 16.9, 10.0 Hz, 1H), 2.54 (dd, *J* = 16.9, 3.9 Hz, 1H), 2.46 (td, *J* = 7.2, 3.7 Hz, 2H), 2.28 – 2.22 (m, 2H), 1.56 (s, 9H), 1.44 (s, 18H).

^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$) δ 206.5, 159.4, 156.6, 148.5, 148.3, 136.9, 135.0, 129.7, 129.4, 128.5, 115.5, 113.9, 83.9, 83.6,73.2, 70.1, 65.9, 55.4, 51.4, 42.2, 40.5, 28.3, 28.0, 27.6.

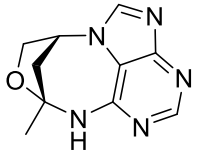
HRMS (ESI) *m/z*: calcd for $[M+H]^+$, $C_{36}H_{52}N_5O_9$, 698.3765; Found 698.3787

General procedure D: Synthesis of Cyclopeltain B analogues (28-32) from the Aza-Michael key intermediates (23-27):

23-27 **28-32**

R= methyl, *n*-butyl, phenethyl, *iso*-butyl and 1-butenyl

To a stirred solution of Aza-Michael key intermediates (**23–27**) (1.0 equiv.) in CH_2Cl_2 (12 mL) was added a solution of $TiCl_4$ (1 M in CH_2Cl_2, 2.0 equiv.) under a nitrogen atmosphere at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, then allowed to warm slowly to room temperature and stirred for an additional 2 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by column chromatography to afford the final Cyclopeltain B analogues (**28–32**).



28

10-methyl-7,8,10,11-tetrahydro-7,10-methano[1,3,6]oxadiazocino[6,5,4-*gh*]purine (28):

Compound **28** was synthesized by following general procedure D and purified by silica gel column chromatography (9:1 CH_2Cl_2: MeOH).

R_f: 0.3 (9:1 CH_2Cl_2: MeOH), **Yield:** 21 mg (26%), yellow solid.

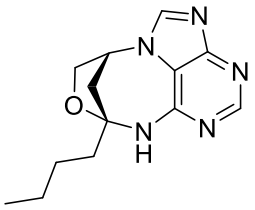
IR υ_{max}(film): 3738, 2928, 2361, 1739, 1709, 1618, 1569, 1399, 1215 cm^{-1}.

^{1}H NMR (500 MHz, CD_3OD) δ 8.38 (s, 1H), 8.37 (s, 1H), 5.37 (dd, *J* = 5.4, 3.4 Hz, 1H), 4.11 (dd, *J* = 9.5, 3.4 Hz, 1H), 3.89 (dd, *J* = 9.5, 1.8 Hz, 1H), 2.76 (dd, *J* = 14.3, 5.5 Hz, 1H), 2.57 (dd, *J* = 14.3, 1.6 Hz, 1H), 1.80 (s, 3H).

^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 160.0, 153.8, 151.7, 145.4, 112.4, 93.2, 74.6, 60.2,

46.1, 27.3.

HRMS (ESI) *m/z*: calcd for $[M+H]^+$, $C_{10}H_{12}N_5O$, 218.1041; Found, 218.1047



29

10-butyl-7,8,10,11-tetrahydro-7,10-methano[1,3,6]oxadiazocino[6,5,4-*gh*]purine (29):

Compound **29** was synthesized by following general procedure D and purified by silica gel column chromatography (9:1 CH_2Cl_2: MeOH).

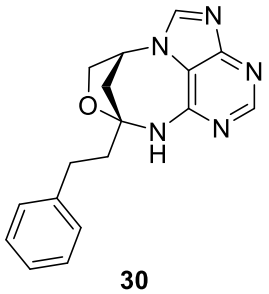
R_f: 0.4 (9:1 CH_2Cl_2: MeOH), **Yield:** 38 mg (29%), yellow solid.

IR υ_{max}(film): 3230, 2986, 2854, 1730, 1617, 1401, 1374, 1248, 1195, 1043 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.42 (s, 1H), 8.41 (s, 1H), 8.33 (s, 1H), 5.34 (dd, *J* = 5.3, 3.2 Hz, 1H), 3.90 (dd, *J* = 9.2, 3.3 Hz, 1H), 3.75 (dd, *J* = 9.2, 1.5 Hz, 1H), 2.68 (dd, *J* = 14.1, 5.5 Hz, 1H), 2.31 (dd, *J* = 14.1, 1.4 Hz, 1H), 2.07 (ddd, *J* = 15.8, 11.5, 4.4 Hz, 1H), 1.83 (td, *J* = 13.5, 3.9 Hz, 1H), 1.53 – 1.46 (m, 1H), 1.41-1.31 (m, 3H), 0.92 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 159.5, 152.2, 150.0, 144.0, 110.7, 94.0, 72.9, 57.5, 42.5, 26.1, 22.4, 14.0.

HRMS (ESI) *m/z*: calcd for $[M+H]^+$, $C_{13}H_{18}N_5O$, 260.1511; found, 260.1509.



30

10-phenethyl-7,8,10,11-tetrahydro-7,10-methano[1,3,6]oxadiazocino[6,5,4-*gh*]purine (30):

Compound **30** was synthesized by following general procedure D and purified by silica gel column chromatography (9:1 CH_2Cl_2: MeOH).

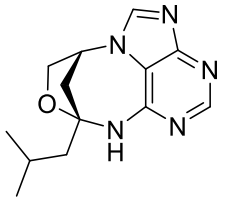
R_f: 0.5 (9:1 CH_2Cl_2: MeOH), **Yield:** 43 mg (35%), yellow solid.

IR υ_{max}(film): 3739, 3020, 1708, 1615, 1515, 1399, 1107, 1043, cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD) δ 8.39 (d, *J* = 3.0 Hz, 2H), 7.32 – 7.27 (m, 4H), 7.19 (ddd, *J* = 8.6, 5.6, 2.9 Hz, 1H), 5.39 (dd, *J* = 5.4, 3.3 Hz, 1H), 4.10 (dd, *J* = 9.6, 3.4 Hz, 1H), 3.93 (dd, *J* = 9.6, 1.6 Hz, 1H), 2.97 – 2.76 (m, 4H), 2.53 – 2.44 (m, 2H), 2.25 (ddd, *J* = 13.7, 12.1, 5.3 Hz, 1H).

^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 160.1, 153.8, 152.0, 145.4, 142.5, 129.5, 129.5, 127.1, 112.4, 95.4, 74.7, 59.9, 43.9, 43.0, 31.6.

HRMS (ESI) *m/z*: calcd for $[M+H]^+$, $C_{17}H_{18}N_5O$, 308.1511; found, 308.1523



31

10-isobutyl-7,8,10,11-tetrahydro-7,10-methano[1,3,6]oxadiazocino[6,5,4-gh]purine (31) :

Compound **31** was synthesized by following general procedure D and purified by silica gel column chromatography (9:1 CH_2Cl_2: MeOH).

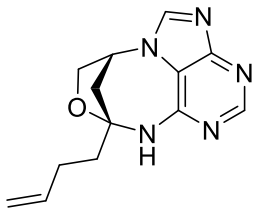
R_f: 0.4 (9:1 CH_2Cl_2: MeOH), **Yield:** 30 mg (20%), yellow solid.

IR υ_{max}(film): 3408, 2927, 2858, 2253, 1618, 1568, 1399, 1028 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.34 (s, 1H), 8.31 (s, 1H), 5.35 (dd, *J* = 5.0, 3.4 Hz, 1H), 3.91 (dd, *J* = 9.2, 3.3 Hz, 1H), 3.72 (d, *J* = 9.2 Hz, 1H), 2.72 (dd, *J* = 14.0, 5.5 Hz, 1H), 2.39 (d, *J* = 14.1 Hz, 1H), 2.07 (dd, *J* = 13.8, 5.3 Hz, 1H), 1.91 (tt, *J* = 13.0, 6.5 Hz, 1H), 1.75 (dd, *J* = 13.8, 7.5 Hz, 1H), 1.00 – 0.96 (m, 6H).

^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 159.5, 152.0, 149.8, 143.9, 110.7, 94.0, 72.4, 57.5, 47.7, 42.9, 24.0, 23.8, 23.4.

HRMS (ESI) *m/z*: calcd for $[M+H]^+$, $C_{13}H_{18}N_5O$, 260.1511; found, 260.1520



32

10-(but-3-en-1-yl)-7,8,10,11-tetrahydro-7,10-methano[1,3,6]oxadiazocino[6,5,4-*gh*]purine (32):

Compound **32** was synthesized by following general procedure **D** and purified by silica gel column chromatography (9:1 CH_2Cl_2: MeOH).

R_f: 0.3, (9:1, CH_2Cl_2: MeOH), **Yield:** 27 mg (31%), yellow solid.

IRυ_{max}(film): 3234, 3077, 2854, 1618, 1573, 1440, 1280, 1037 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD) δ 8.38 (s, 2H), 5.94 (ddt, *J* = 16.7, 10.2, 6.3 Hz, 1H), 5.38 (dd, *J* = 5.4, 3.3 Hz, 1H), 5.17 – 5.12 (m, 1H), 5.05 – 5.02 (m, 1H), 4.07 (dd, *J* = 9.6, 3.4 Hz, 1H), 3.91 (dd, *J* = 9.6, 1.8 Hz, 1H), 2.83 (dd, *J* = 14.3, 5.6 Hz, 1H), 2.49 (dd, *J* = 14.3, 1.6 Hz, 1H), 2.39 – 2.22 (m, 4H).

^{13}C{^{1}H} NMR (175 MHz, CD_3OD) δ 160.1, 153.8, 151.9, 145.4, 138.8, 115.7, 112.3, 95.4, 74.6, 59.9, 43.9, 40.2, 29.7.

HRMS (ESI) *m/z*: calcd for $[M+H]^+$, $C_{13}H_{15}N_5O$, 258.1354; found, 258.1339

X-ray Crystallography:

X-ray data for the compound was collected at room temperature on a Bruker D8 VENTURE instrument with an IμS Cu micro source (λ = 1.54184 Å) and a Bruker PHOTON III C14 detector. The raw data frames were reduced and corrected for absorption effects using the Bruker Apex 5 software suite programs.[3] The structure was solved using an intrinsic phasing method[4] and further refined with the SHELXL [2] program and expanded using Fourier techniques. Anisotropic displacement parameters were included for all non-hydrogen atoms. Atoms C1/C2 of molecule B were disordered over two positions, and their site occupation factors were refined to 0.665(13) and 0.335(13), respectively. The N-H atoms were located in the difference Fourier map, and

their positions and isotropic displacement parameters were refined. All C-bound H atoms were positioned geometrically and treated as riding on their parent C atoms [C-H = 0.93-0.97 Å, and Uiso (H) = 1.5U eq. (C) for methyl H or 1.2U eq. (C) for other H atom

Crystal structure determination of (±)-Cyclopeltain B (2)

Crystal Data for $C_{11}H_{13}N_5O$ (M =231.26 g/mol): monoclinic, space group Cc (no. 9), a = 5.3290(2) Å, b = 21.6590(10) Å, c = 18.7684(9) Å, β = 92.958(2)°, V = 2163.38(17) Å^3, Z = 8, T = 294.15 K, μ(CuKα) = 0.801 mm^{-1}, $Dcalc$ = 1.420 g/cm^3, 23094 reflections measured (8.164° ≤ 2Θ ≤ 149.098°), 4075 unique (R_{int} = 0.0865, R_{sigma} = 0.0736) which were used in all calculations. The final R_1 was 0.0408 (I > 2σ(I)), and wR_2 was 0.1070 (all data). **CCDC2451791** deposition number contains the supplementary crystallographic data for this paper, which can be obtained free of charge at https://www.ccdc.cam.ac.uk/structures/

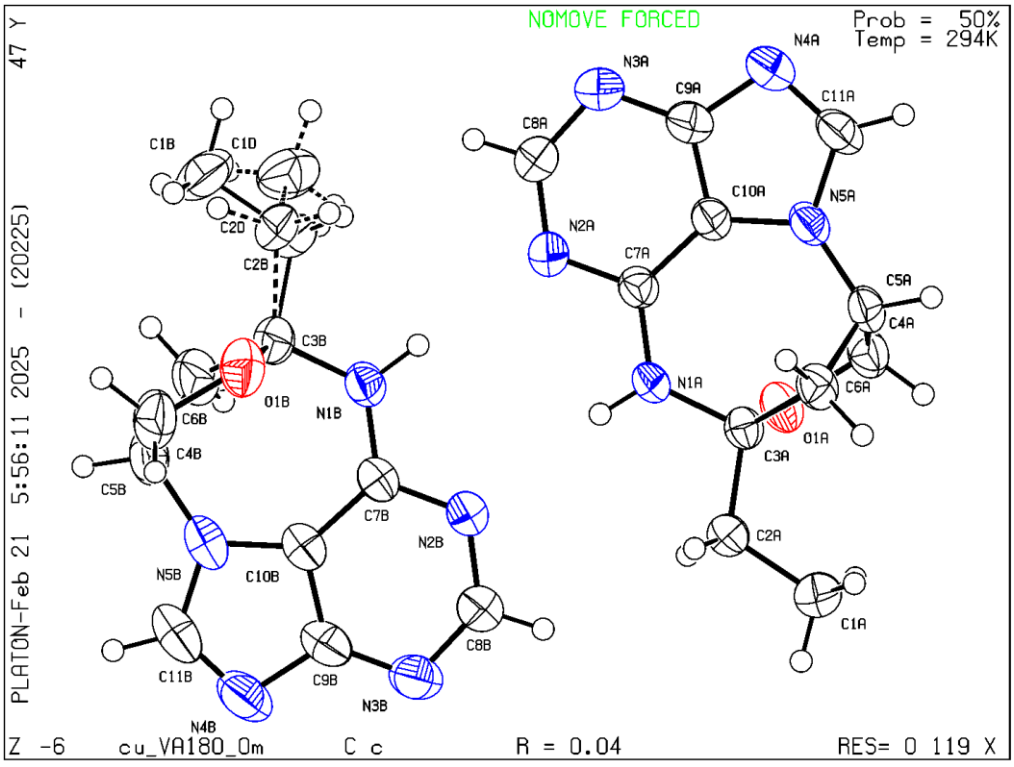


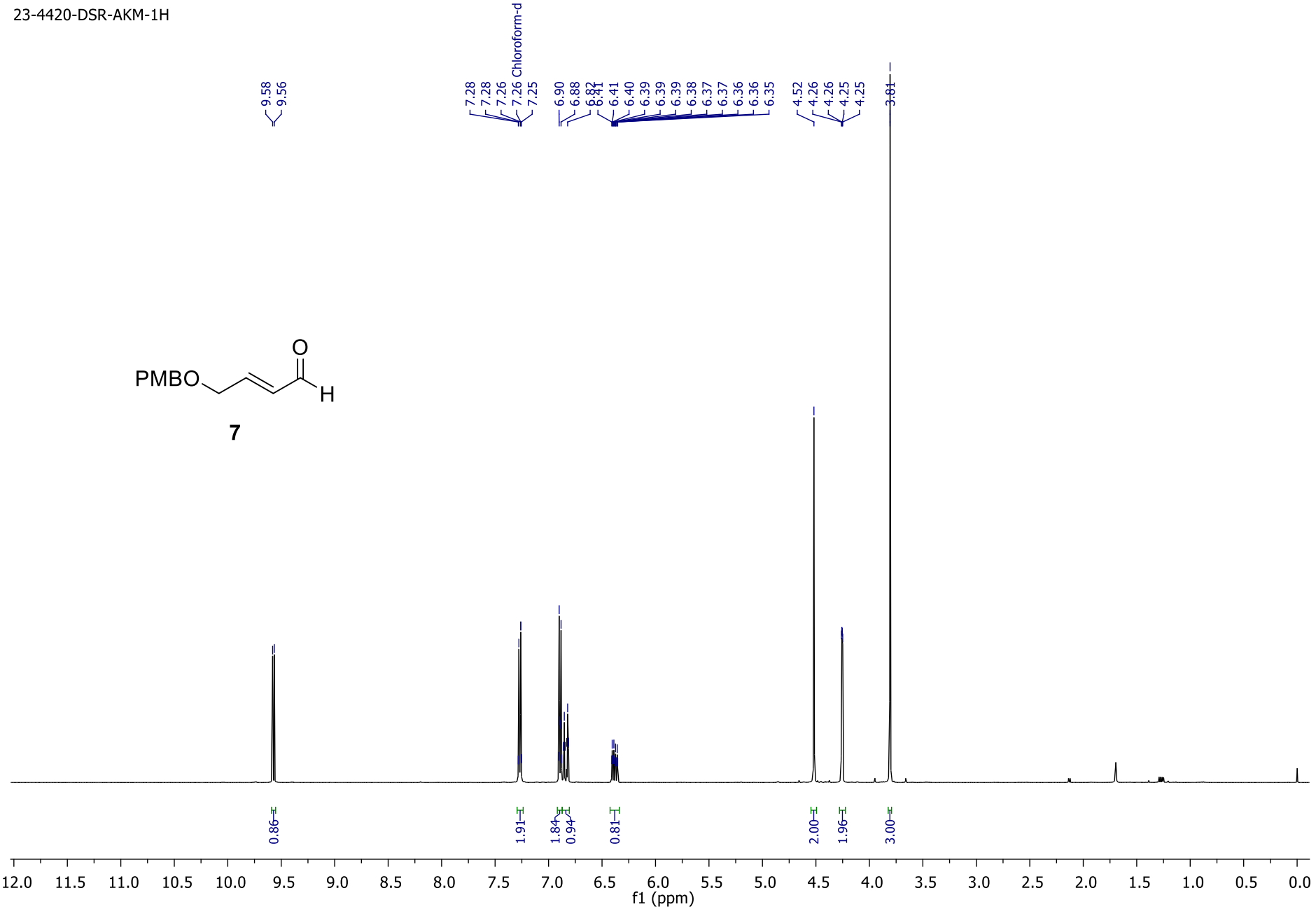
Figure 1: ORTEP diagram of (±)-Cyclopeltain B **(2)** with the atom-numbering. Displacement ellipsoids are drawn at the 30% probability level, and H atoms are shown as small spheres of arbitrary radius. The minor component of the disordered atoms was omitted for clarity.

References:

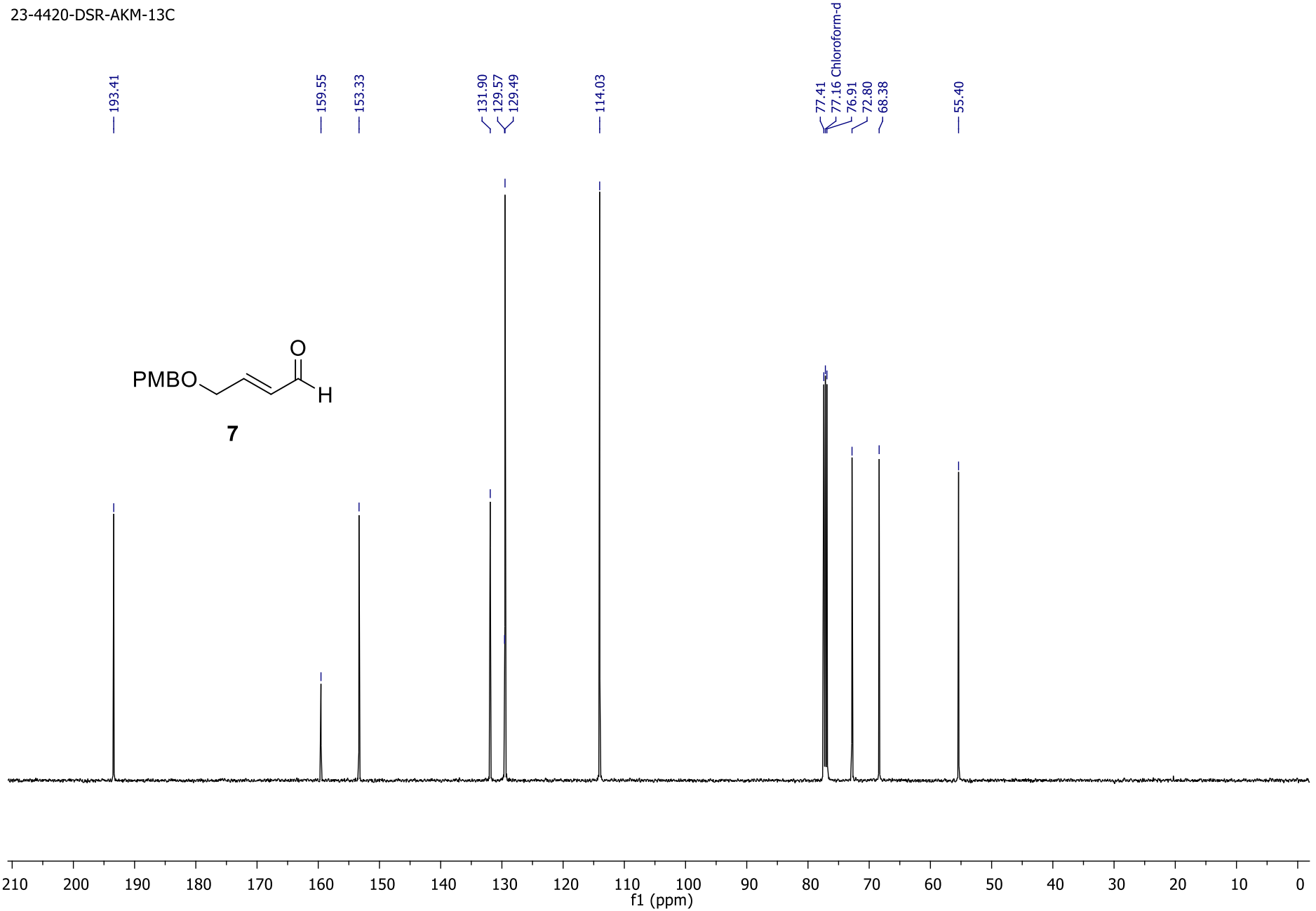
1. Fluorinated triazole-containing sphingosine analogues. Syntheses and in vitro evaluation as SPHK inhibitors. *Org. Biomol. Chem.* **2018**, *16*, 7230–7235.
2. Aarhus, T. I.; Fritze, U. F.; Hennum, M.; Gundersen, L.L. Sodium borohydride mediated reduction of *N*-Boc protected purines and applications in the synthesis of 7-alkyladenines and tetrahydro[1,4]diazepino-[1,2,3-*gh*]purines. *Tet. Lett.* **2014**, *55*, 5748–5750.
3. Bruker (**2023**). APEX5, SAINT and SADABS. Bruker AXS, Inc., Madison, Wisconsin, USA.
4. Sheldrick G. M. (**2019**). Acta Crystallogr C71: 3–8.

Copies of ^{1}H and $^{13}C\{^{1}H\}$ NMR Spectra

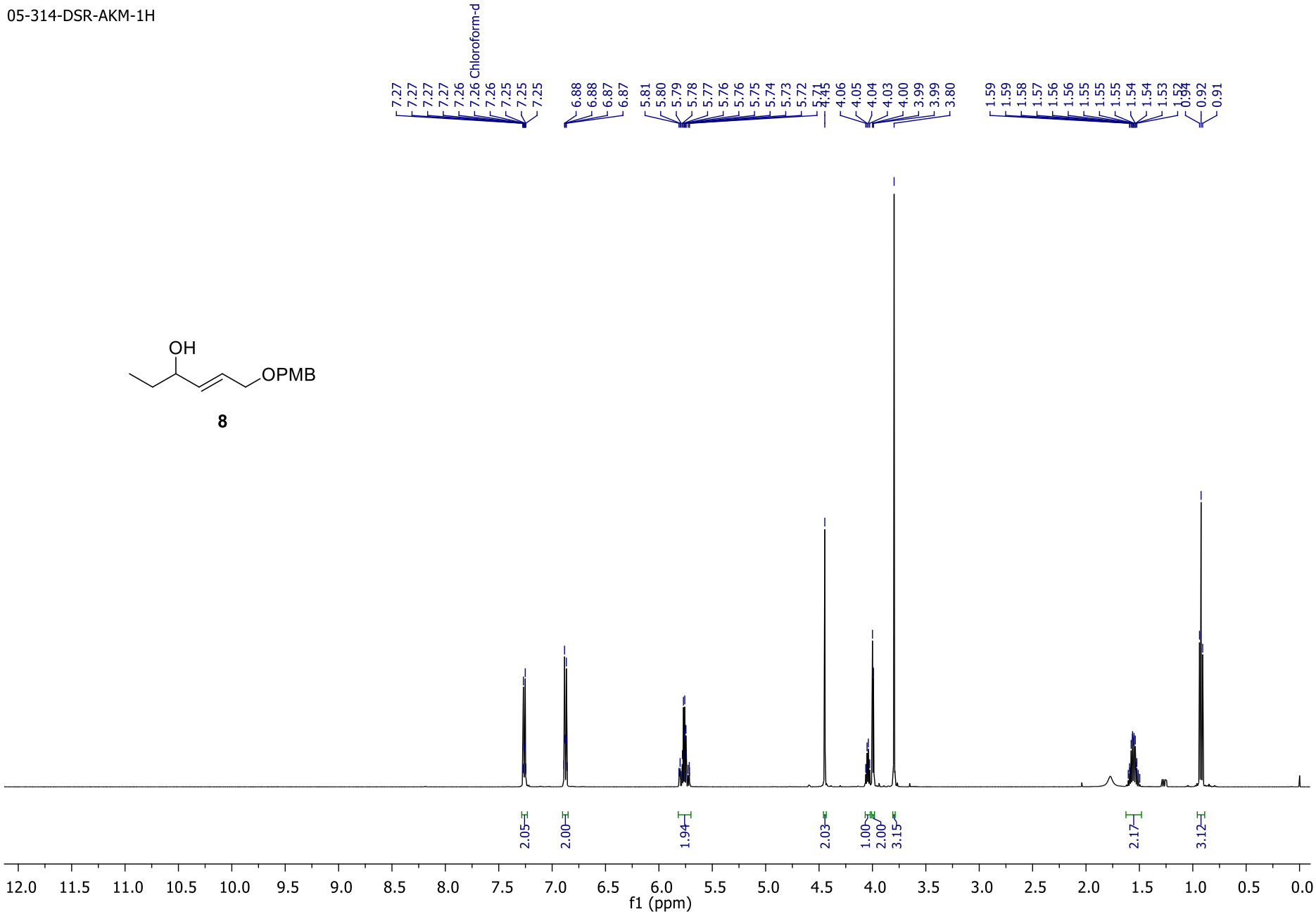
^{1}H NMR of Compound 7 in $CDCl_3$ at 500 MHz



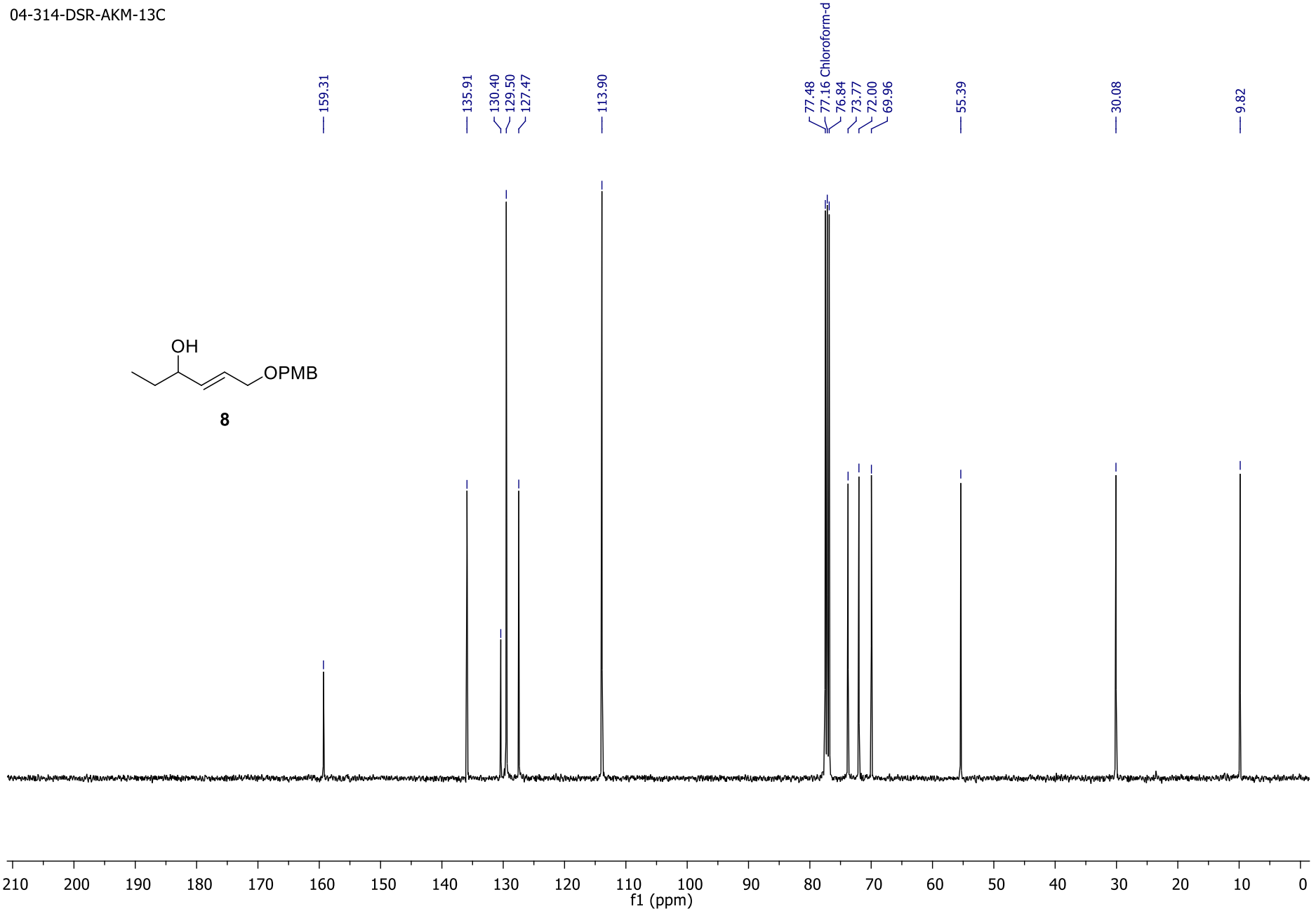
$^{13}C\{^{1}H\}$ NMR of Compound 7 in $CDCl_3$ at 125 MHz



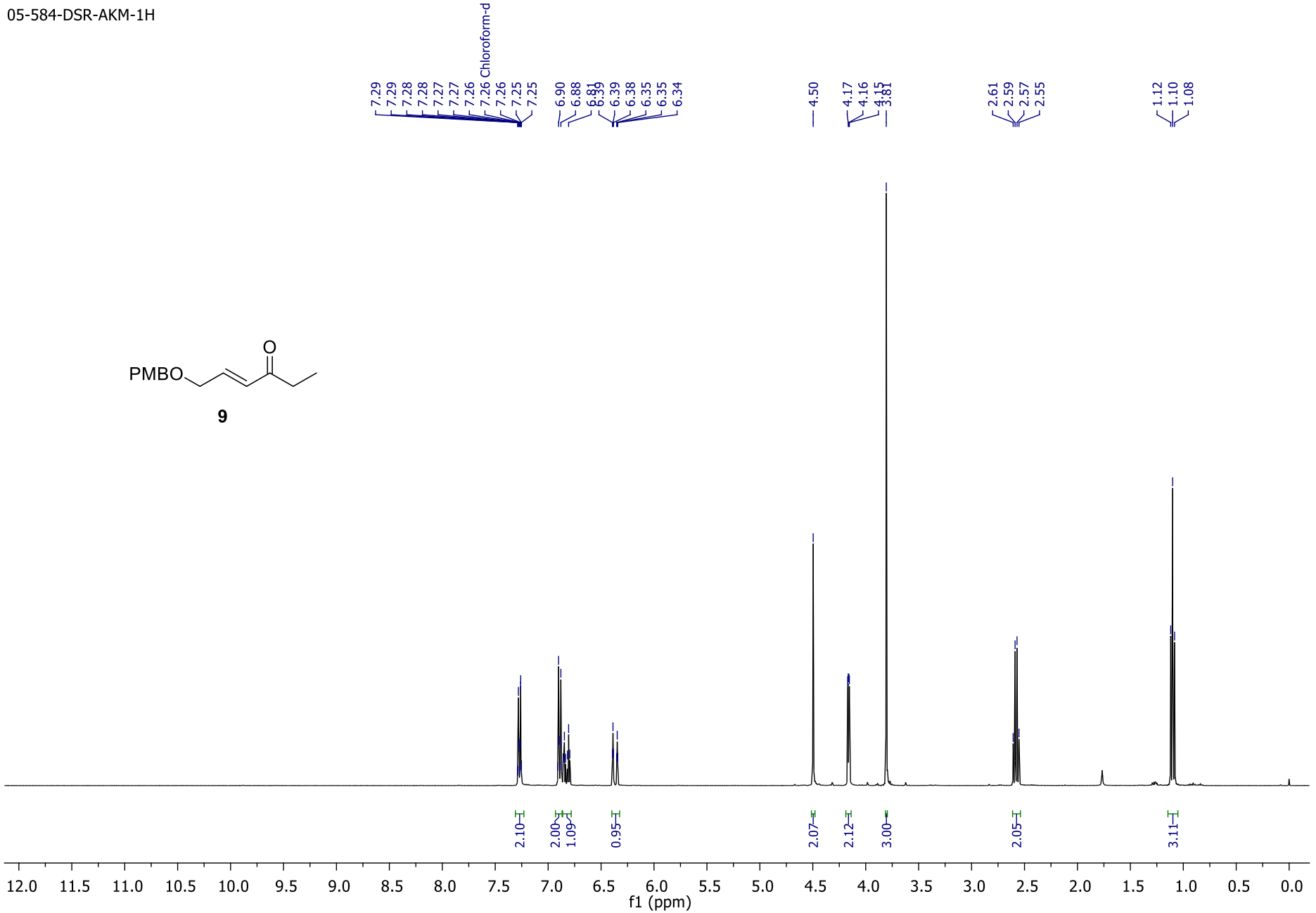
^{1}H NMR of Compound 8 in $CDCl_3$ at 500 MHz



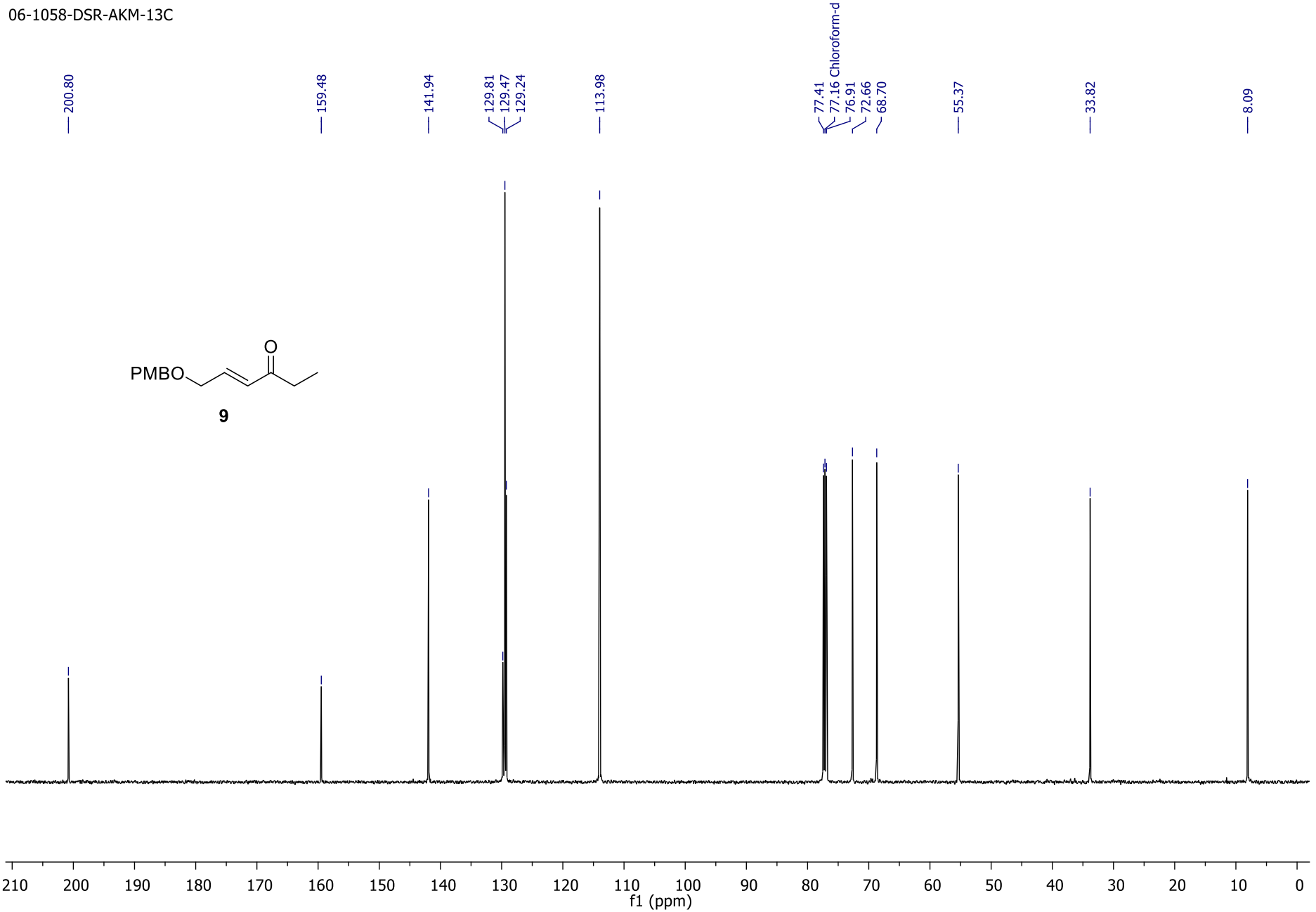
$^{13}C\{^{1}H\}$ NMR of Compound 8 in $CDCl_3$ at 100 MHz



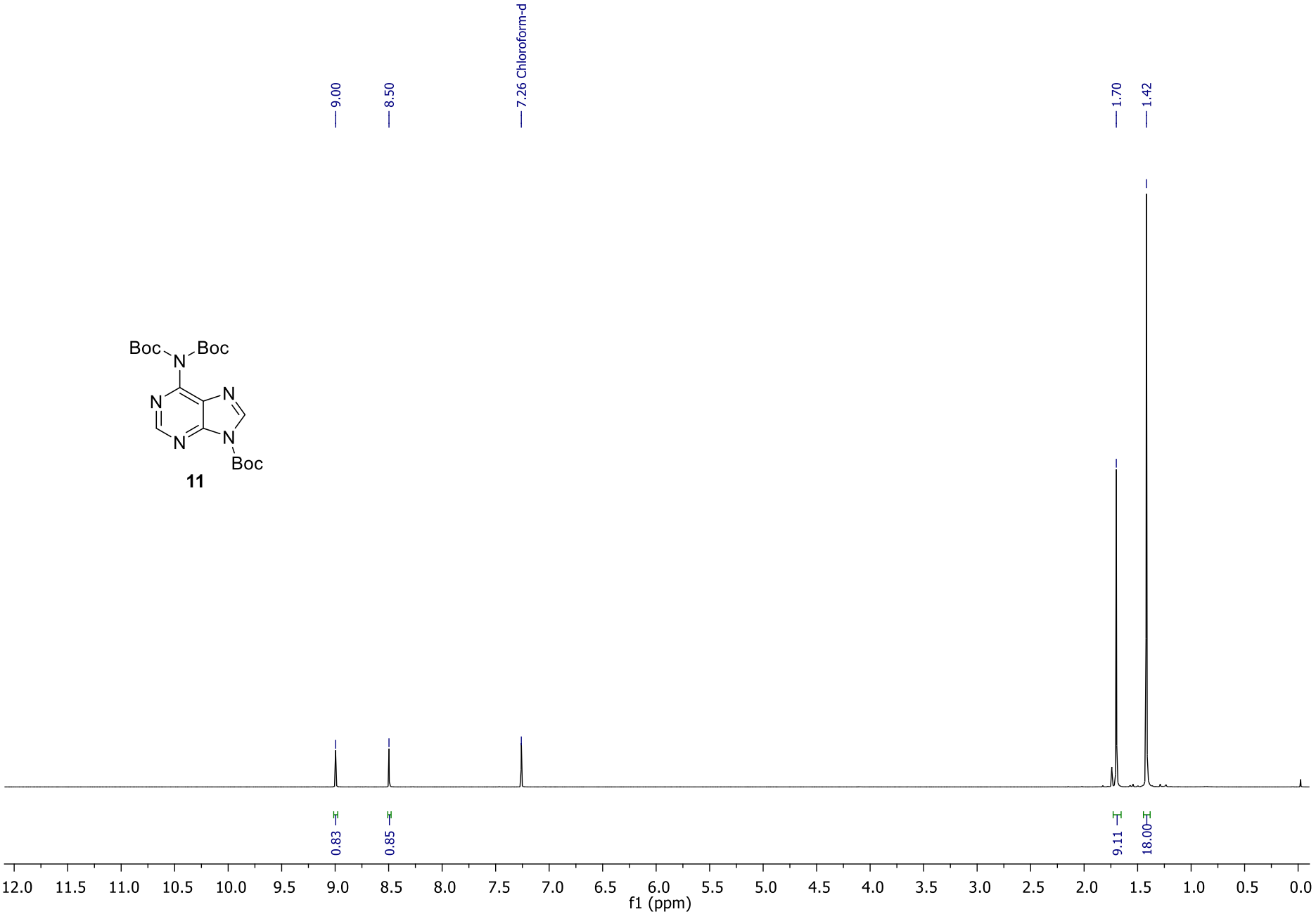
^{1}H NMR of Compound 9 in $CDCl_3$ at 400 MHz



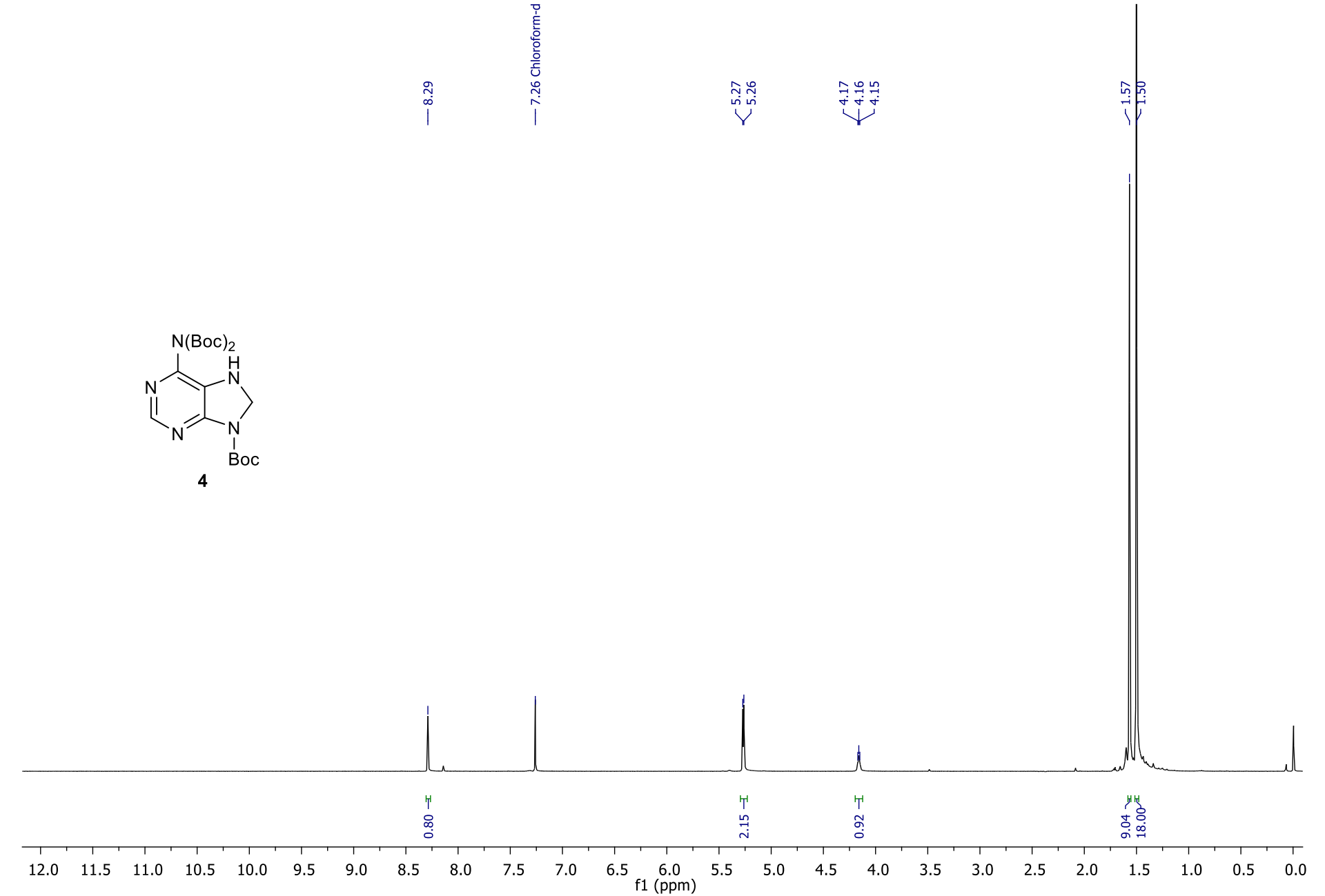
$^{13}C\{^{1}H\}$ NMR of Compound 9 in $CDCl_3$ at 125 MHz



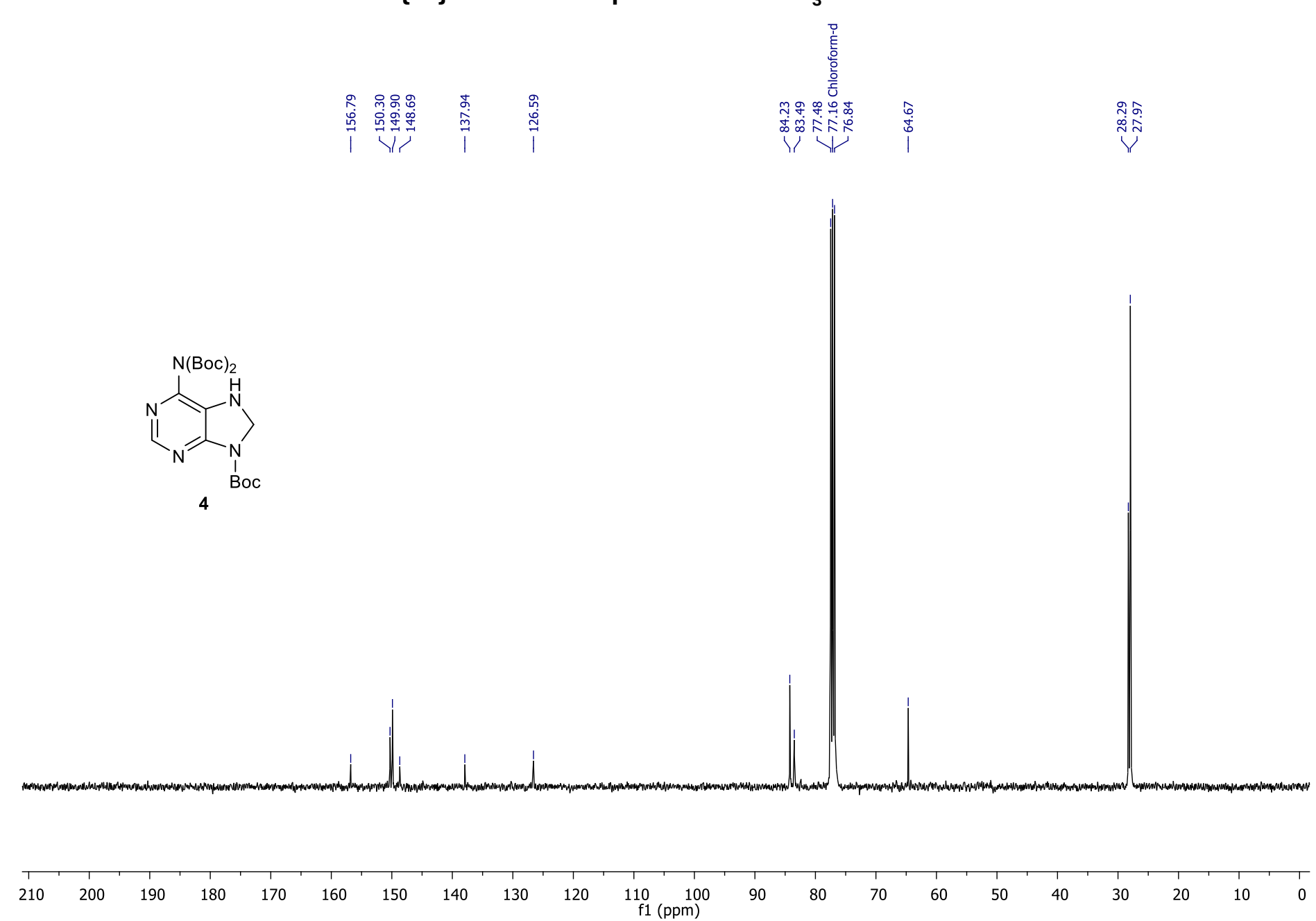
^{1}H NMR of Compound 11 in $CDCl_3$ at 500 MHz



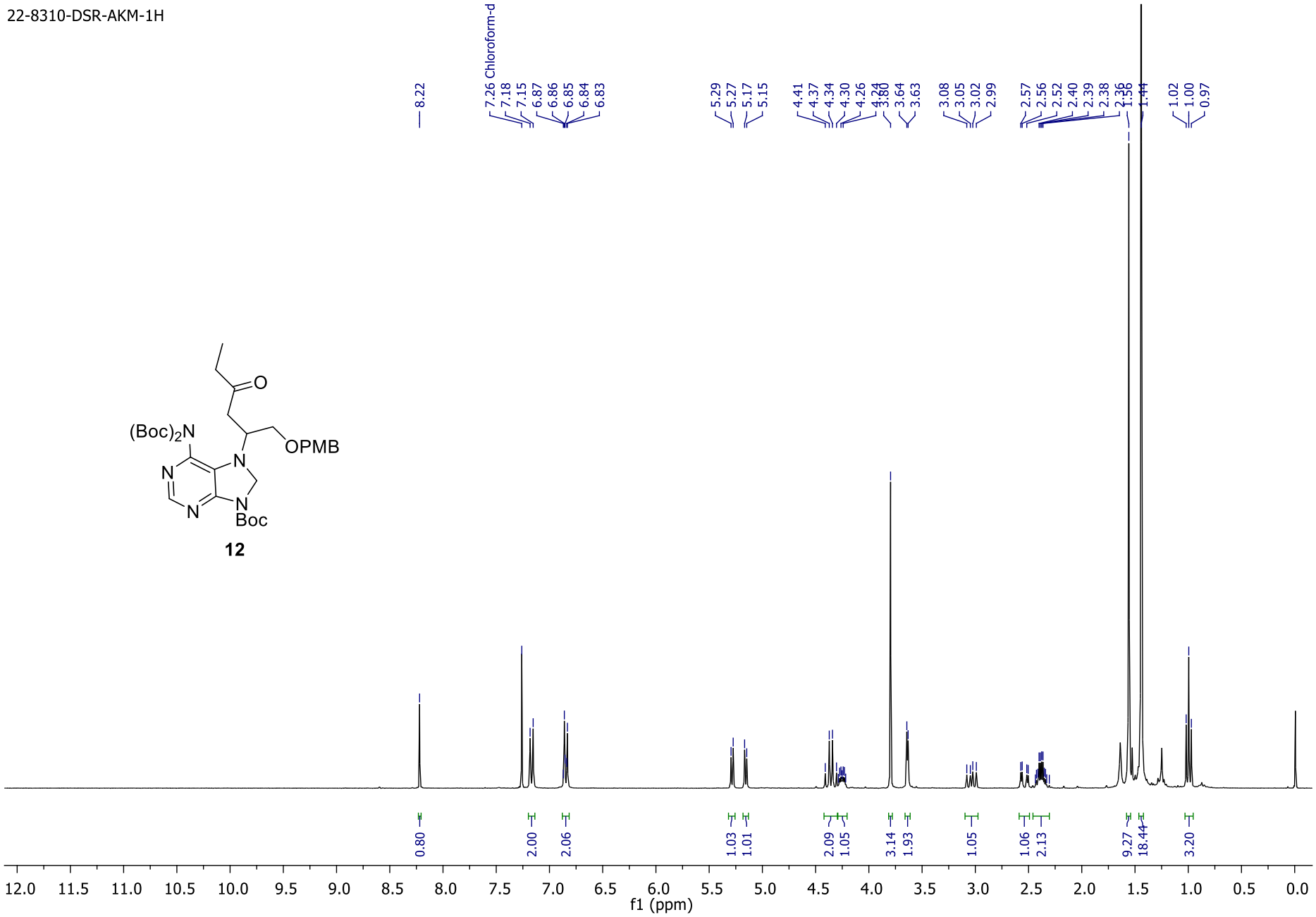
^{1}H NMR of Compound 4 in $CDCl_3$ at 400 MHz



$^{13}C\{^{1}H\}$ NMR of Compound 4 in $CDCl_3$ at 100 MHz

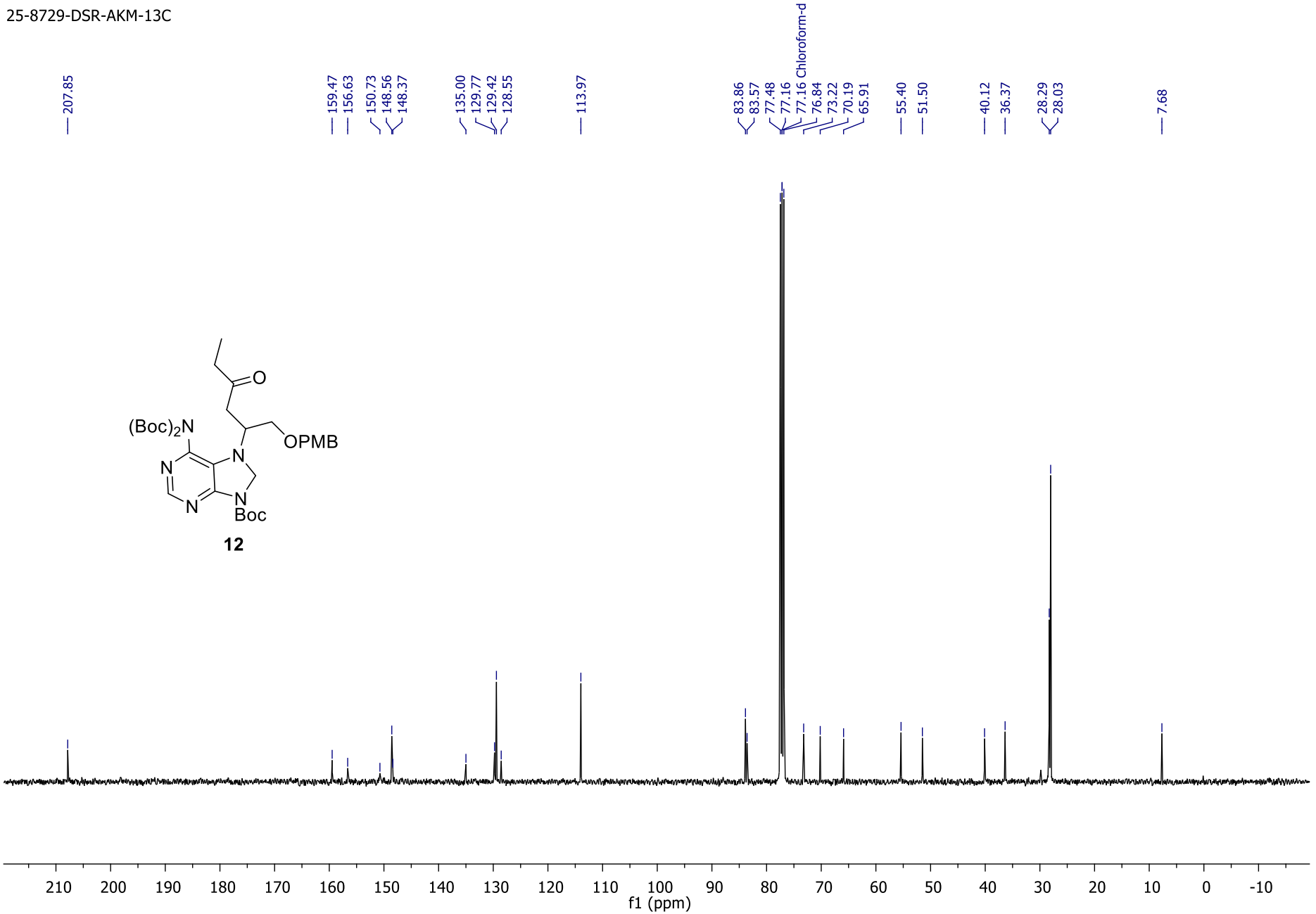


^{1}H NMR of Compound 12 in $CDCl_3$ at 300 MHz

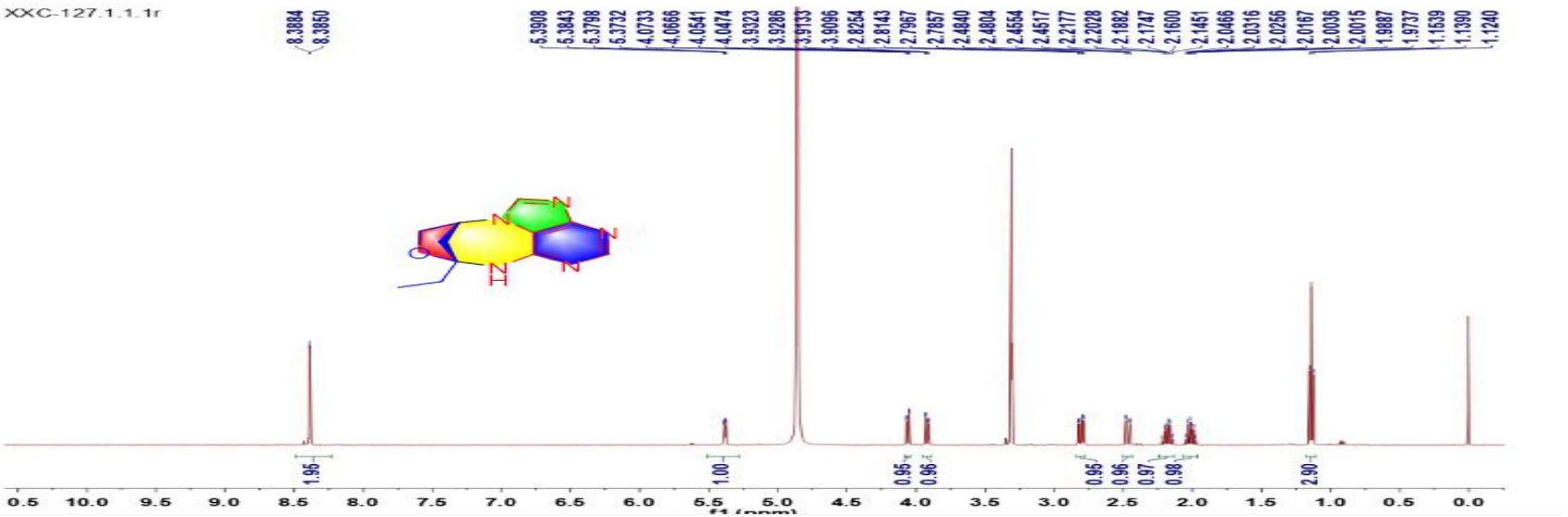


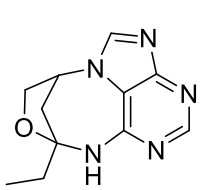
$^{13}C\{^{1}H\}$ NMR of Compound 12 in $CDCl_3$ at 100 MHz

25-8729-DSR-AKM-13C



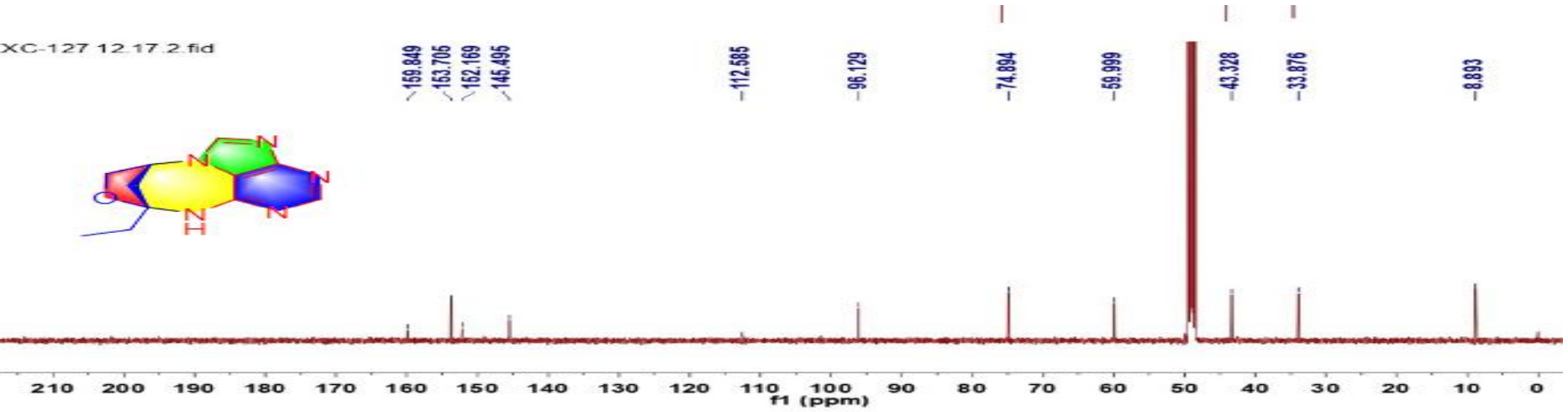
Comparison of the ^{1}H NMR spectra of the natural product. Top: spectrum reported in the original isolation study (Ref. https://doi.org/10.1039/D1QO01603B). Bottom: spectrum of the synthetic material prepared in this work.

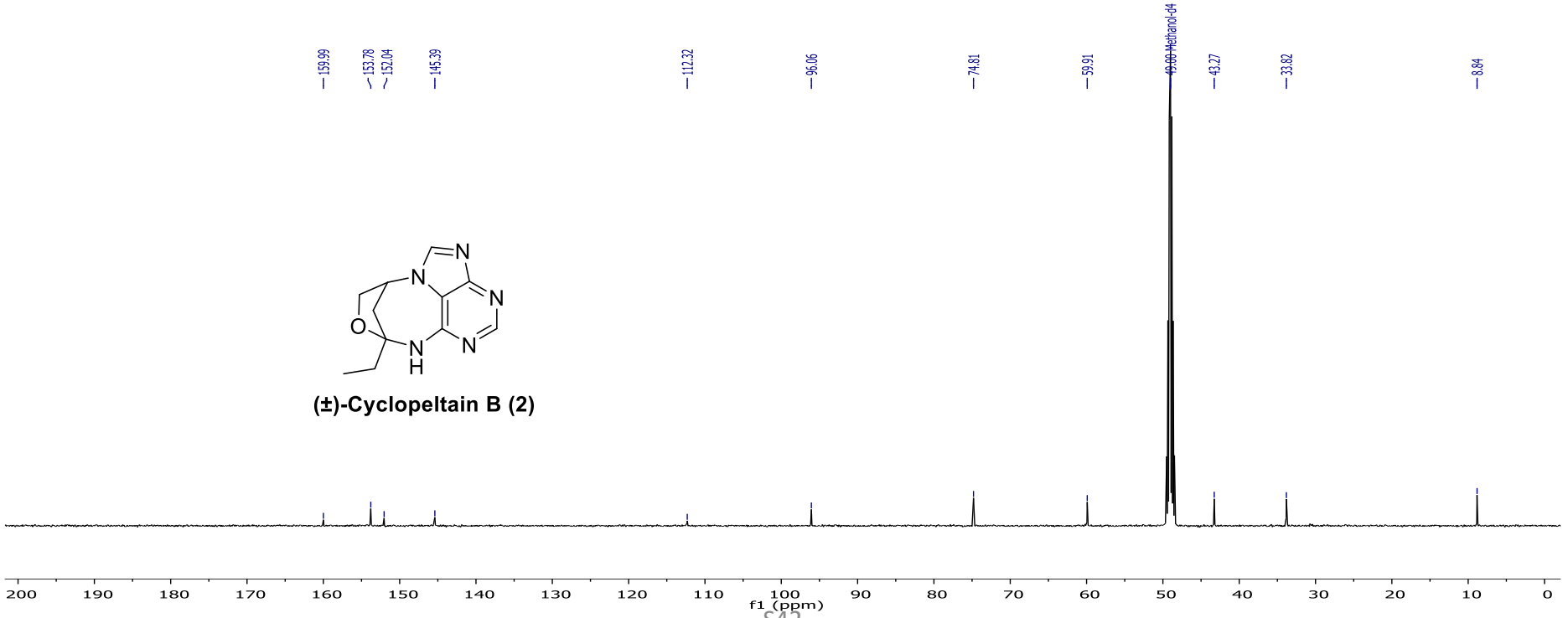




(±)-Cyclopeltain B (2)

Comparison of the ^{13}C NMR spectra of the natural product. Top: spectrum reported in the original isolation study (Ref. https://doi.org/10.1039/D1QO01603B). Bottom: spectrum of the synthetic material prepared in this work.

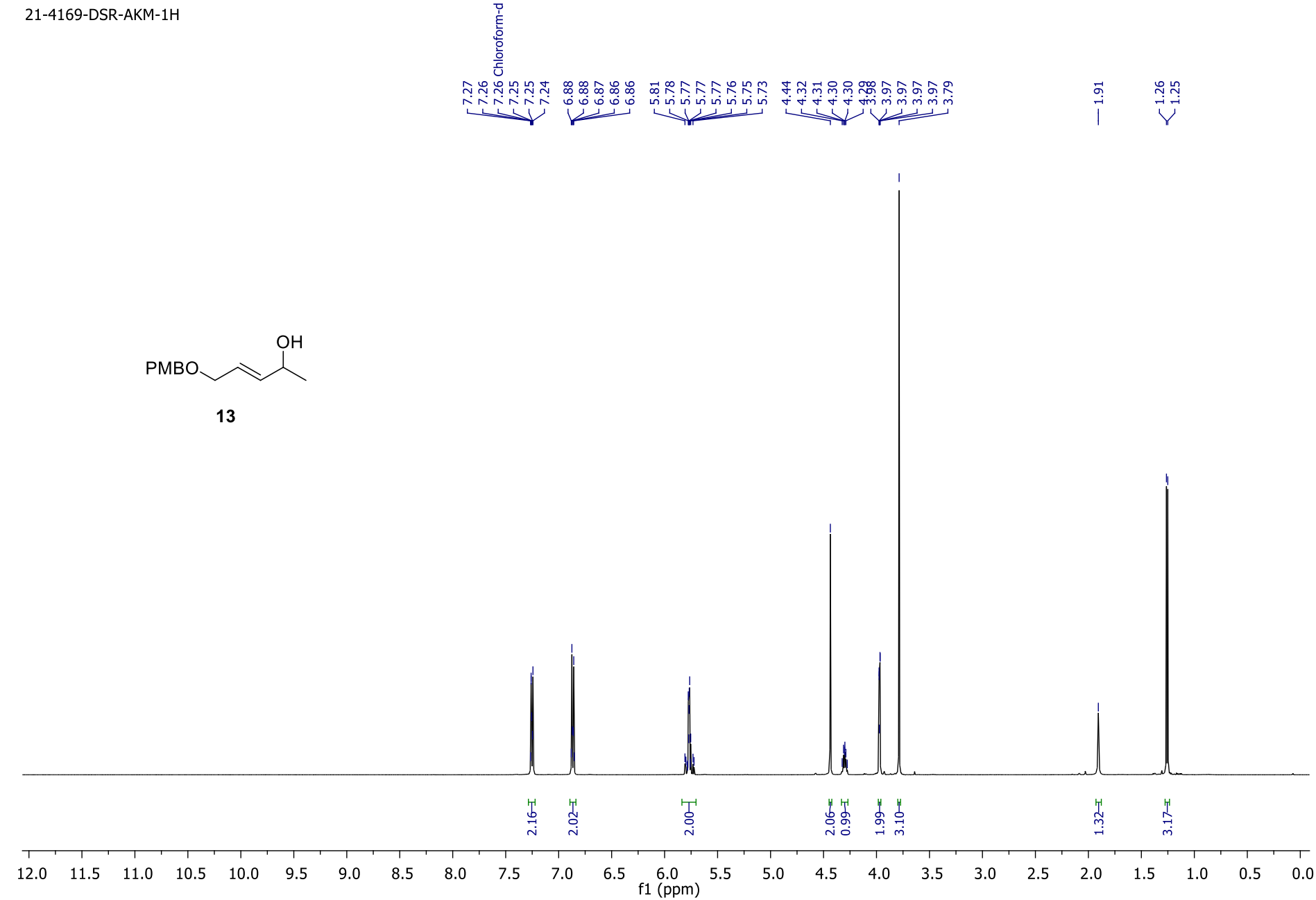




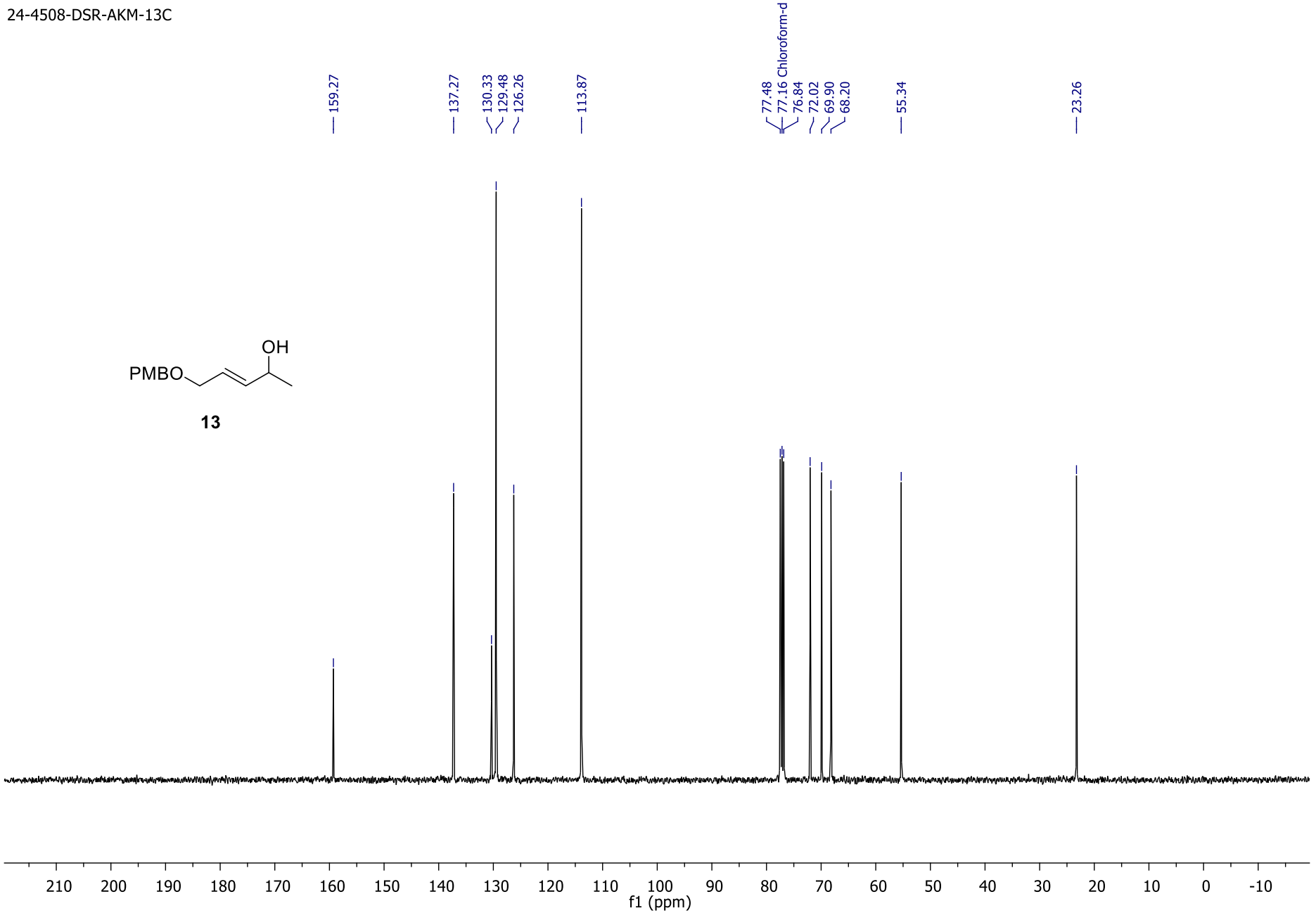
(±)-Cyclopeltain B (2)

^{1}H NMR of Compound 13 in $CDCl_3$ at 500 MHz

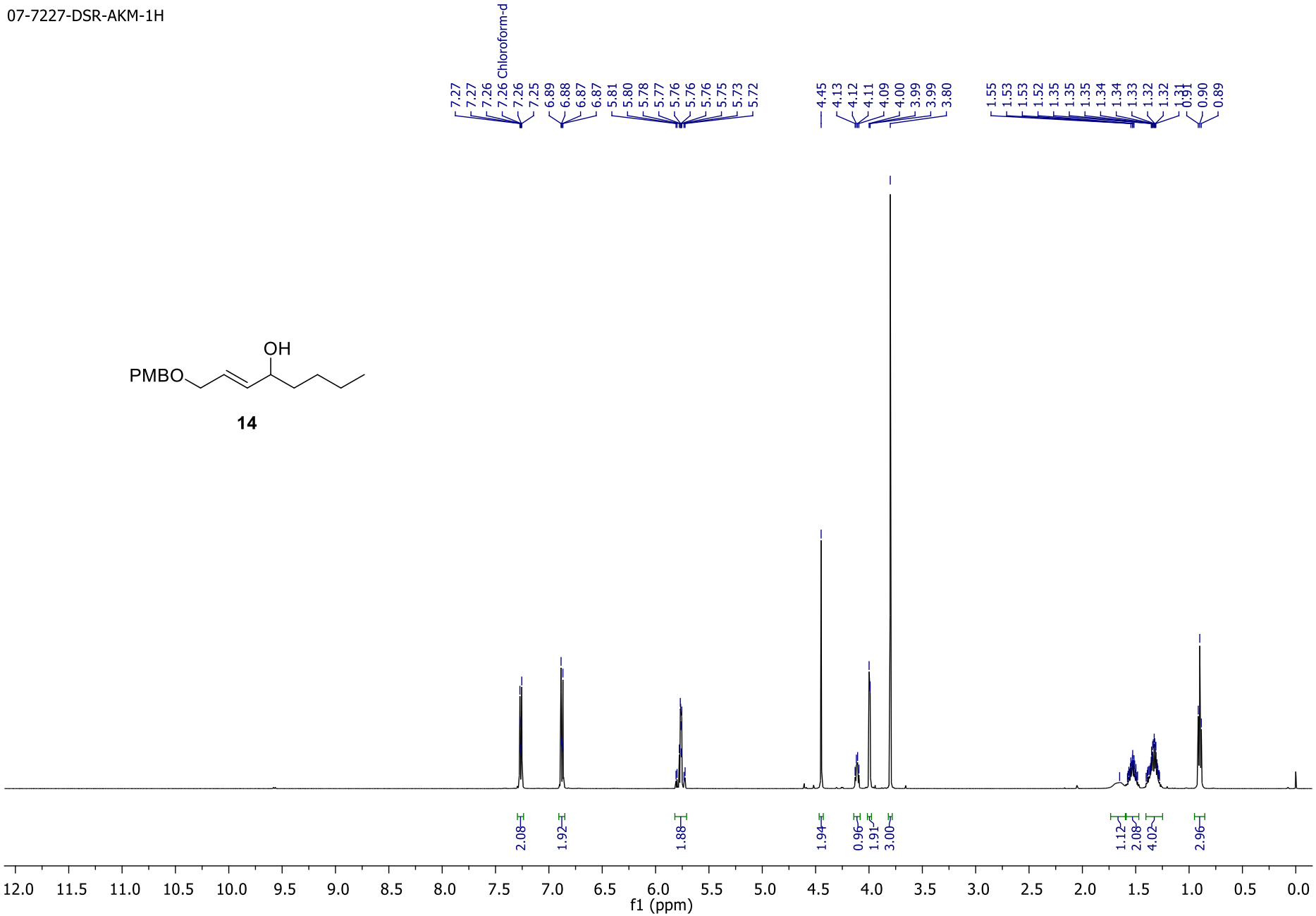
21-4169-DSR-AKM-1H



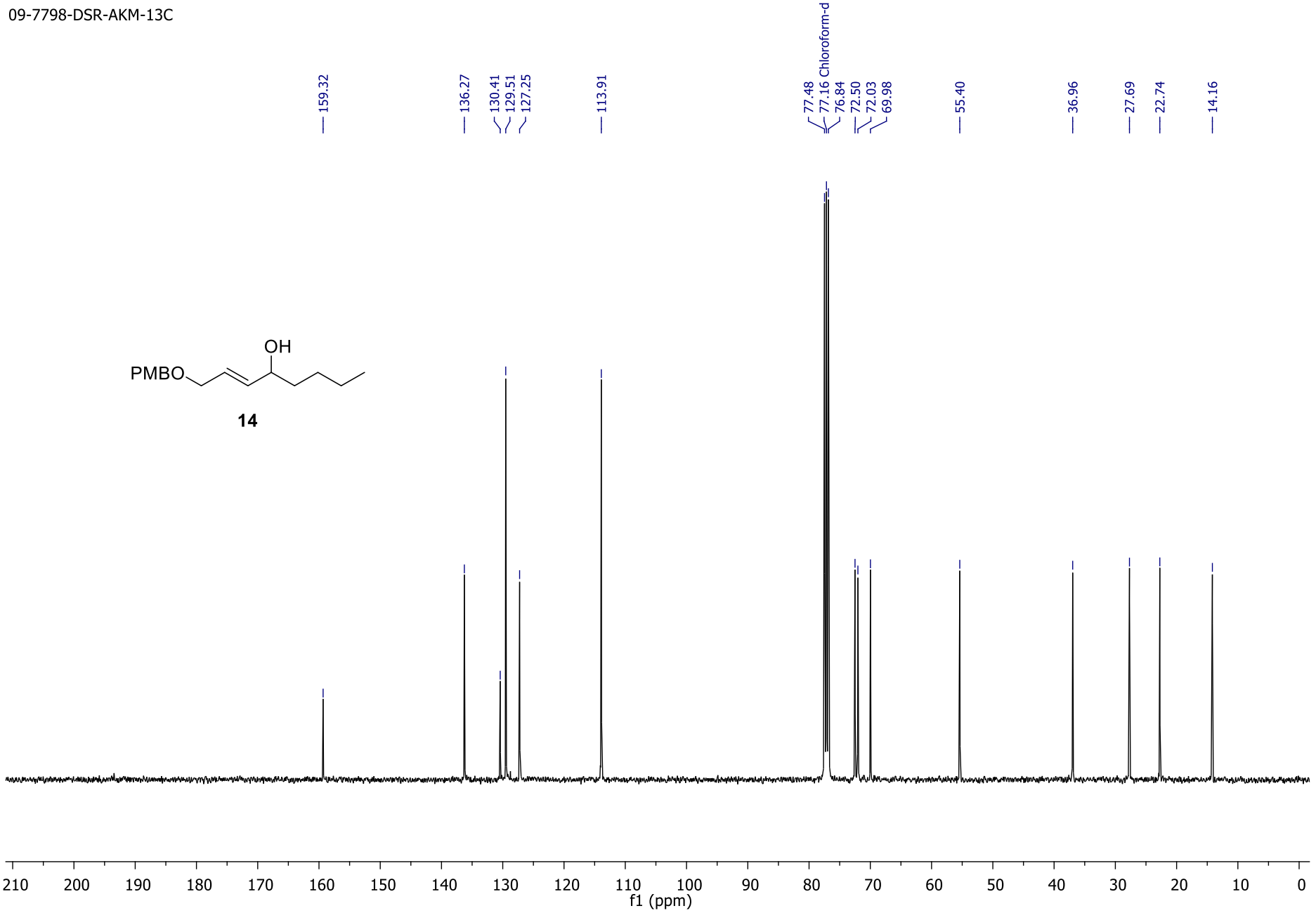
$^{13}C\{^{1}H\}$ NMR of Compound 13 in $CDCl_3$ at 100 MHz



^{1}H NMR of Compound 14 in $CDCl_3$ at 500 MHz

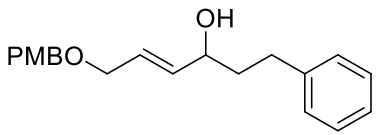


$^{13}C\{^{1}H\}$ NMR of Compound 14 in $CDCl_3$ at 100 MHz



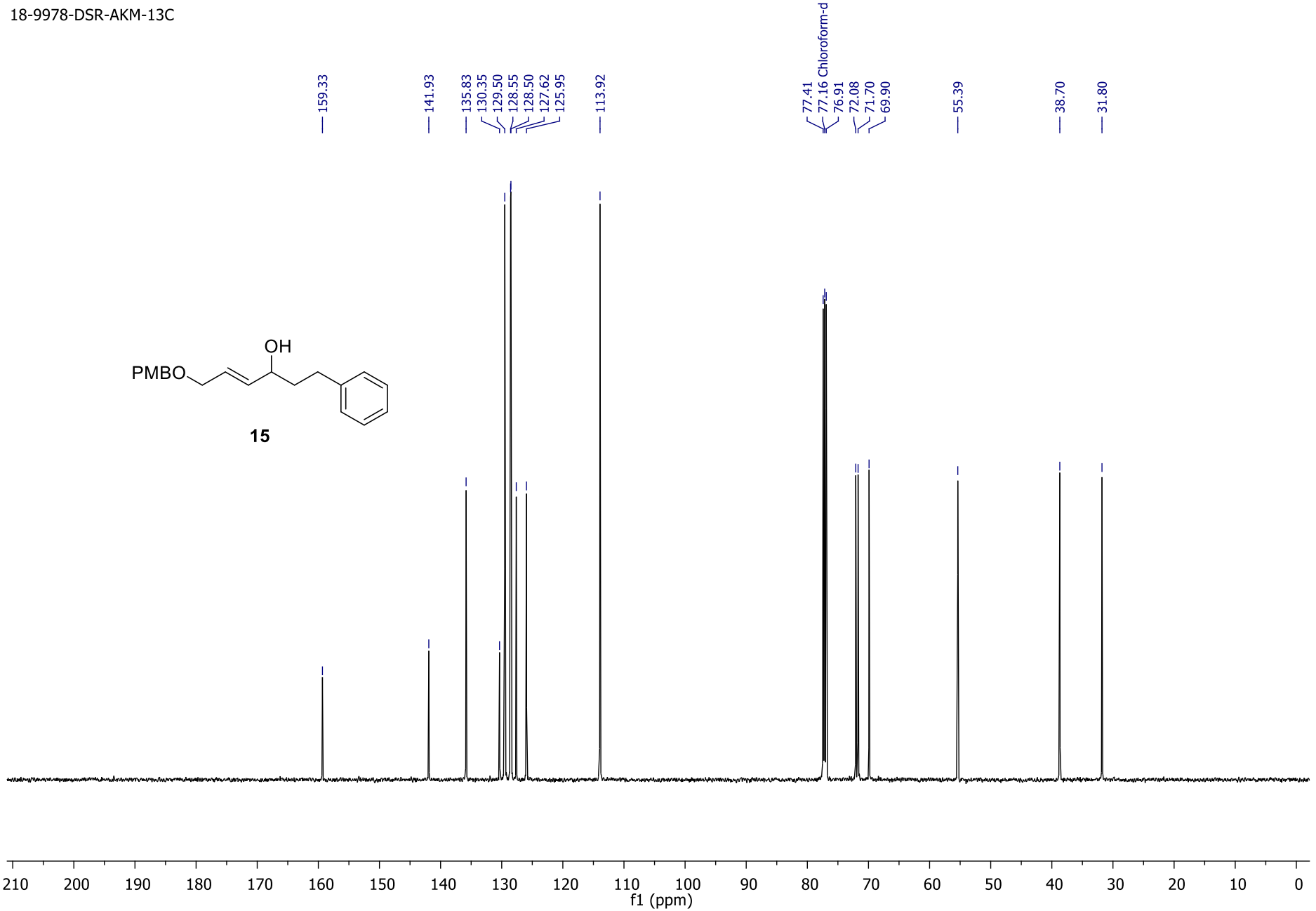
^{1}H NMR of Compound 15 in $CDCl_3$ at 400 MHz

16-9578-DSR-AKM-1H

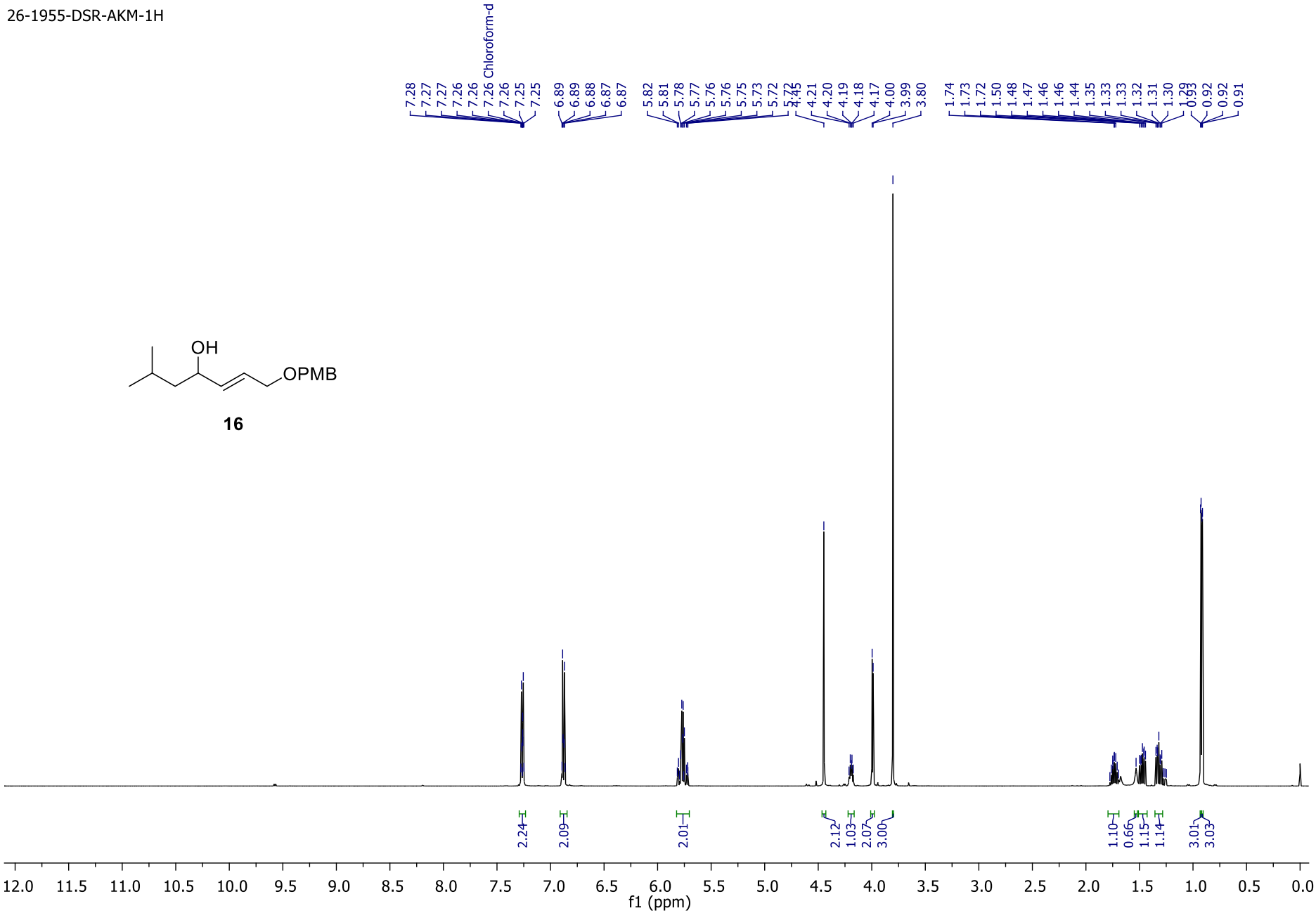


15

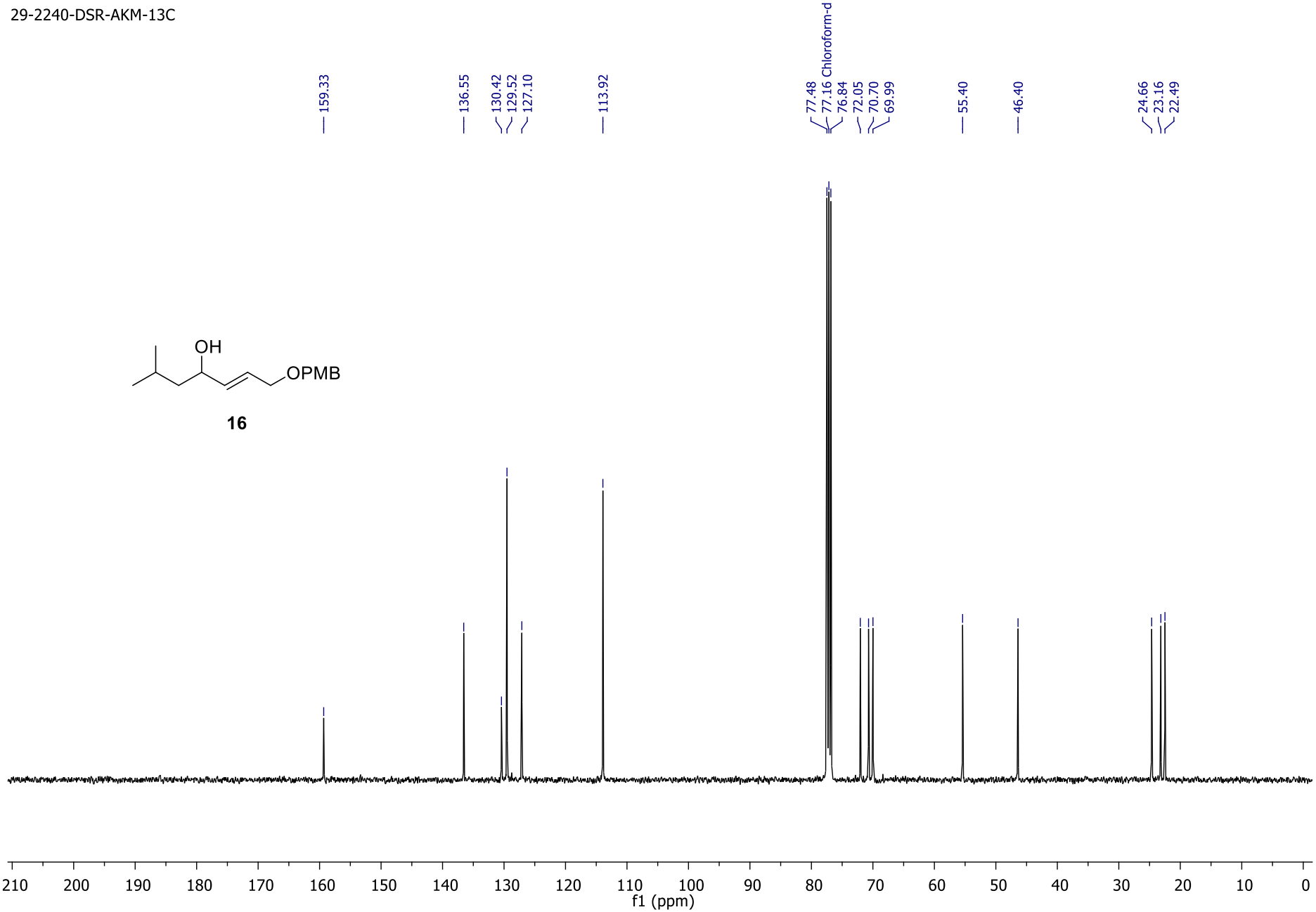
$^{13}C\{^{1}H\}$ NMR of Compound 15 in $CDCl_3$ at 125 MHz



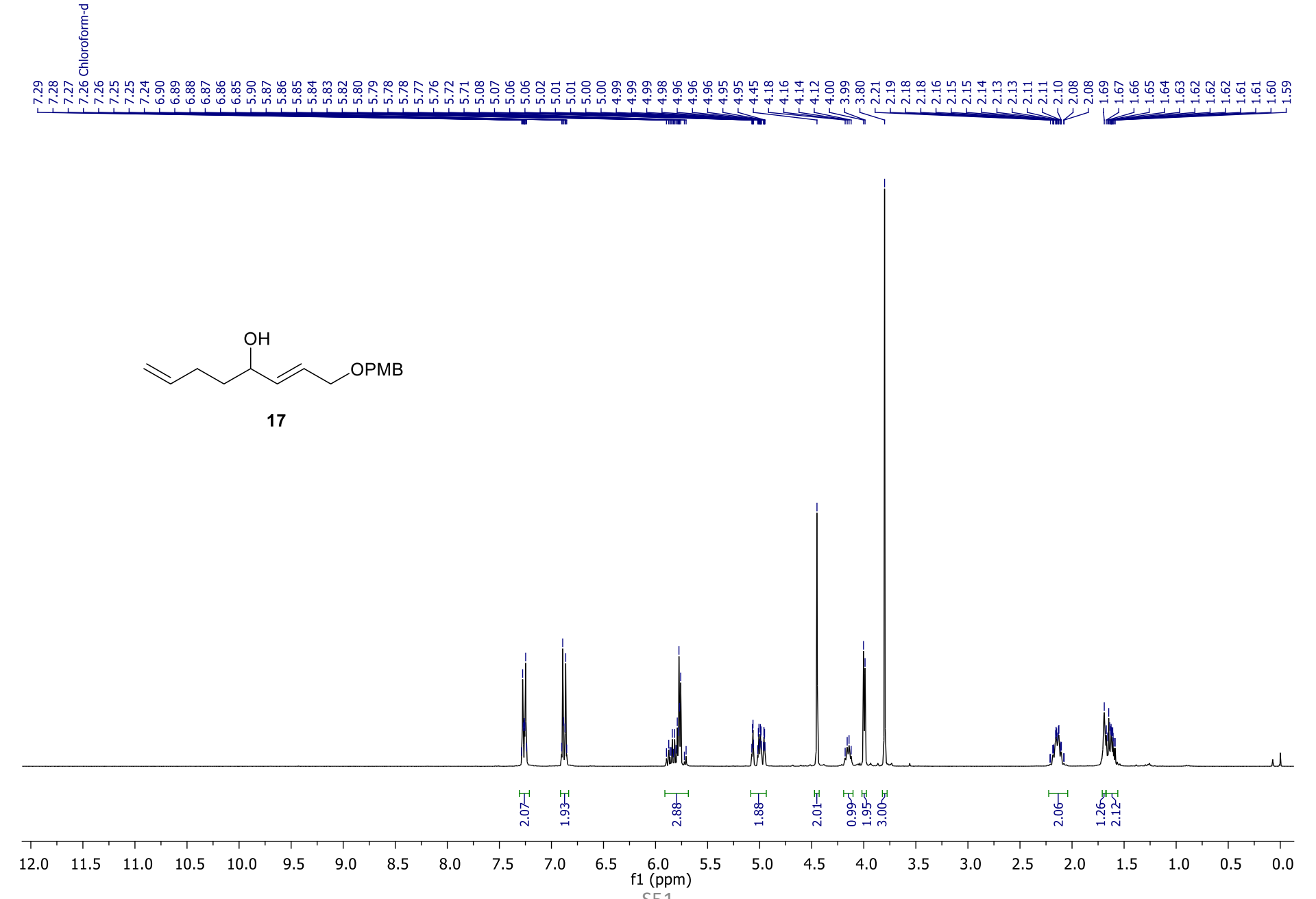
^{1}H NMR of Compound 16 in $CDCl_3$ at 500 MHz



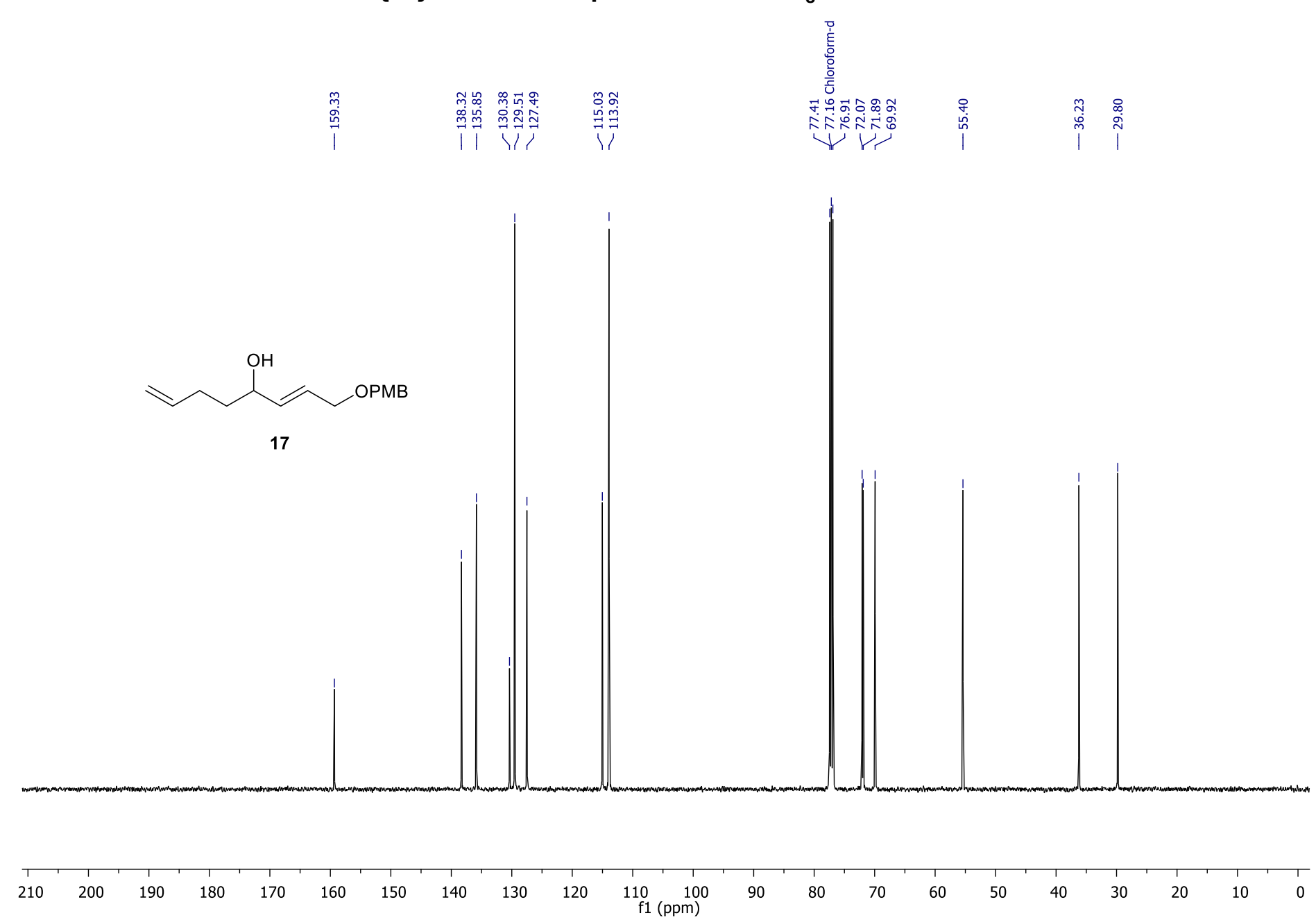
$^{13}C\{^{1}H\}$ NMR of Compound 16 in $CDCl_3$ at 100 MHz



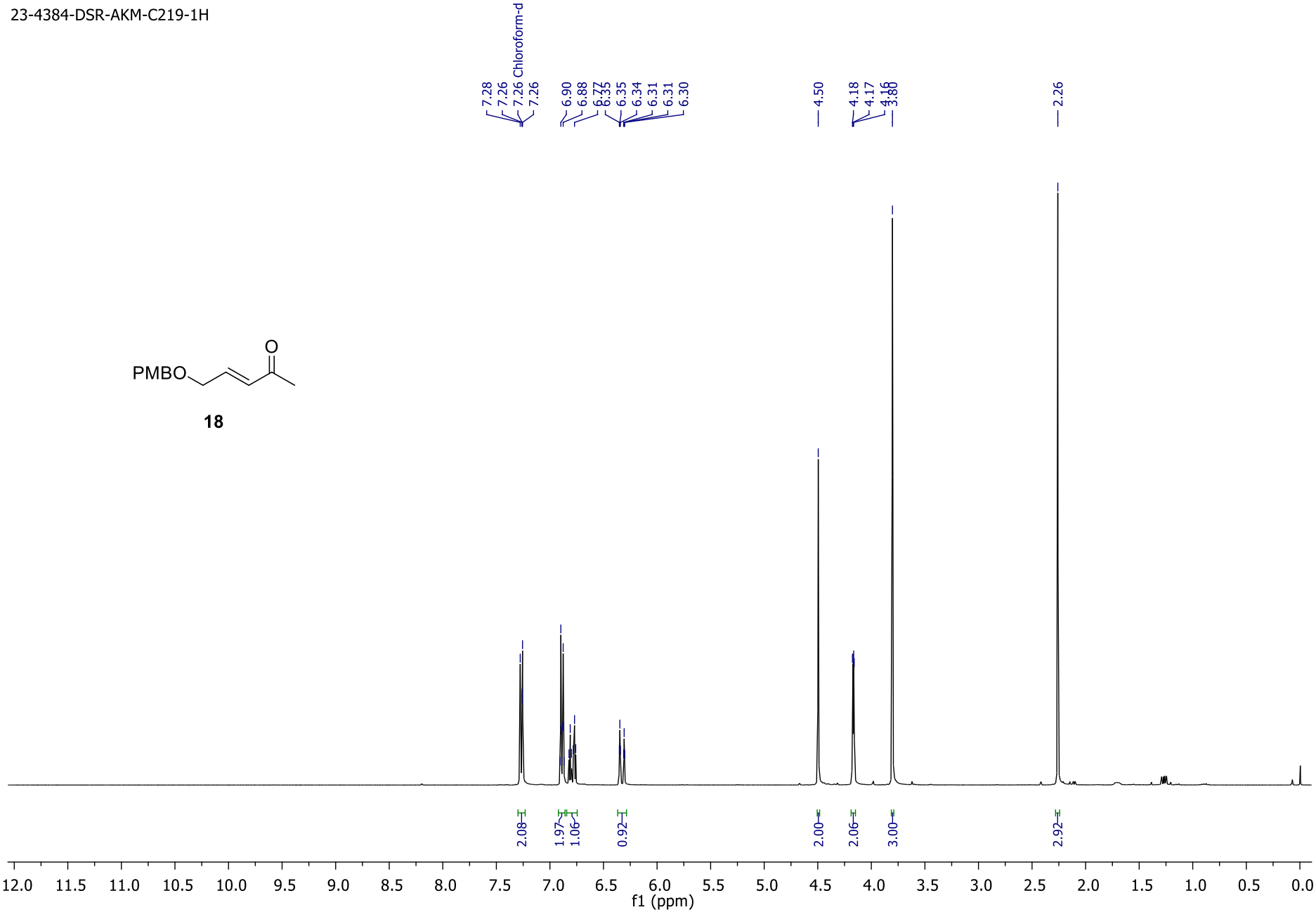
^{1}H NMR of Compound 17 in $CDCl_3$ at 300 MHz



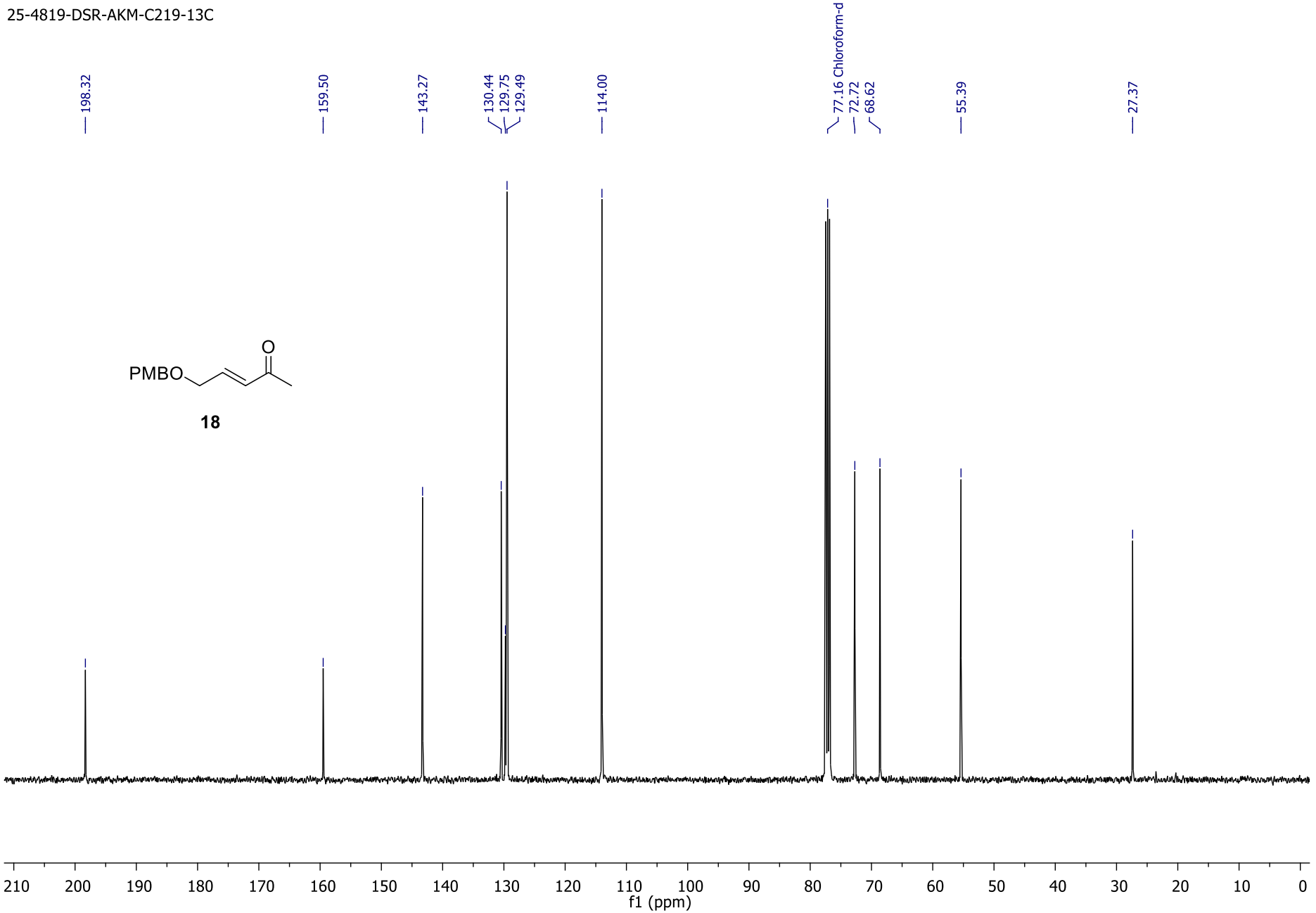
$^{13}C\{^{1}H\}$ NMR of Compound 17 in $CDCl_3$ at 125 MHz



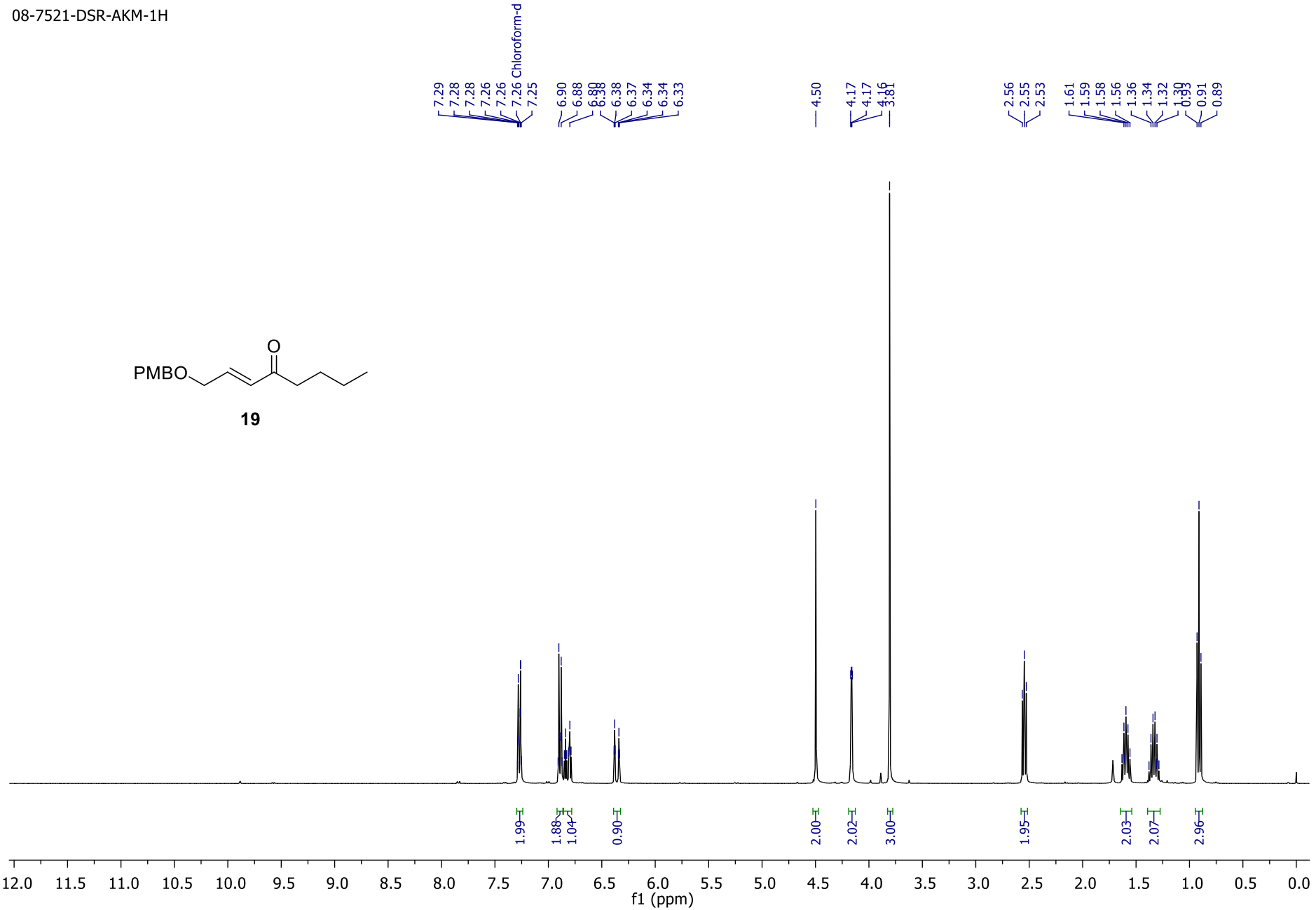
^{1}H NMR of Compound 18 in $CDCl_3$ at 400 MHz



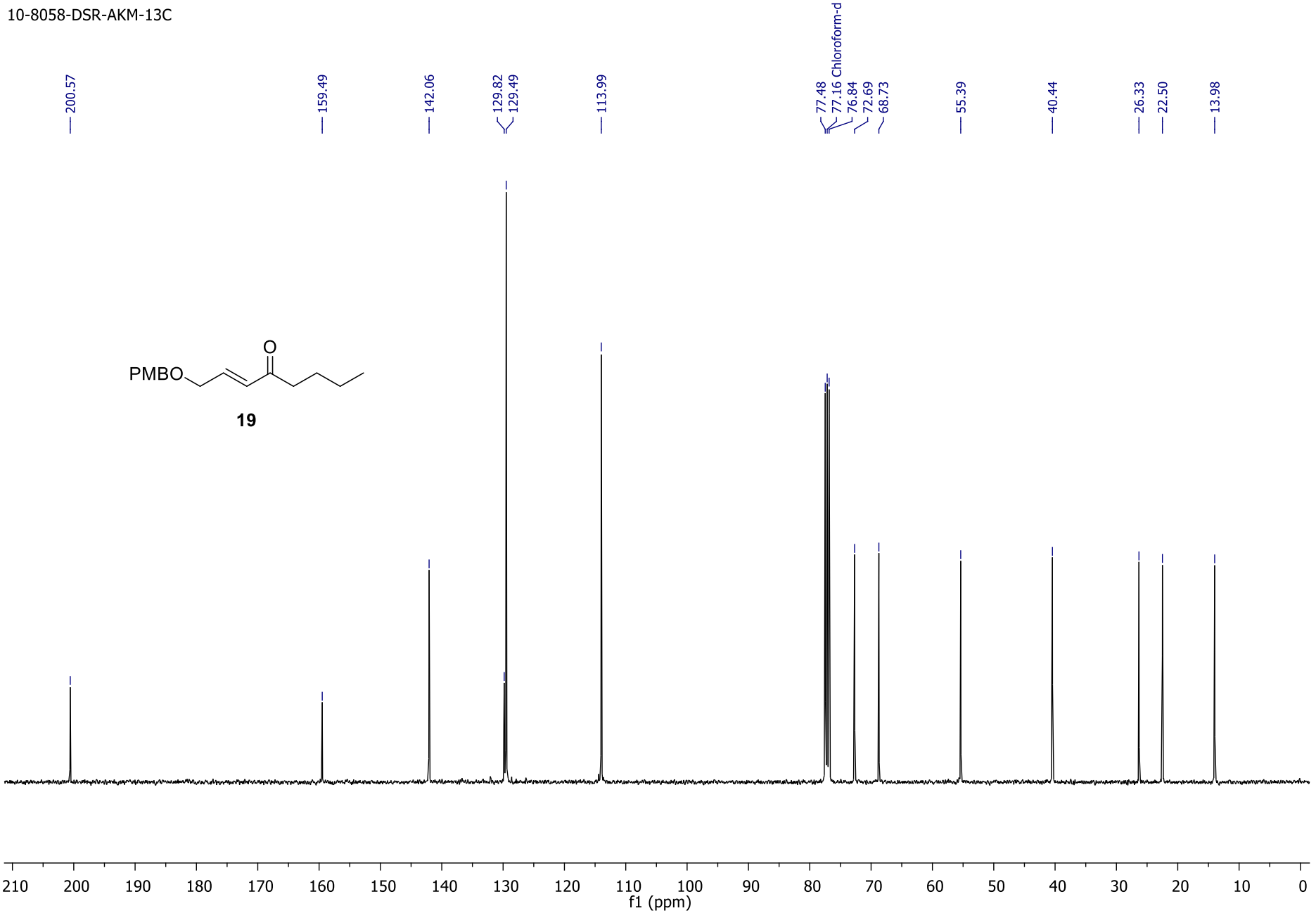
$^{13}C\{^{1}H\}$ NMR of Compound 18 in $CDCl_3$ at 100 MHz



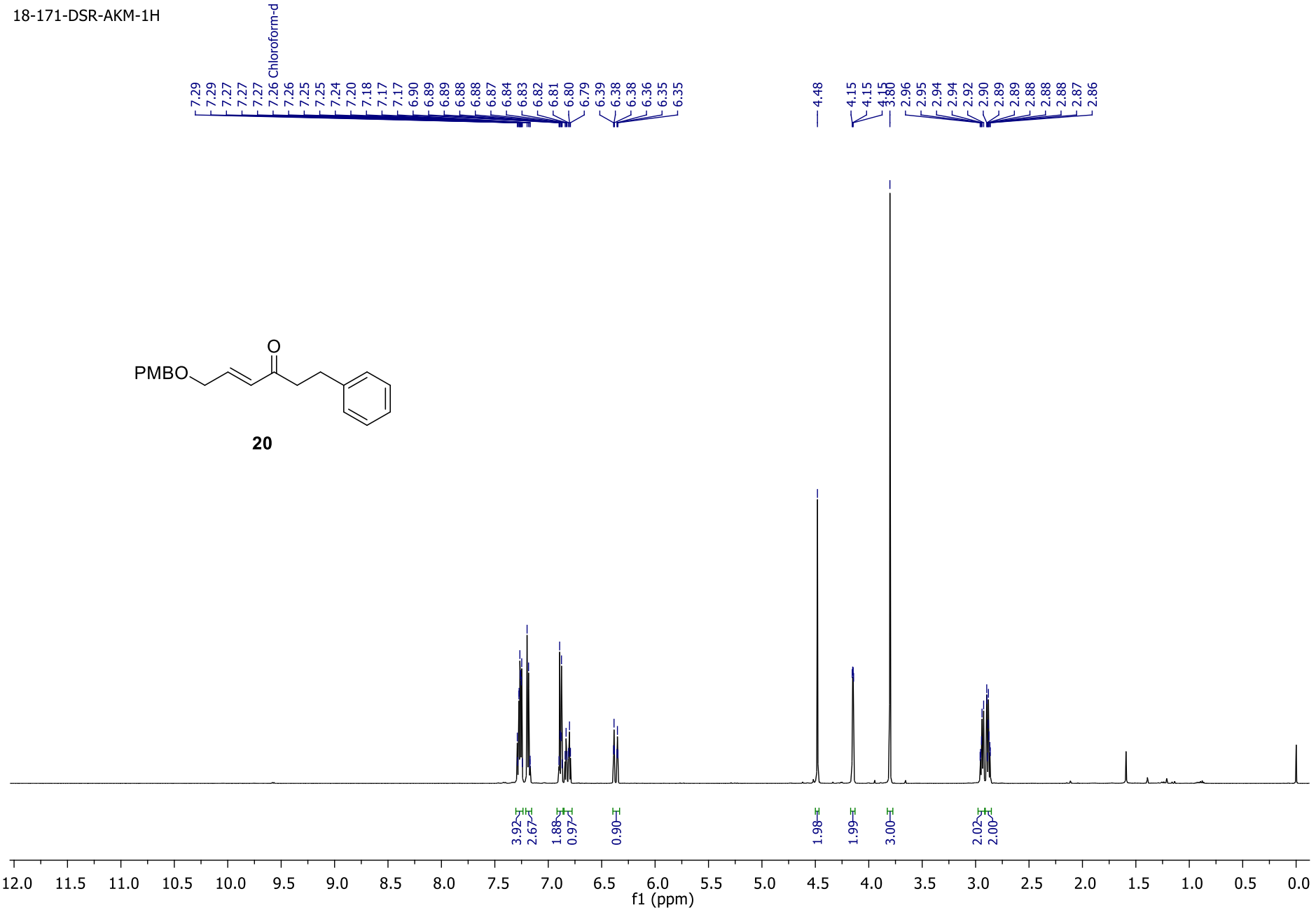
^{1}H NMR of Compound 19 in $CDCl_3$ at 400 MHz



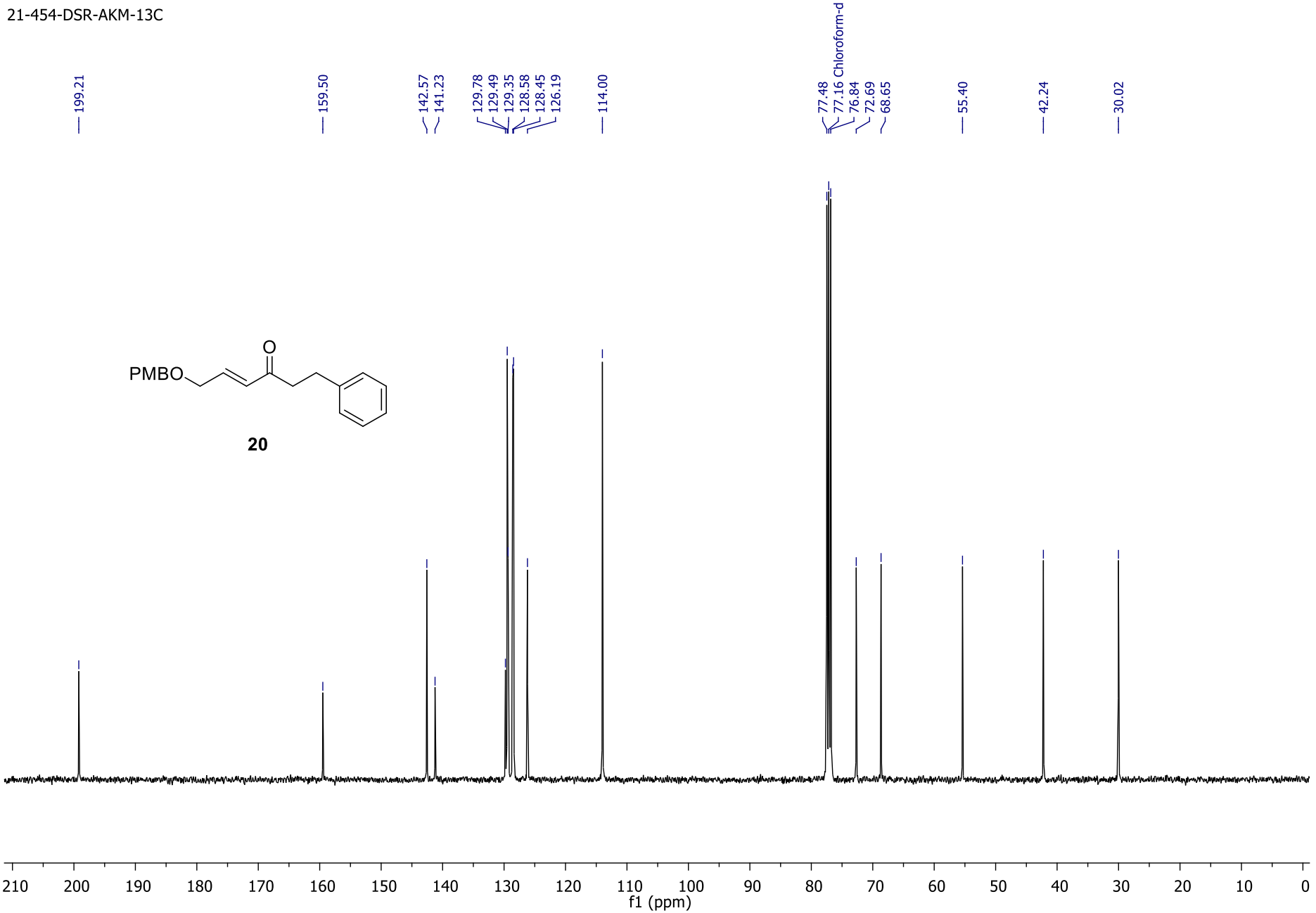
$^{13}C\{^{1}H\}$ NMR of Compound 19 in $CDCl_3$ at 100 MHz



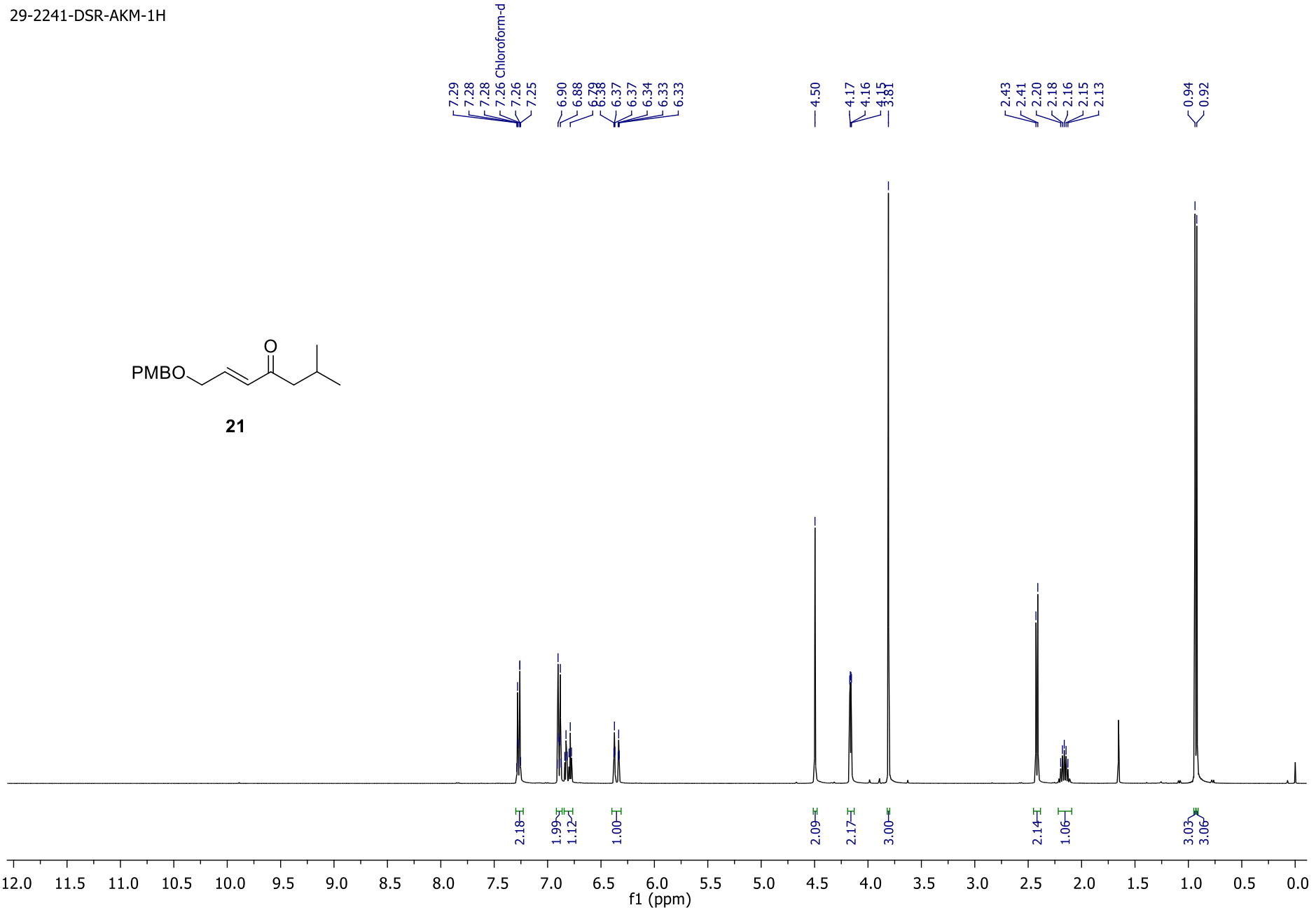
^{1}H NMR of Compound 20 in $CDCl_3$ at 500 MHz



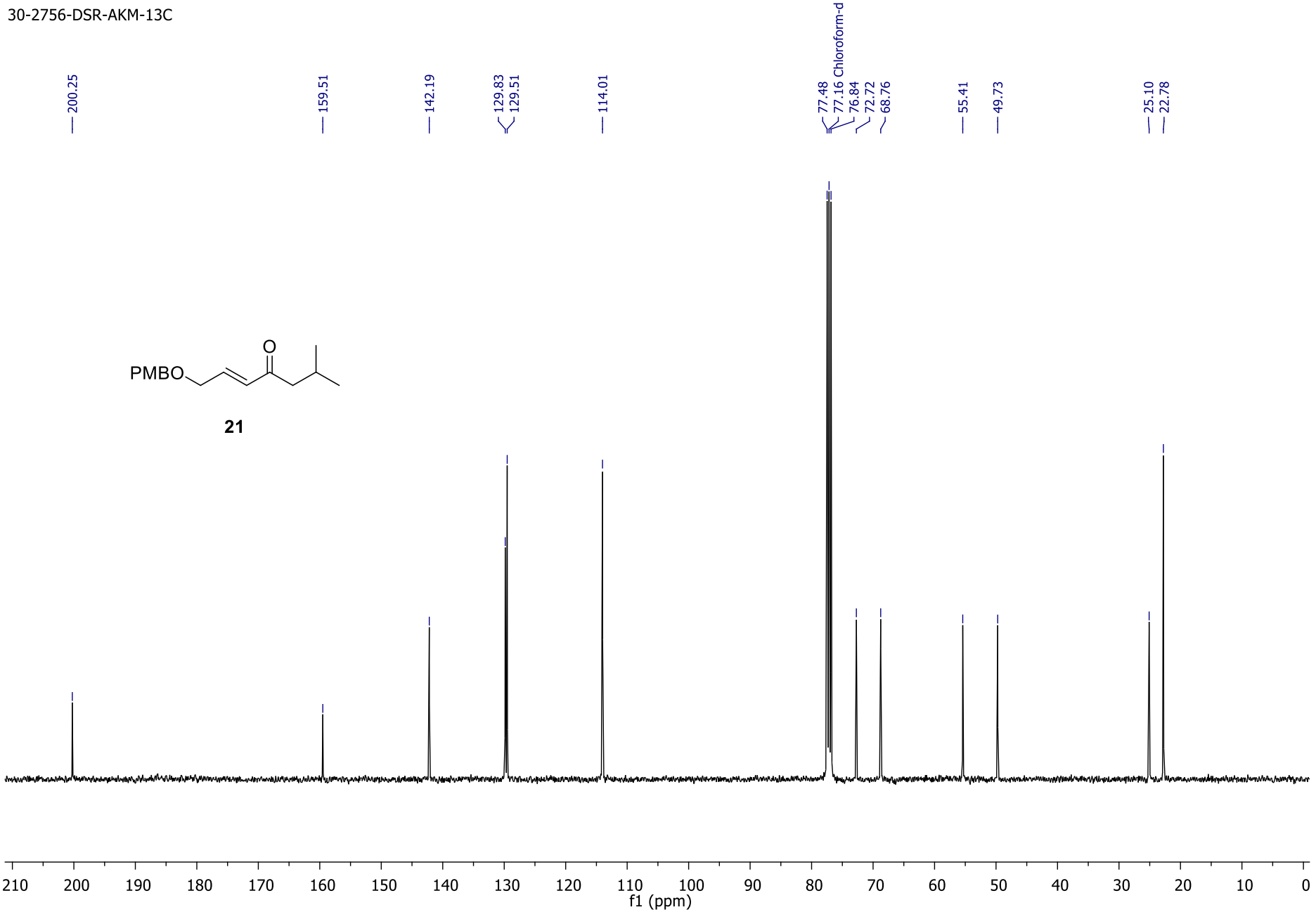
$^{13}C\{^{1}H\}$ NMR of Compound 20 in $CDCl_3$ at 100 MHz



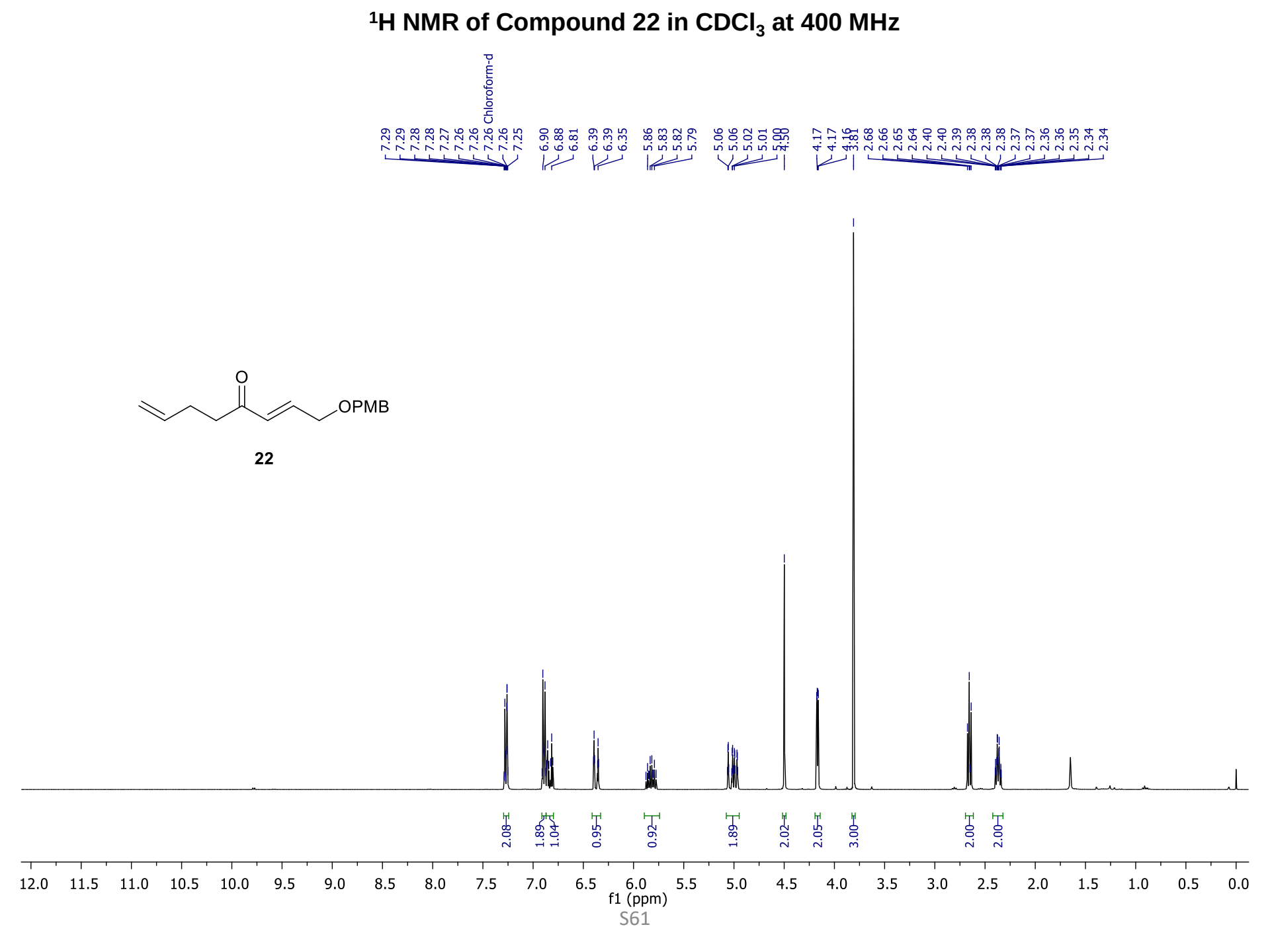
^{1}H NMR of Compound 21 in $CDCl_3$ at 400 MHz



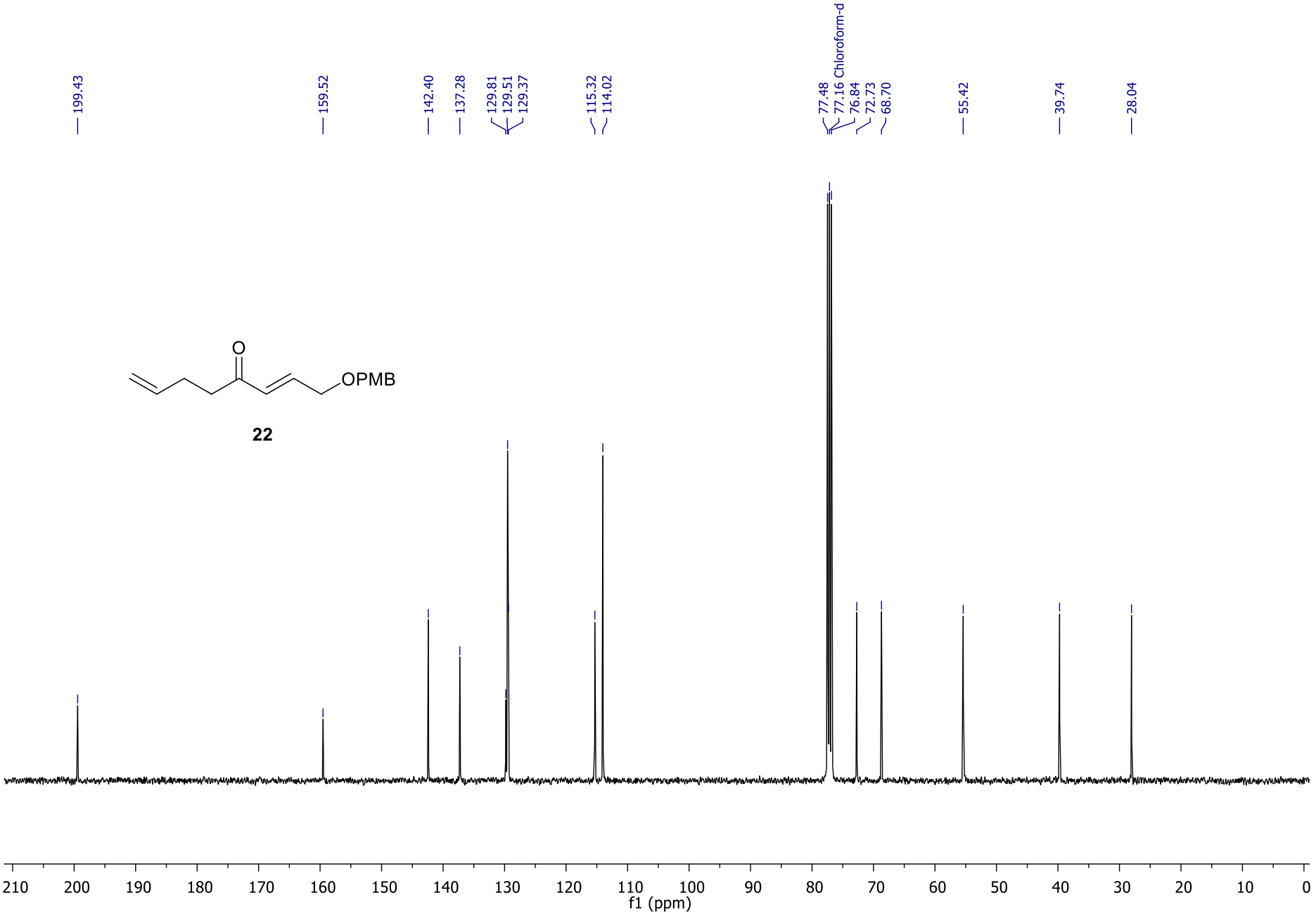
$^{13}C\{^{1}H\}$ NMR of Compound 21 in $CDCl_3$ at 100 MHz



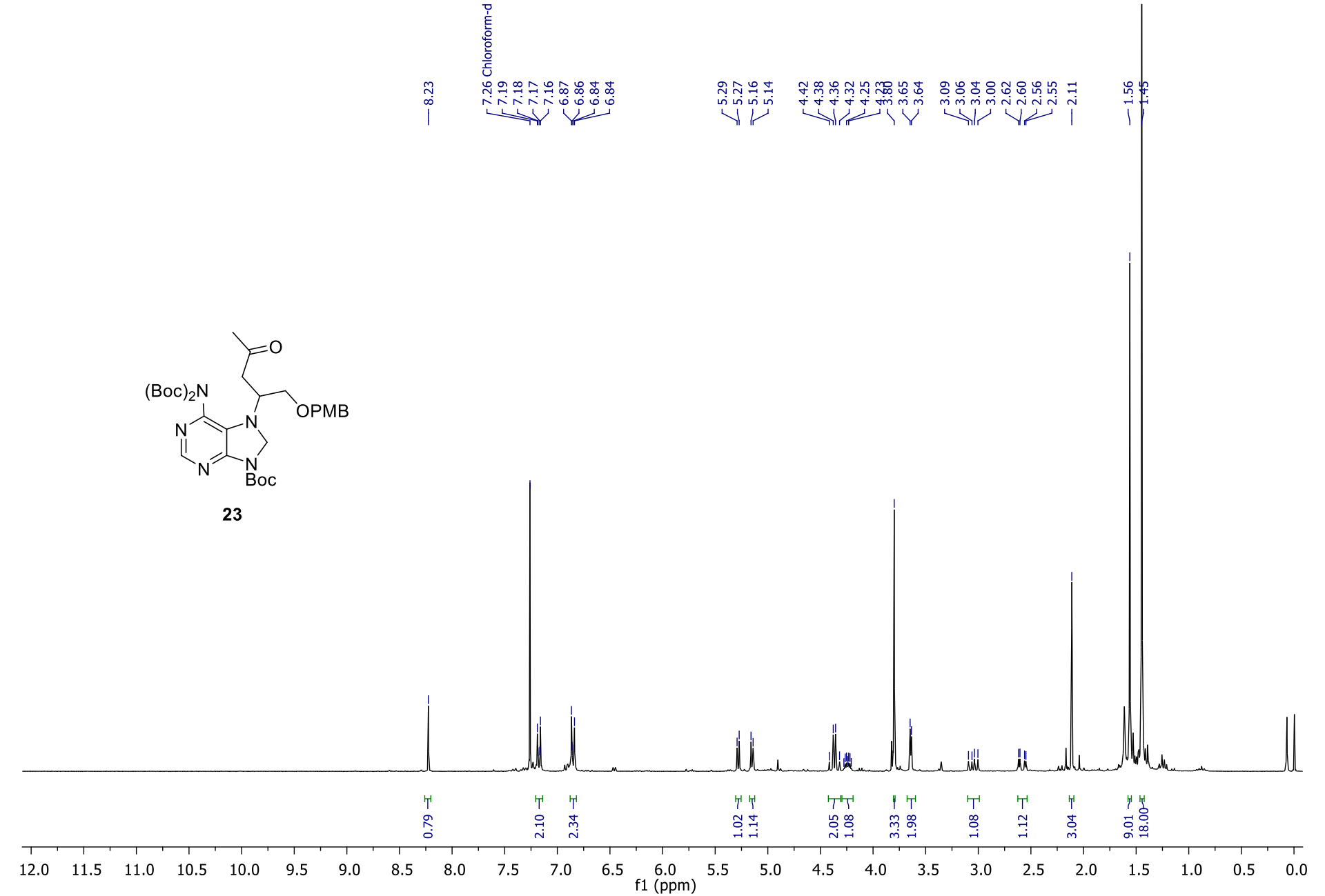
^{1}H NMR of Compound 22 in $CDCl_3$ at 400 MHz



$^{13}C\{^{1}H\}$ NMR of Compound 22 in $CDCl_3$ at 100 MHz

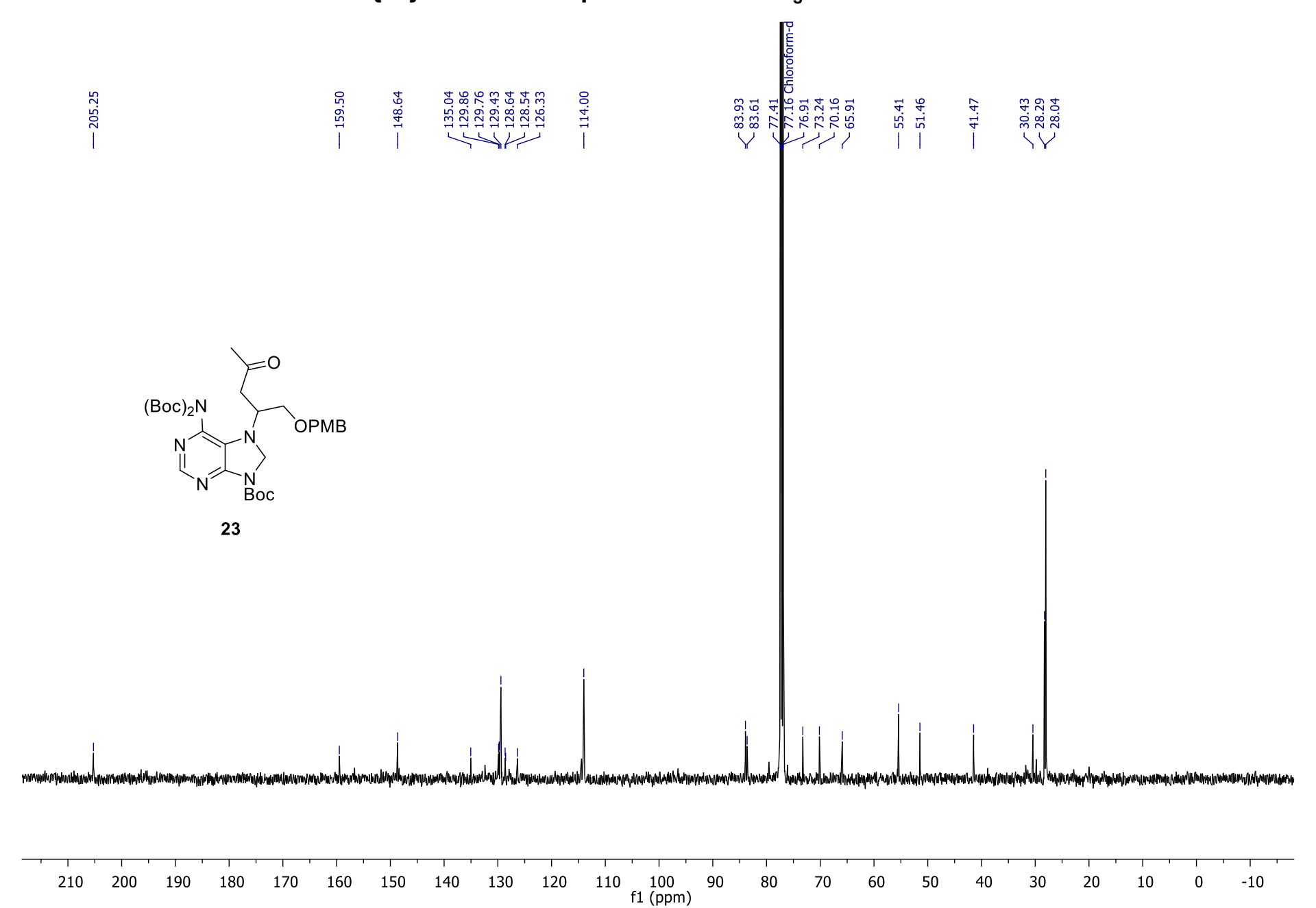


^{1}H NMR of Compound 23 in $CDCl_3$ at 300 MHz



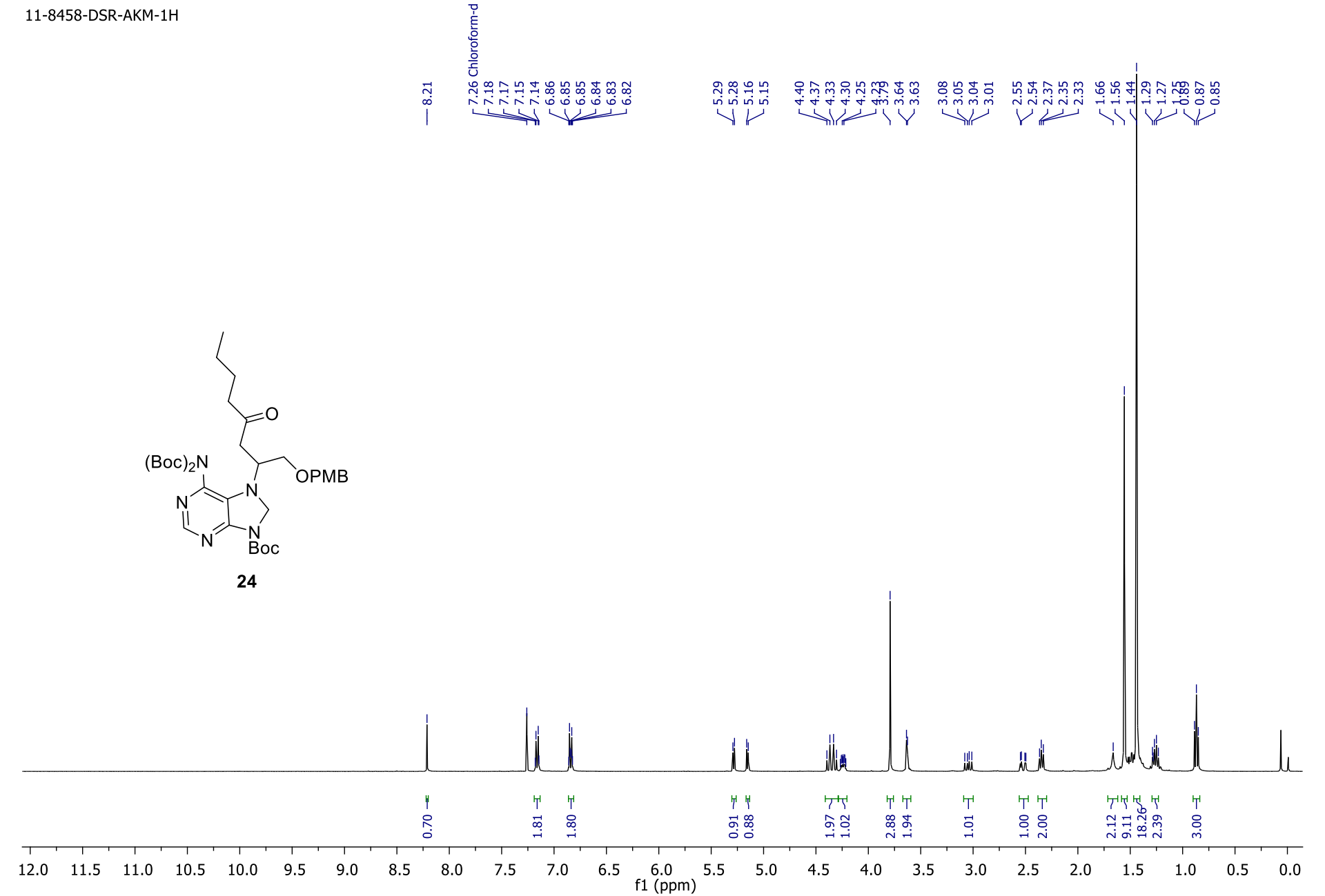
23

$^{13}C\{^{1}H\}$ NMR of Compound 23 in $CDCl_3$ at 125 MHz



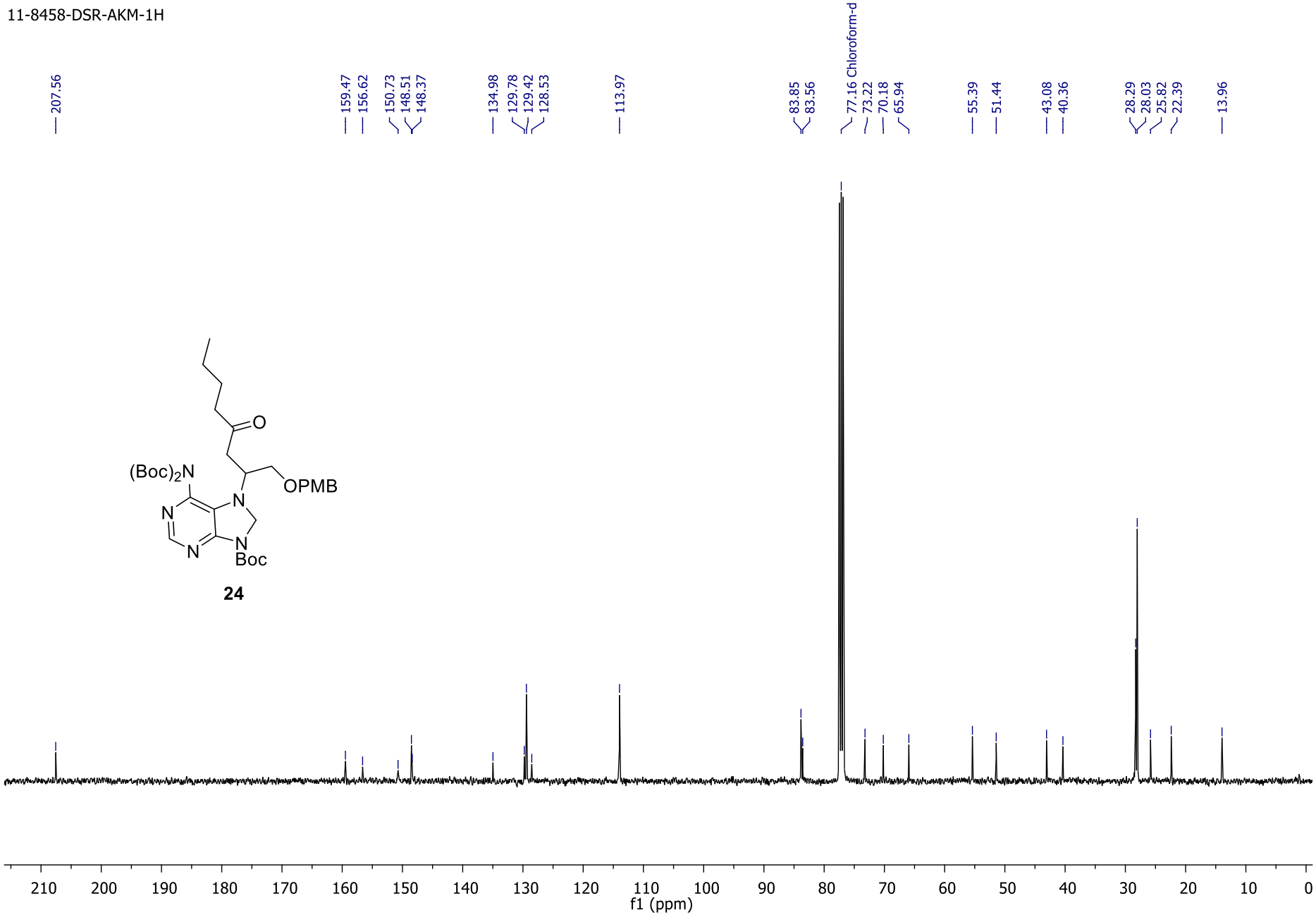
^{1}H NMR of Compound 24 in $CDCl_3$ at 400 MHz

11-8458-DSR-AKM-1H

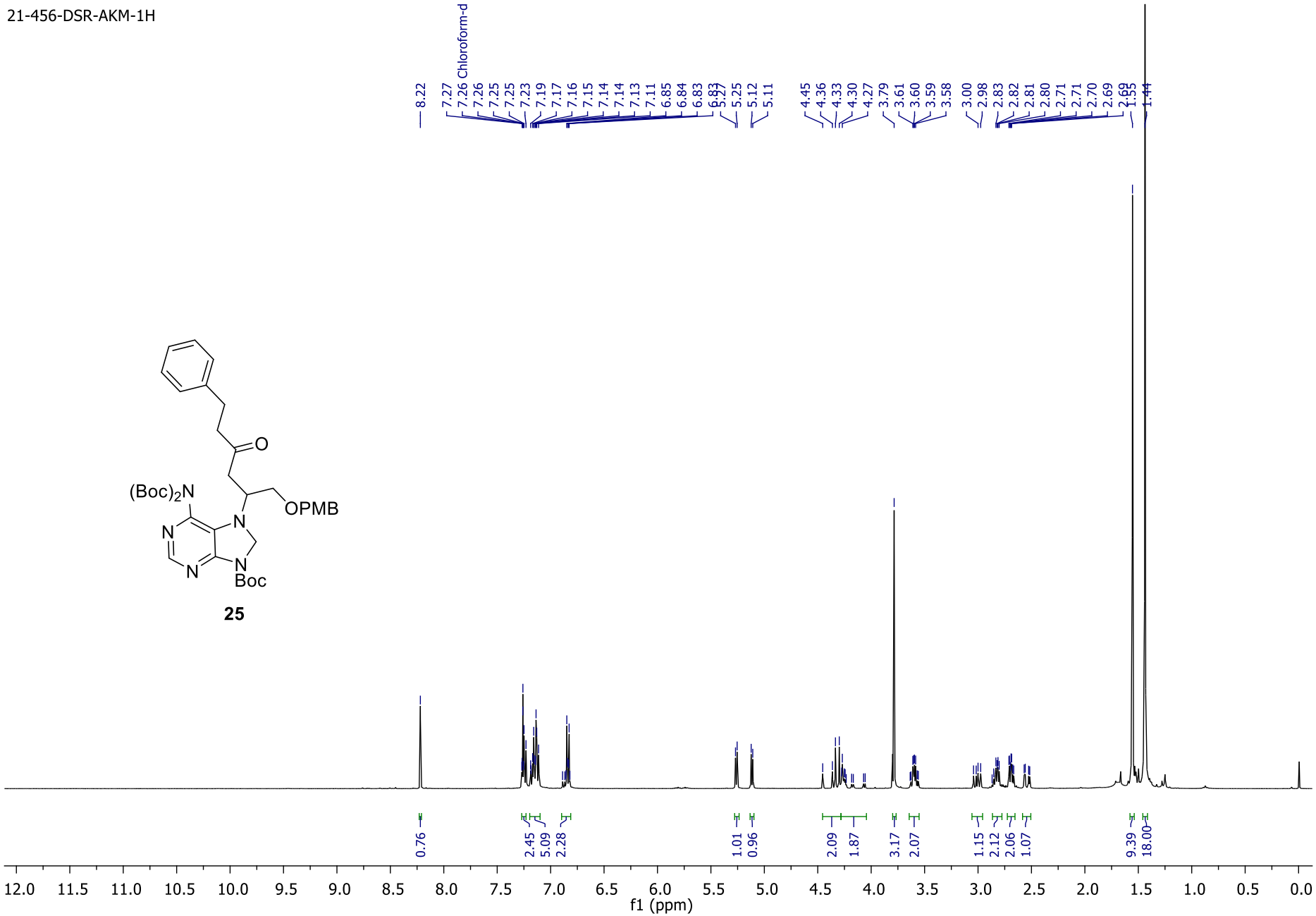


24

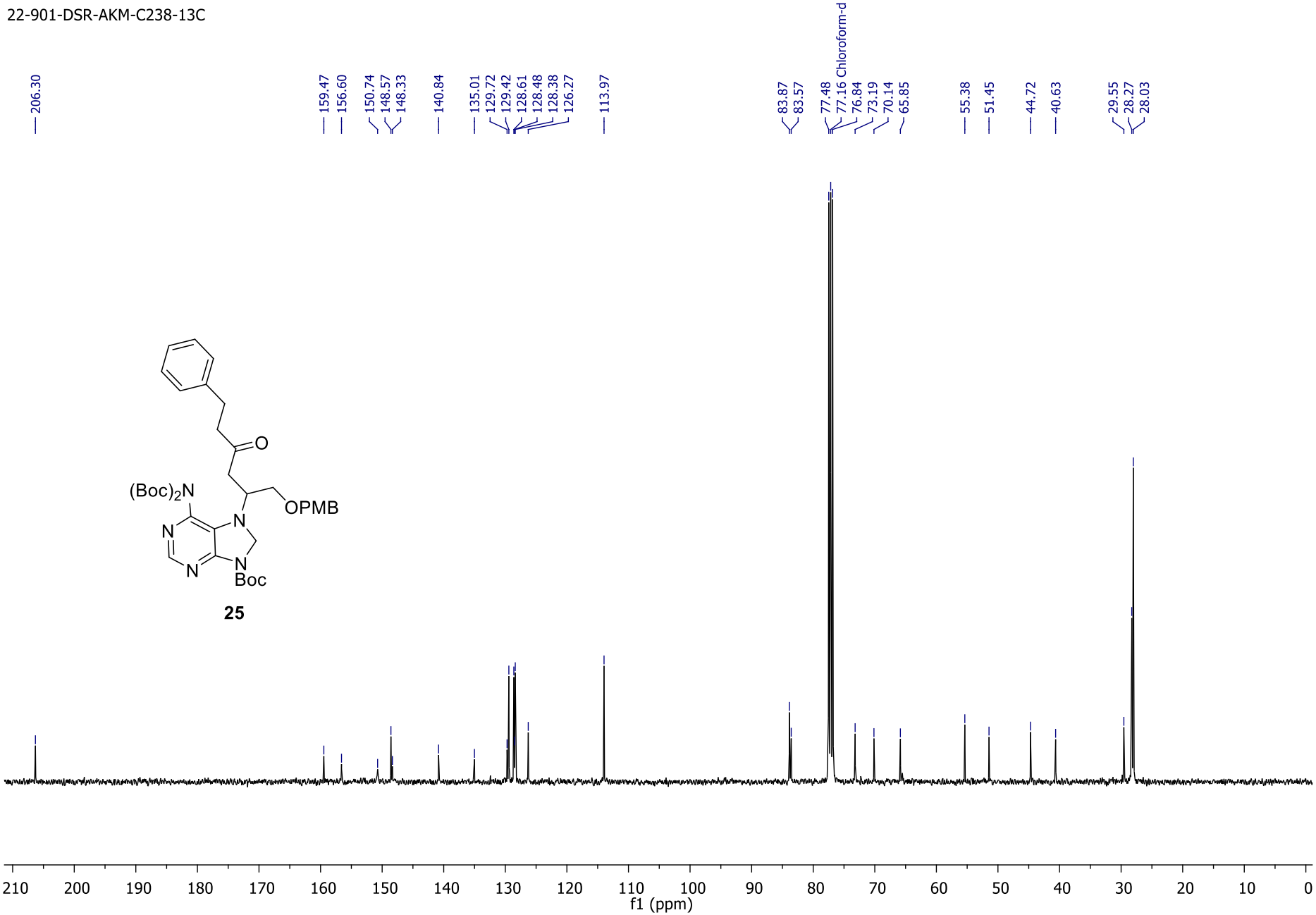
$^{13}C\{^{1}H\}$ NMR of Compound 24 in $CDCl_3$ at 100 MHz



^{1}H NMR of Compound 25 in $CDCl_3$ at 400 MHz

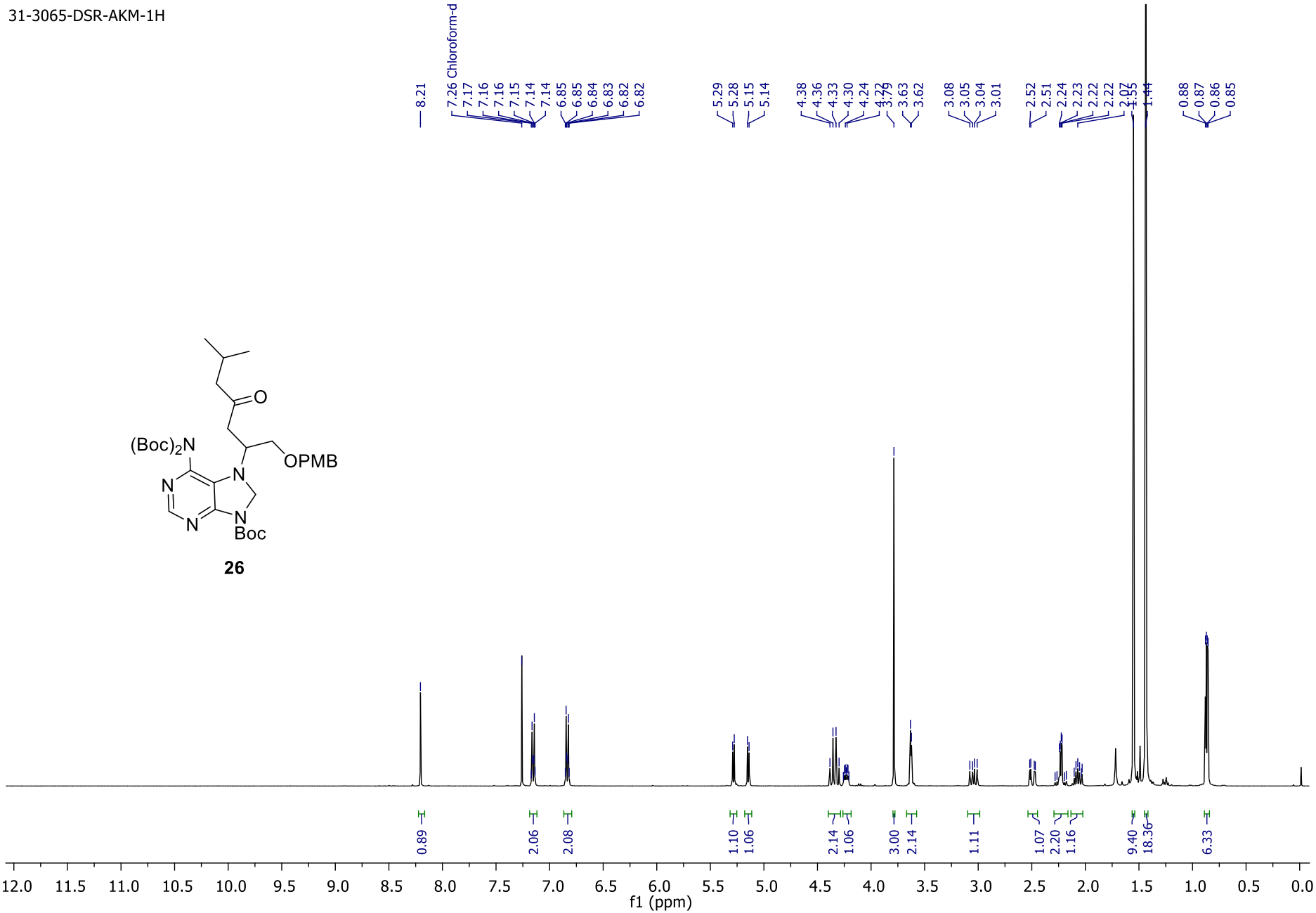


$^{13}C\{^{1}H\}$ NMR of Compound 25 in $CDCl_3$ at 100 MHz



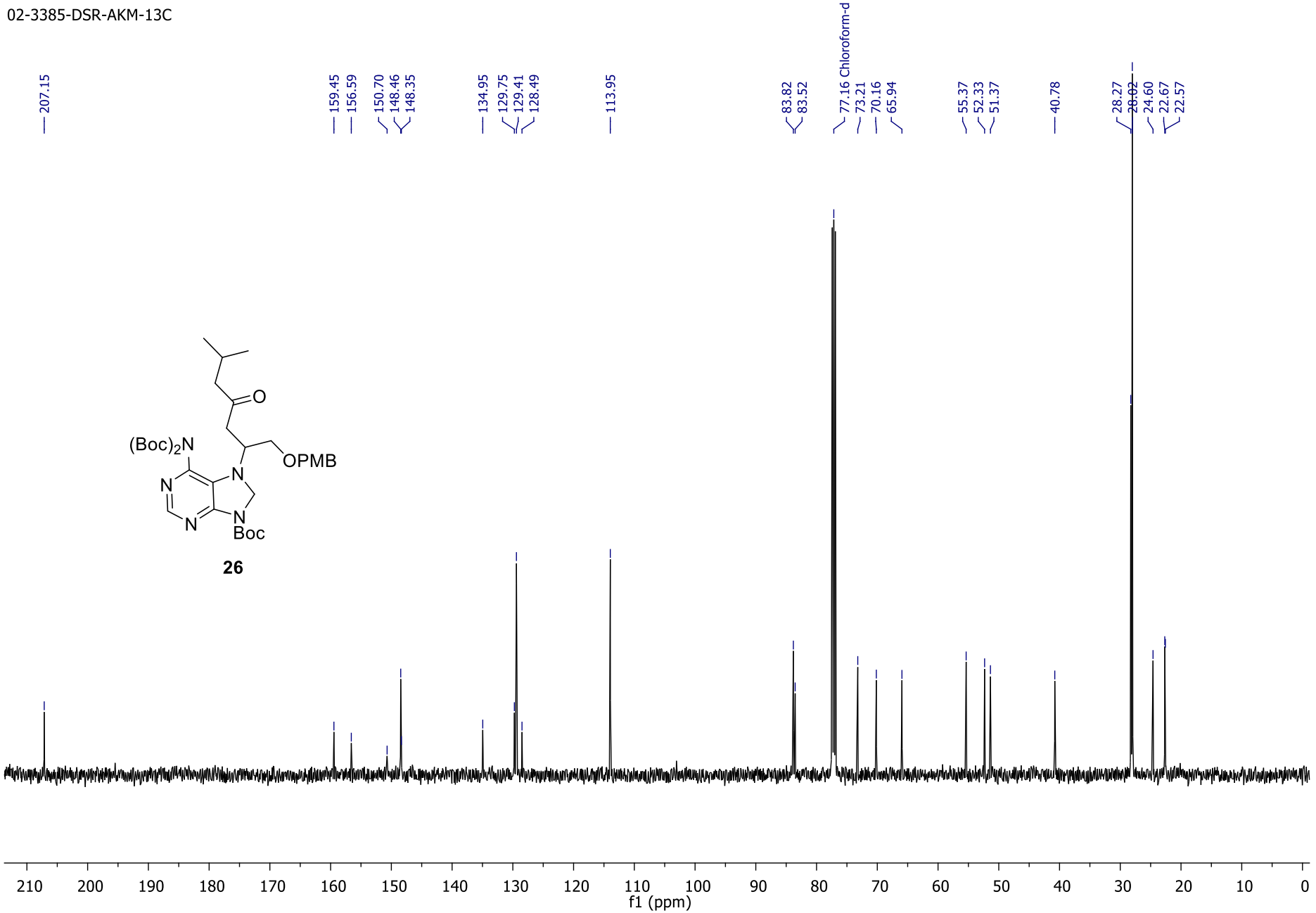
^{1}H NMR of Compound 26 in $CDCl_3$ at 400 MHz

31-3065-DSR-AKM-1H

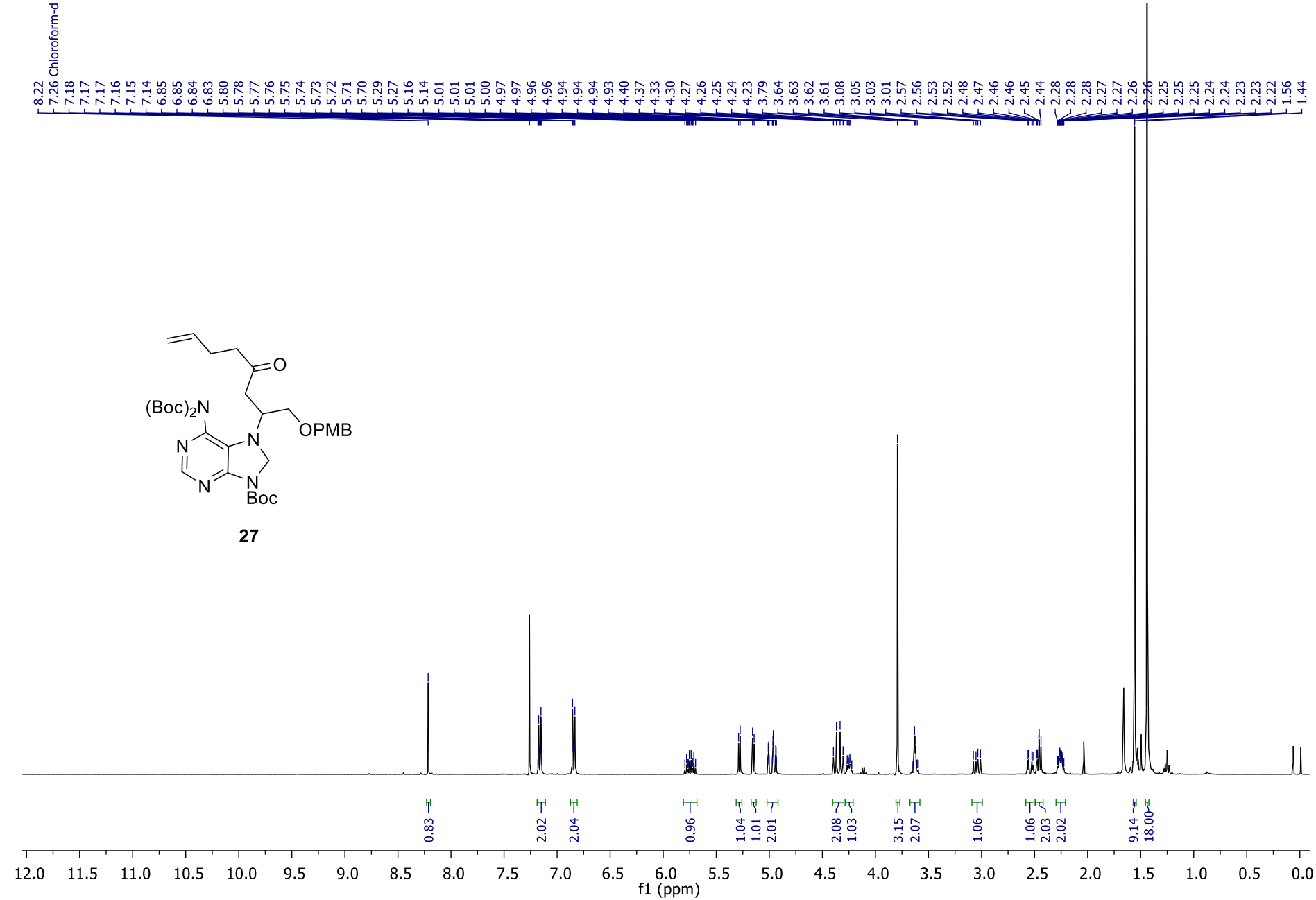


26

$^{13}C\{^{1}H\}$ NMR of Compound 26 in $CDCl_3$ at 125 MHz

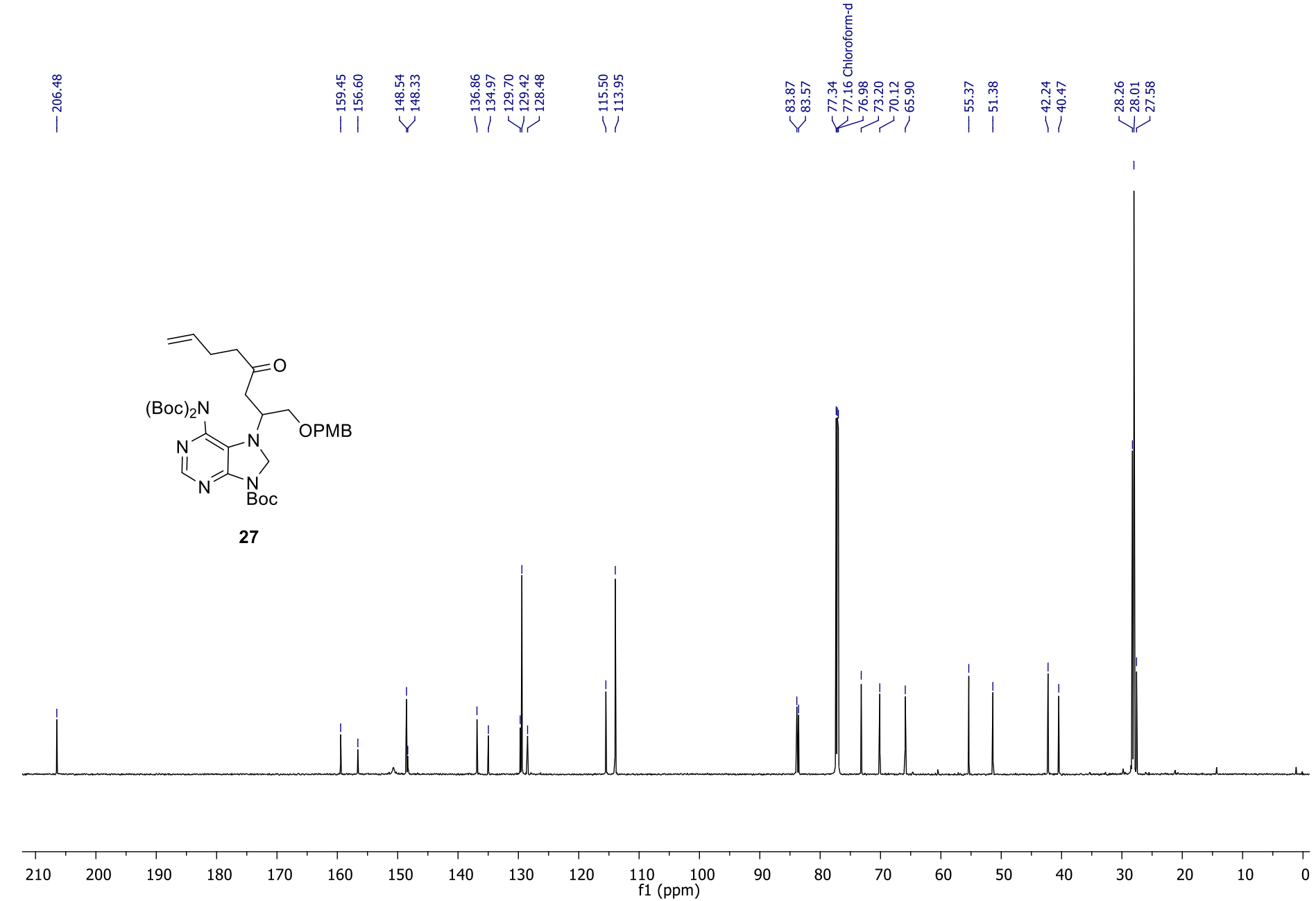


^{1}H NMR of Compound 27 in $CDCl_3$ at 400 MHz



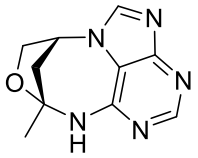
27

$^{13}C\{^{1}H\}$ NMR of Compound 27 in $CDCl_3$ at 175 MHz



^{1}H NMR of Compound 28 in CD_3OD at 500 MHz

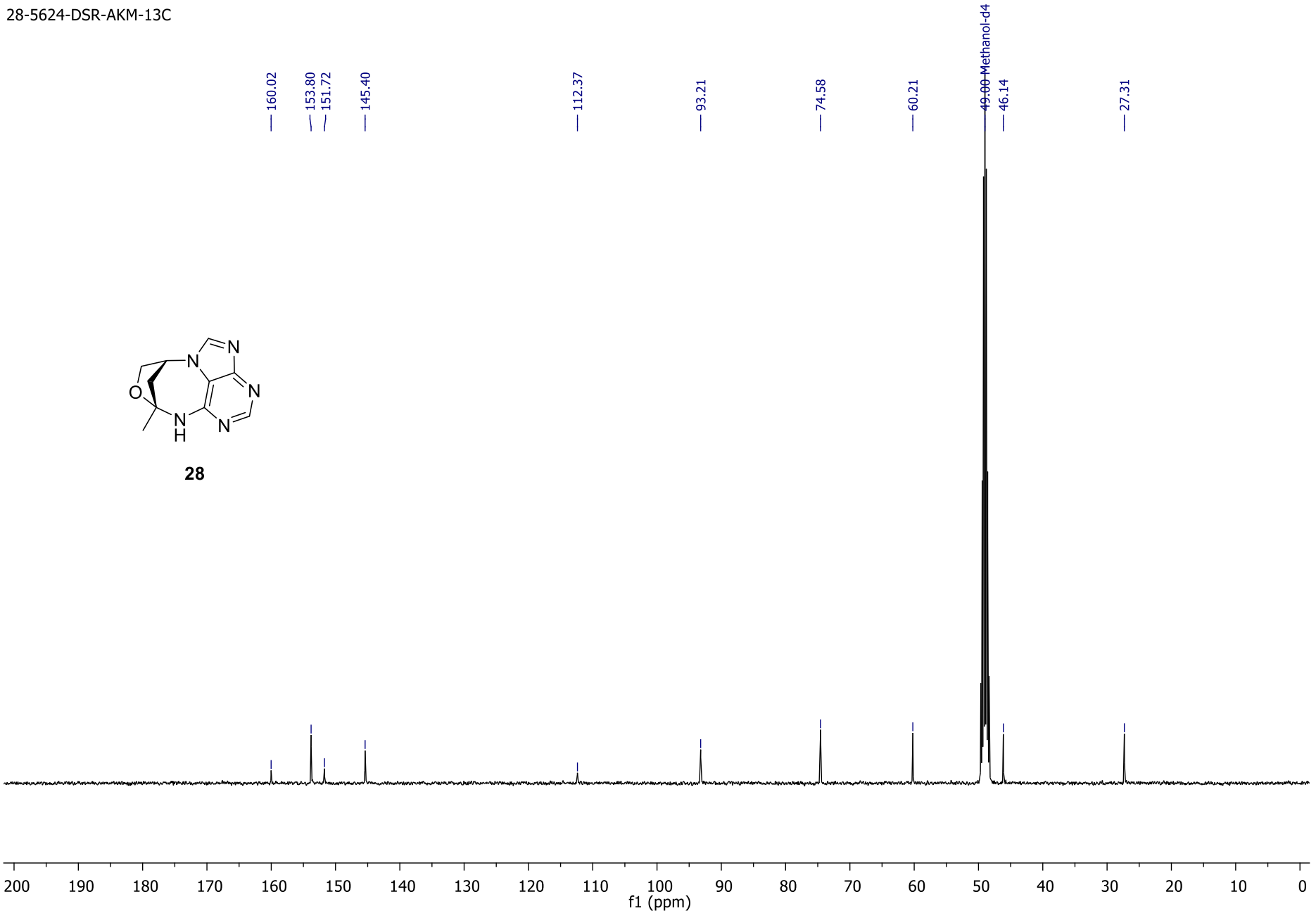
28-5624-DSR-AKM-1H



28

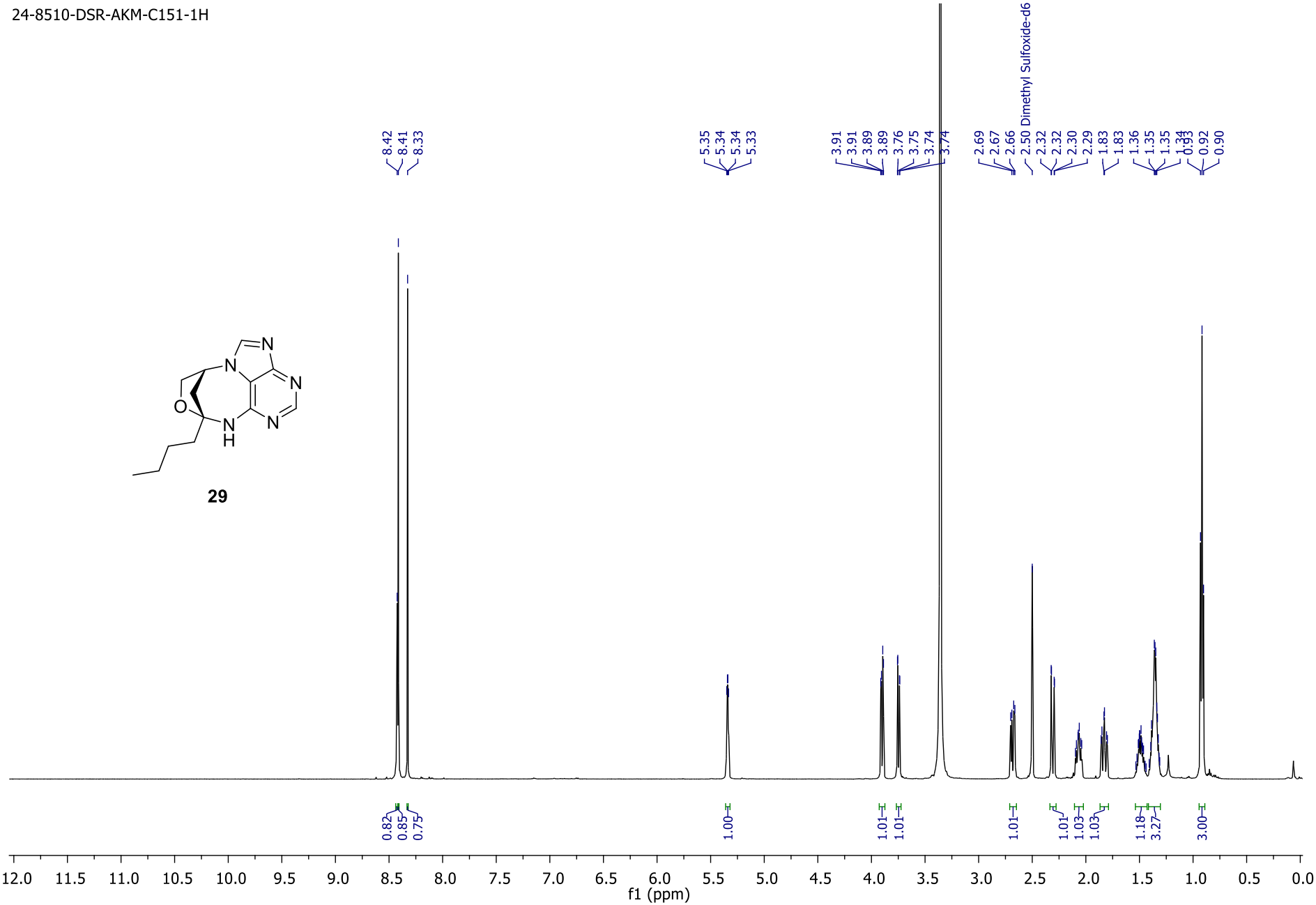
$^{13}C\{^{1}H\}$ NMR of Compound 28 in CD_3OD at 100 MHz

28-5624-DSR-AKM-13C



28

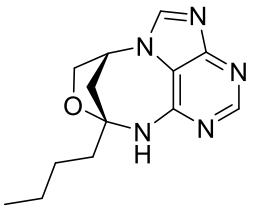
^{1}H NMR of Compound 29 in DMSO-d_6 at 500 MHz



29

$^{13}C\{^{1}H\}$ NMR of Compound 29 in DMSO-d_6 at 125 MHz

25-8902-DSR-AKM-13C

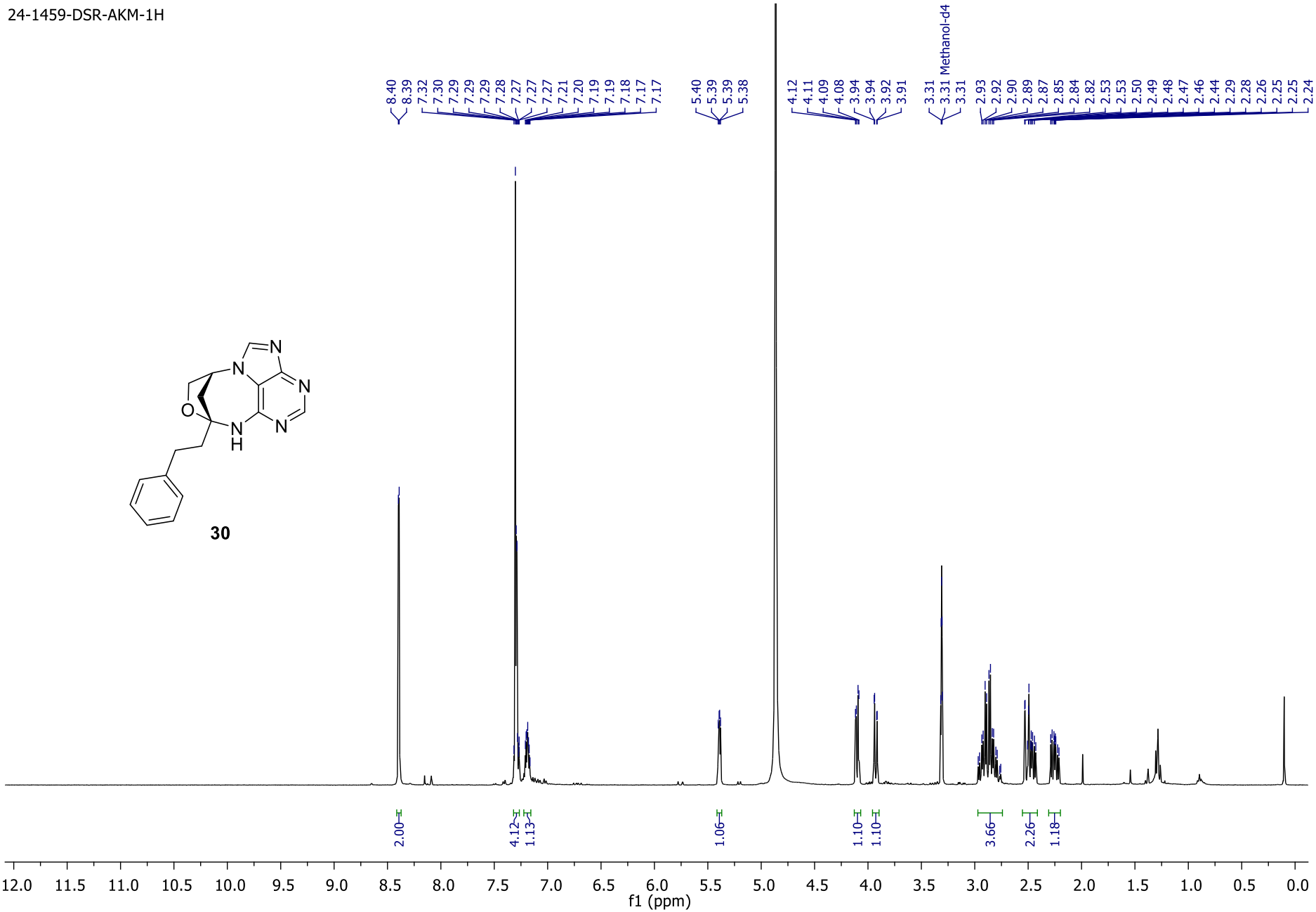


29

159.50
152.17
150.01
143.97
110.74
94.01
72.90
57.51
42.46
40.02
39.85
39.69
39.52 Dimethyl Sulfoxide-d6
39.35
39.19
39.02
26.06
22.37
13.99

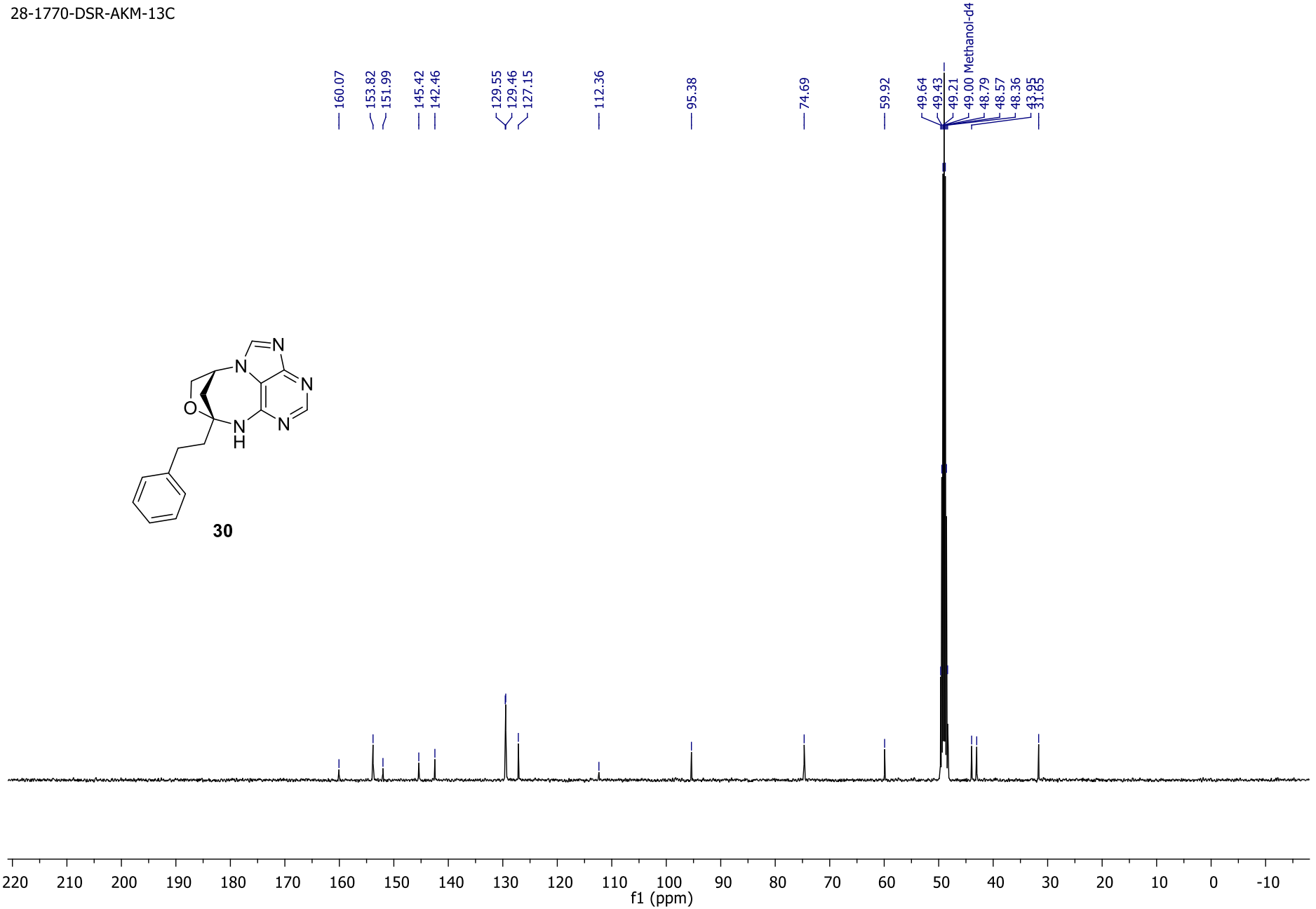
f1 (ppm)

^{1}H NMR of Compound 30 in CD_3OD at 400 MHz



$^{13}C\{^{1}H\}$ NMR of Compound 30 in CD_3OD at 100 MHz

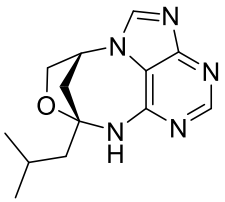
28-1770-DSR-AKM-13C



30

^{1}H NMR of Compound 31 in DMSO-d_6 at 400 MHz

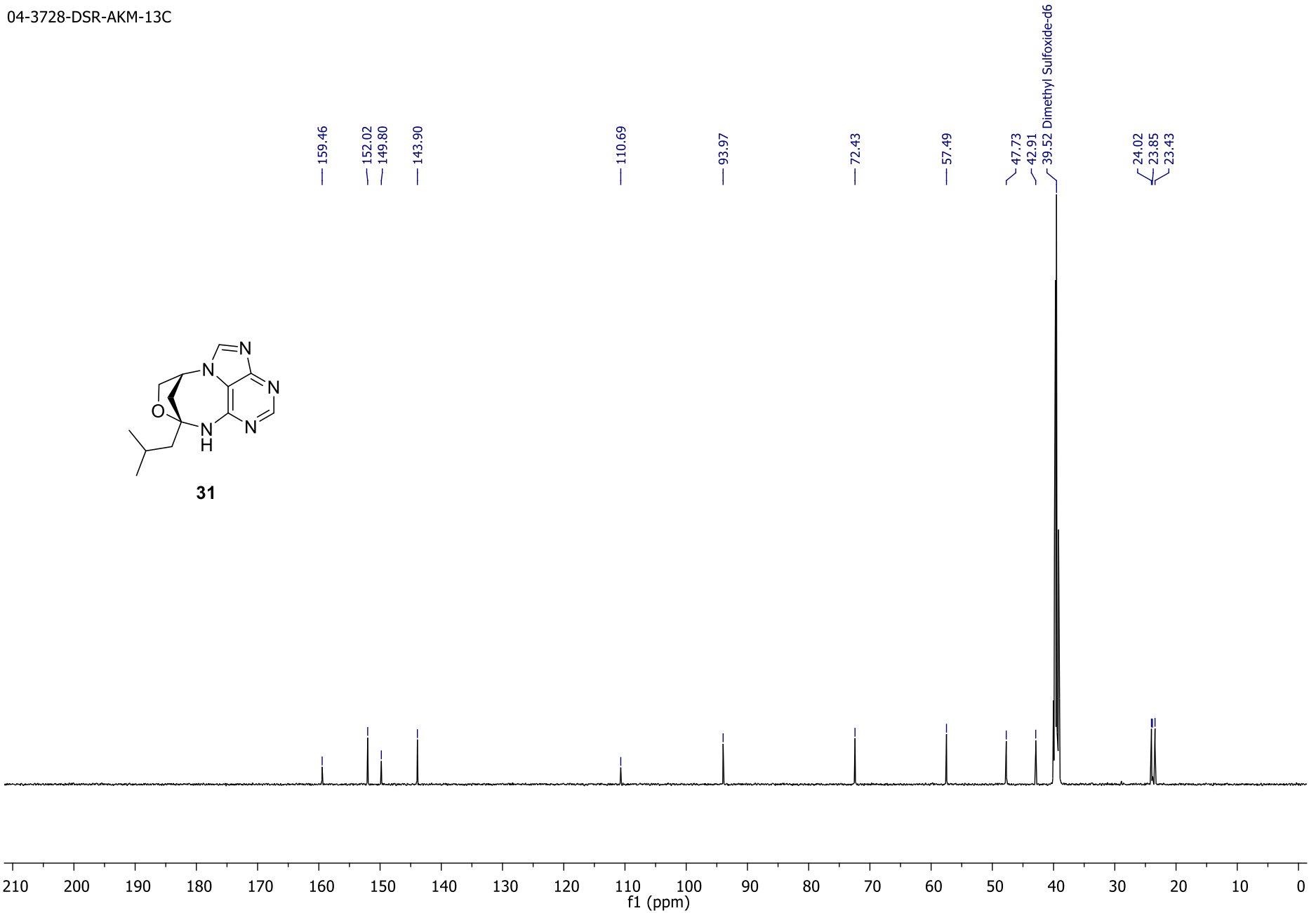
02-3448-DSR-AKM-1H



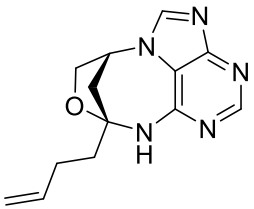
31

$^{13}C\{^{1}H\}$ NMR of Compound 31 in DMSO-d_6 at 125 MHz

04-3728-DSR-AKM-13C



^{1}H NMR of Compound 32 in $CDCl_3$ at 400 MHz



32

$^{13}C\{^{1}H\}$ NMR of Compound 32 in $CDCl_3$ at 175 MHz