Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Total synthesis of a piperidine alkaloid, Microcosamine A

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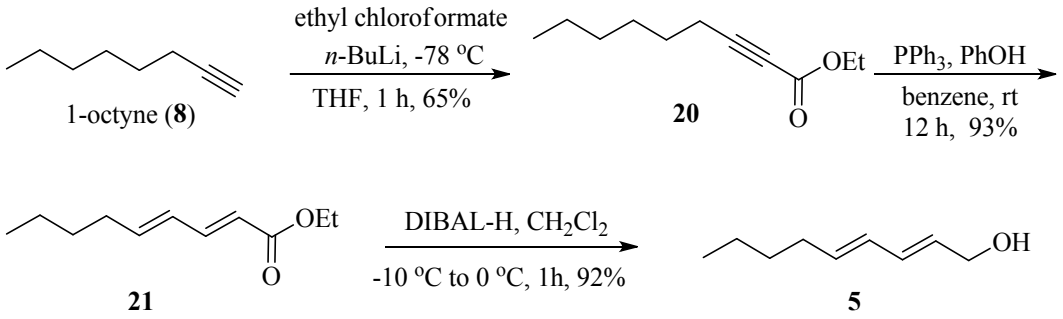
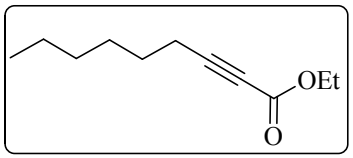
Scheme S1: Preparation of conjugated alcohol **5** from 1-octyne (**8**)

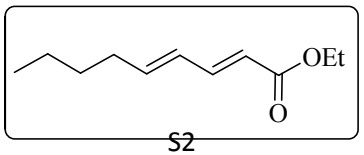


Ethyl non-1-ynoate (20):



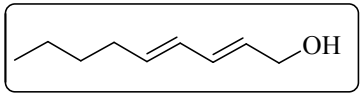
To a solution of alkyne **8** (5.5 g, 50 mmol) in dry THF (100 mL) at -78 ºC was added dropwise *n*-BuLi (24 mL, 2.5 M in hexanes, 60 mmol). The solution was stirred for 1 hour at same temperature before adding ethyl chloroformate (5.5 mL, 60 mmol) in THF (15 mL) at -78 ºC. The reaction mixture was stirred at that temperature for 1 h and then warmed to 0 ºC. After stirring for 1 h at 0 ºC, the reaction was quenched with a saturated aqueous NH_4Cl solution (50 mL). The aqueous layer was separated and extracted with Et_2O (2 X 100 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography of the crude product over silica gel (hexanes/EtOAc 98:2) gave **20** (5.5 g, 65%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) : δ 4.22 (q, 2H, J = 7.0 Hz), 2.30-2.41 (m, 2H), 1.53-1.61 (m, 2H), 1.37-1.43 (m, 2H), 1.28-1.33 (m, 7H), 0.89 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) : δ 153.8, 89.4, 73.1, 61.7, 31.2, 28.5, 27.5, 22.4, 18.6; MS (EI): *m/z* 182 $(M+H)^+$.

Ethyl (2*E*,4*E*)-nona-2,4-dienoate (21).



To a stirred solution of alkyne ester **20** (4.0 g, 21.9 mmol) in benzene (45 mL) at room temperature was added PPh_3 (5.75 g, 21.9 mmol) and phenol (2.05 g, 21.9 mmol). The resulting reaction mixture was stirred at room temperature for 12 h. The solution was then diluted with diethyl ether (50 mL) and 1 N NaOH (30 mL), and the organic layer was separated. The aqueous layer was extracted with ether (2 x 50 mL) and the combined organic layers were washed water (50 mL), brine (50 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was dissolved in ether (100 mL) and MeI (2.0 mL) was added to the solution. The reaction mixture was stirred at room temperature for 3 h. Then, the solution was filtered, concentrated and purified by flash chromatography (silica gel, hexanes/EtOAc 97:3) to give diene **21** (3.7 g, 93%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.26 (dd, 1H, J = 15.2, 9.3 Hz), 6.06-6.22 (m, 2H), 5.78 (d, 1H, J = 15.4 Hz), 4.19 (q, 2H, J = 7.1 Hz), 2.14-2.18 (m, 2H), 1.26-1.43 (m, 7H), 0.90 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.2, 145.0, 144.6, 128.3, 119.1, 60.1, 32.6, 30.8, 22.2, 14.2, 13.8.

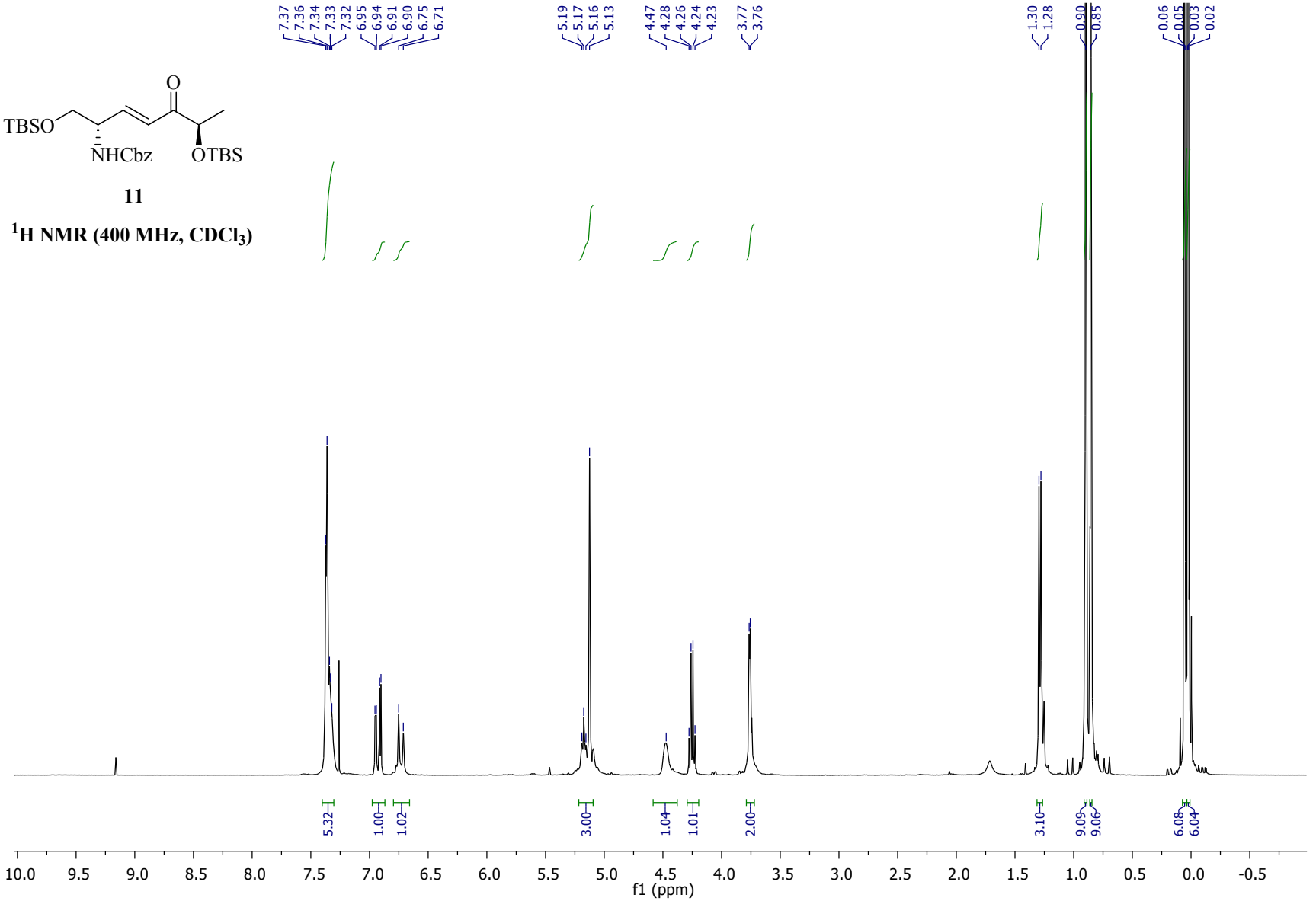
(2*E*,4*E*)-Nona-2,4-dien-1-ol (5):

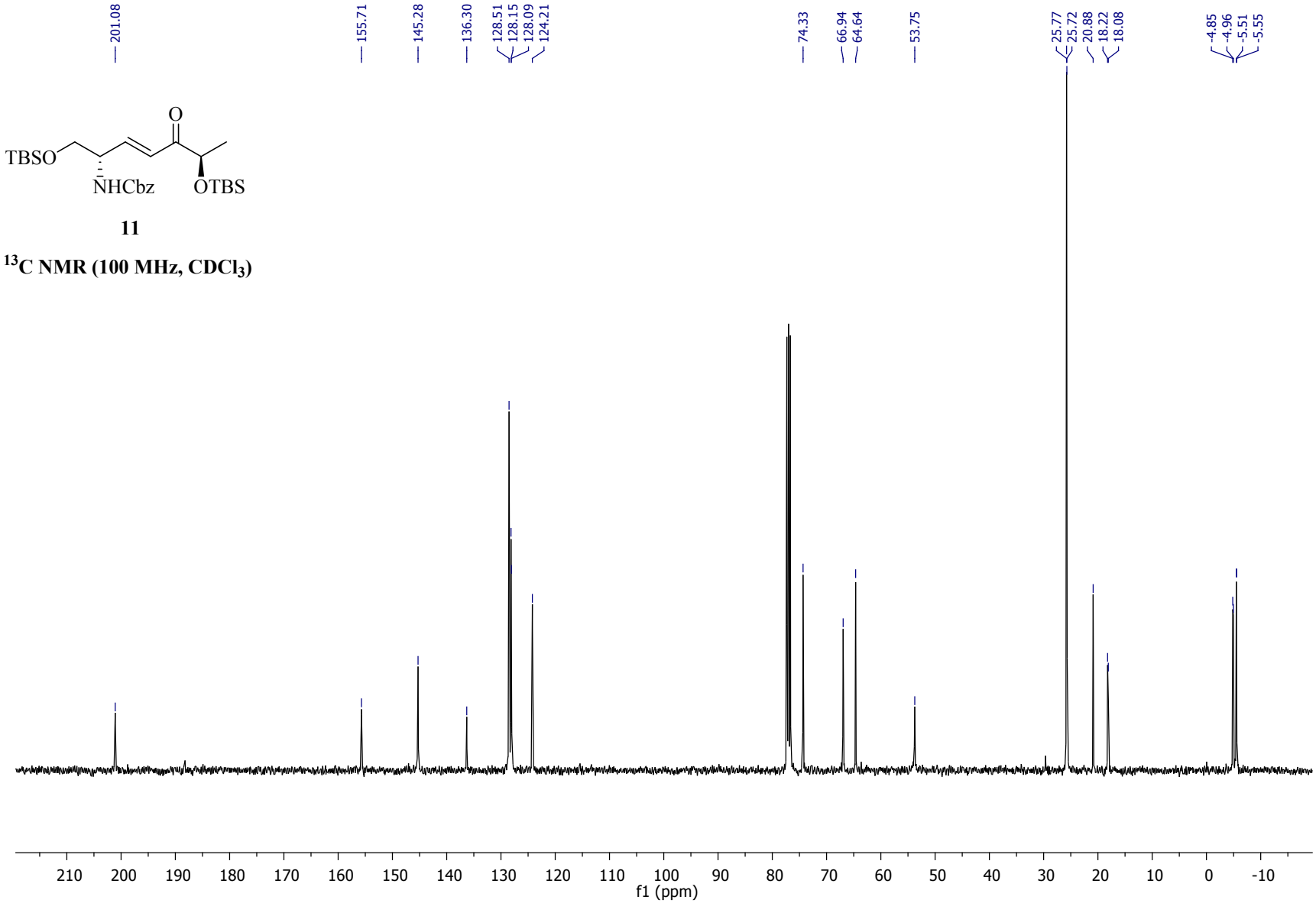


Compound **21** (3.0 g, 1.64 mmol) was taken in dry CH_2Cl_2 (15 mL), cooled to - 78 °C and DIBAL-H (1.0 M in toluene, 4.1 mL, 4.12 mmol) was added dropwise and stirred at that temperature for 15 min. The reaction mixture was slowly warmed to 0 °C, stirred for 1 h. The reaction was then quenched by slow addition of saturated potassium-sodium tartrate solution (10 mL) and brought to room temperature. The reaction mixture was stirred until two layers got separated. Organic layer was taken out, and aqueous layer was further extracted with CH_2Cl_2 (2 x 10 mL), combined organic layers were washed with brine and dried over Na_2SO_4. Solvents were evaporated under reduced pressure. Flash chromatography of the residue over silica gel (hexanes/EtOAc 8:2) gave **5** (2.1 g, 92%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) : δ 6.17 (dd, J = 14.8, 10.4 Hz, IH), 6.00 (dd, J = 14.8, 10.4 Hz, 1H), 5.67 (dt, J = 14.8, 6.7 Hz, 2H), 4.13 (d, J = 6.7 Hz, 2H), 2.05 (q, J= 6.7 Hz, 2H), 1.33 (m, 4H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.7, 132.2, 129.0, 128.6, 63.3, 32.0, 32.0, 21.9, 13.6.

Table S1: Comparison of ^{1}H and ^{13}C NMR ($CDCl_3$) data for natural and synthetic Microcosamine (**2a)**

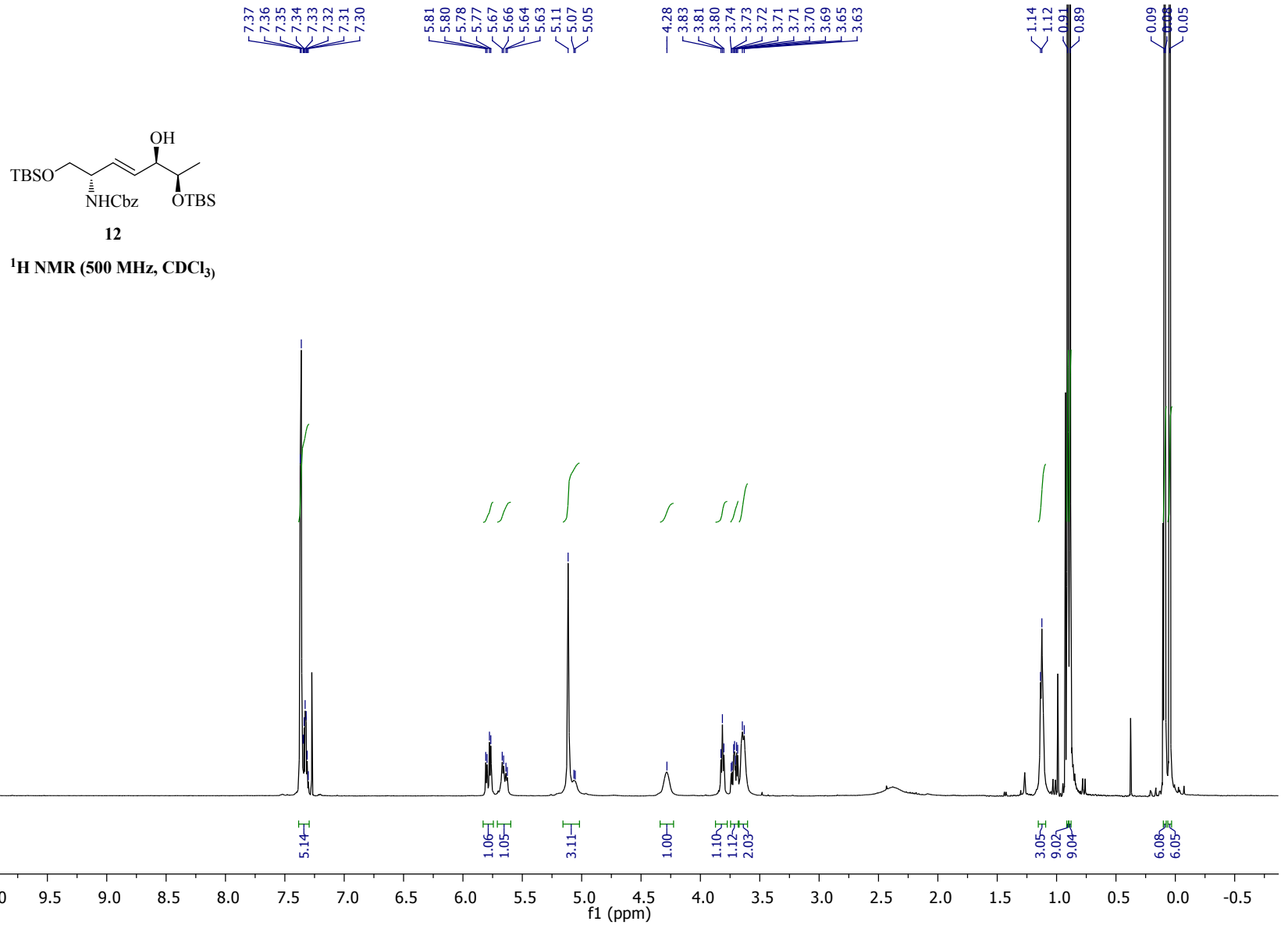
no.	Natural		Synthetic	
	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)
2	58.4	2.50 (dq, J = 10.0, 6.4 Hz)	58.3	2.50-2.57 (m)
3	73.6	3.13 (m)	73.6	3.14-3.23 (m)
4	33.9	1.24-1.37 (m, Hax); 2.04 (m, Heq)	33.9	1.28-1.40 (m); 2.04-2.11 (m)
5	32.0	1.24-1.37 (m, Hax); 1.71 (m, Heq)	31.9	1.28-1.40 (m); 1.71-1.77 (m)
6	58.6	3.16 (m)	58.6	3.14-3.23 (m)
1′	135.2	5.57 (dd, J = 15.2, 7.2 Hz)	135.0	5.66-5.73 (m)
2′	130.1	6.13 (m)	130.1	5.98-6.11 (m)
3′	130.4	6.14 (m)	130.4	6.11-6.22 (m)
4′	132.9	6.15 (m)	132.9	6.11-6.22 (m))
5′	129.9	6.04 (m)	129.8	5.98-6.11 (m)
6′	135.6	5.67 (dt, J = 15.2, 7.2 Hz)	135.6	5.60 (dd, *J* = 15.2, 7.1 Hz)
7′	32.5	2.07 (q, J = 7.2 Hz)	32.4	2.04-2.11 (m)
8′	31.4	1.36 (m)	31.4	1.28-1.40 (m)
9′	22.2	1.34 (m)	22.2	1.28-1.40 (m))
10′	13.9	0.86 (t, J = 6.8 Hz)	13.9	0.89 (t, *J* = 7.1 Hz)
CH_3-2	19.0	1.17 (d, J = 6.4 Hz)	18.9	1.20 (d, *J* = 6.1 Hz)

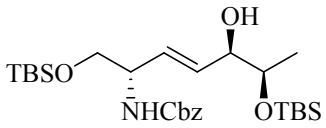

TBSO
O
NHCbz
OTBS
11
1H NMR (400 MHz, CDCl3)
7.37
7.36
7.34
7.33
7.32
6.95
6.94
6.91
6.90
6.75
6.71
5.19
5.17
5.16
5.13
4.47
4.28
4.26
4.24
4.23
3.77
3.76
1.30
1.28
0.90
0.85
0.06
0.05
0.03
0.02
5.32
1.00
1.02
3.00
1.04
1.01
2.00
3.10
9.09
9.06
6.08
6.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)



11

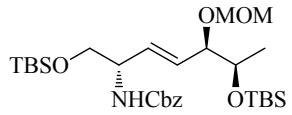
^{13}C NMR (100 MHz, $CDCl_3$)


OH
TBSO
NHCbz
OTBS
12
1H NMR (500 MHz, CDCl3)
7.37
7.36
7.35
7.34
7.33
7.32
7.31
7.30
5.81
5.80
5.78
5.77
5.67
5.66
5.64
5.63
5.11
5.07
5.05
4.28
3.83
3.81
3.80
3.74
3.73
3.72
3.71
3.71
3.70
3.69
3.65
3.63
1.14
1.12
0.91
0.89
0.09
0.08
0.05
5.14
1.06
1.05
3.11
1.00
1.10
1.12
2.03
3.05
9.02
9.04
6.08
6.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)



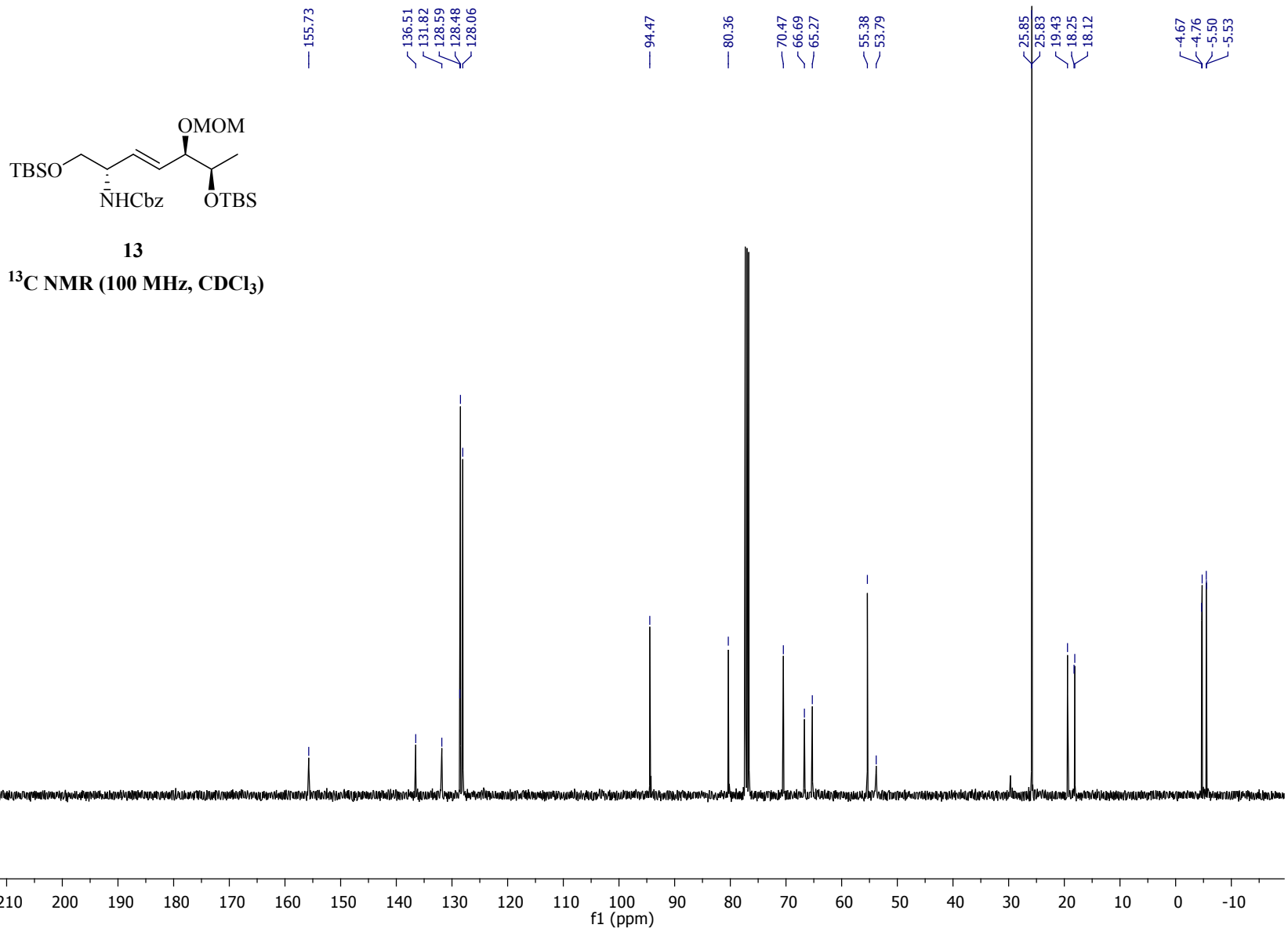
12

^{13}C NMR (125 MHz, $CDCl_3$)



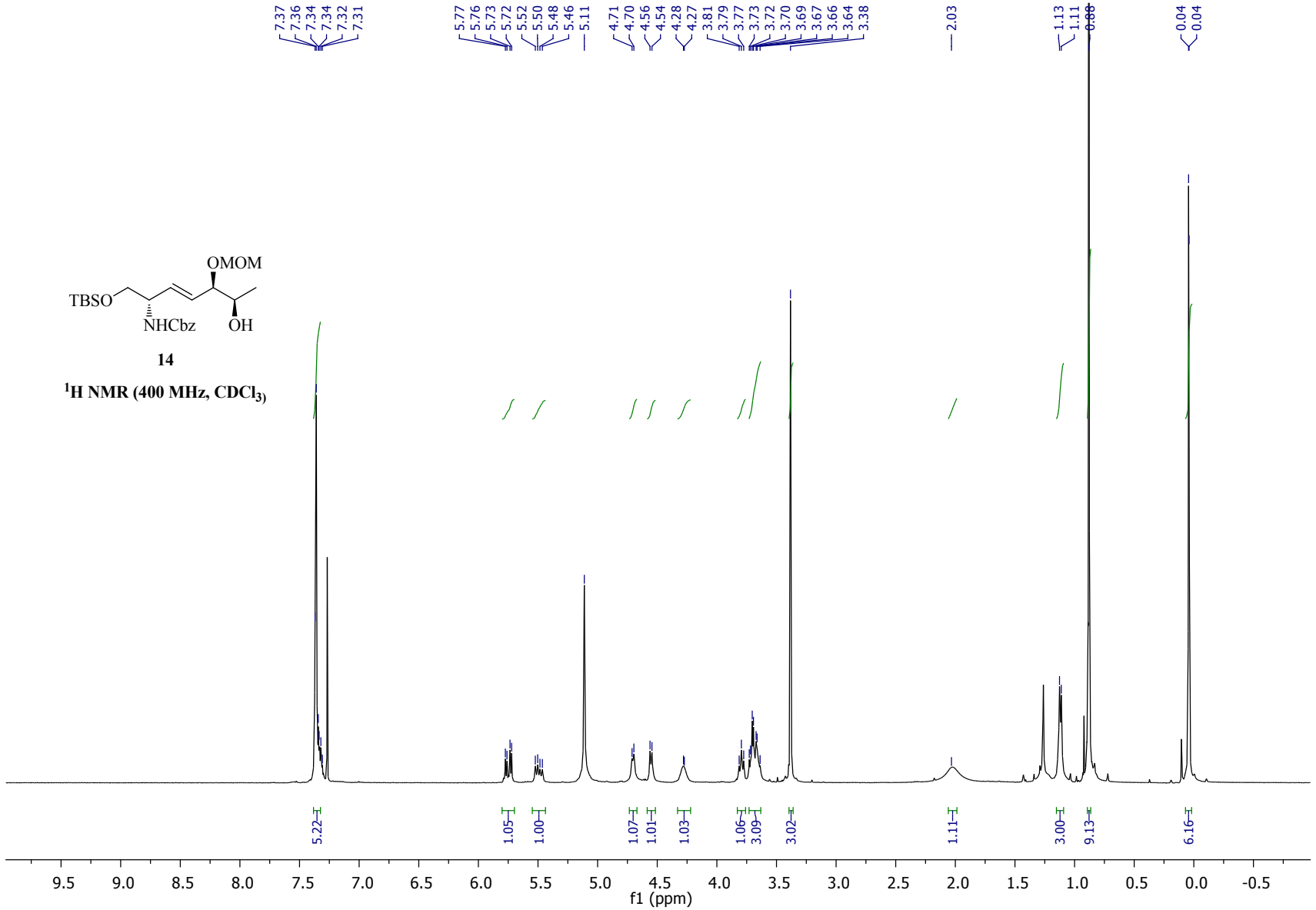
13

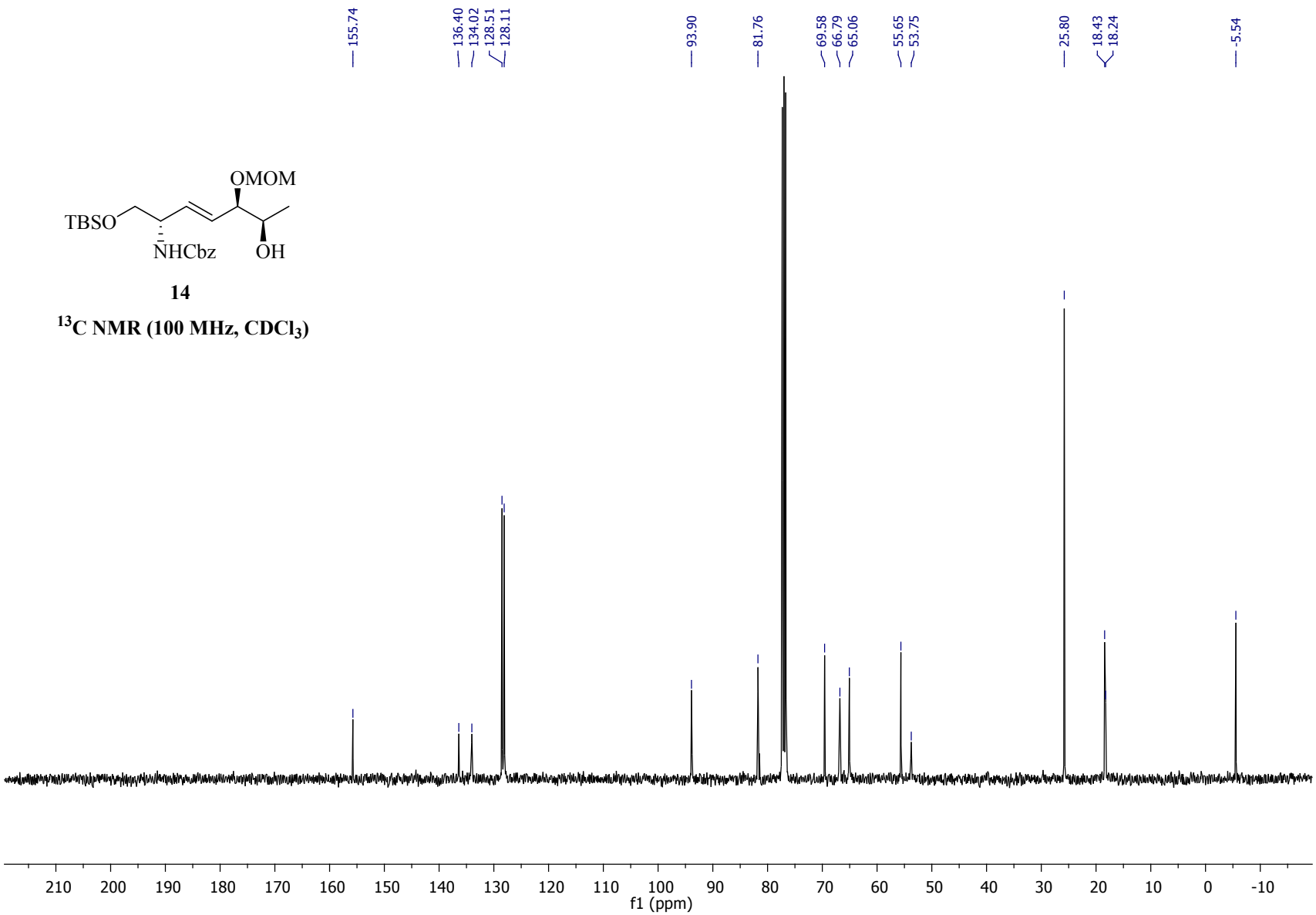
^{1}H NMR (400 MHz, $CDCl_3$)



13

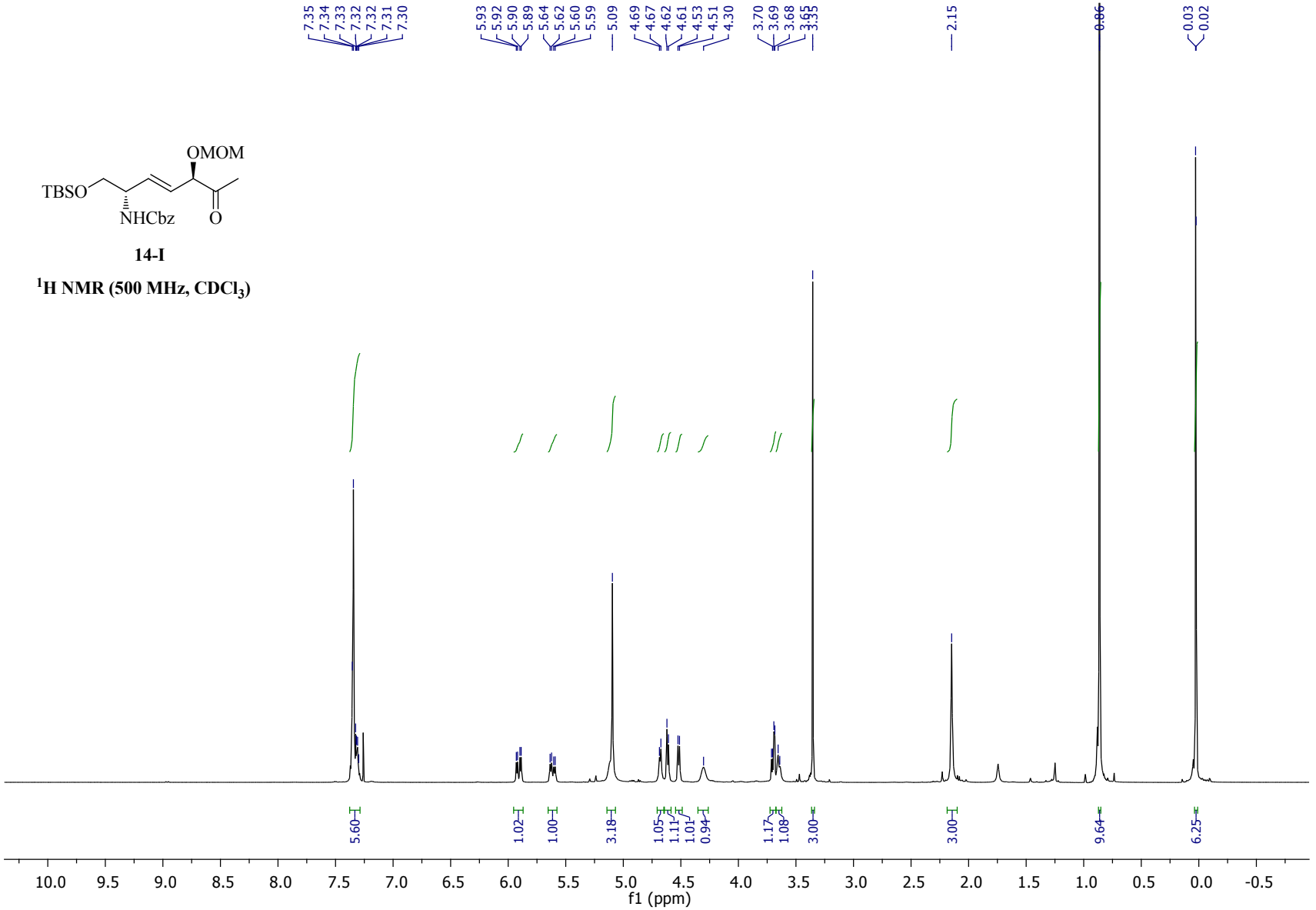
^{13}C NMR (100 MHz, $CDCl_3$)

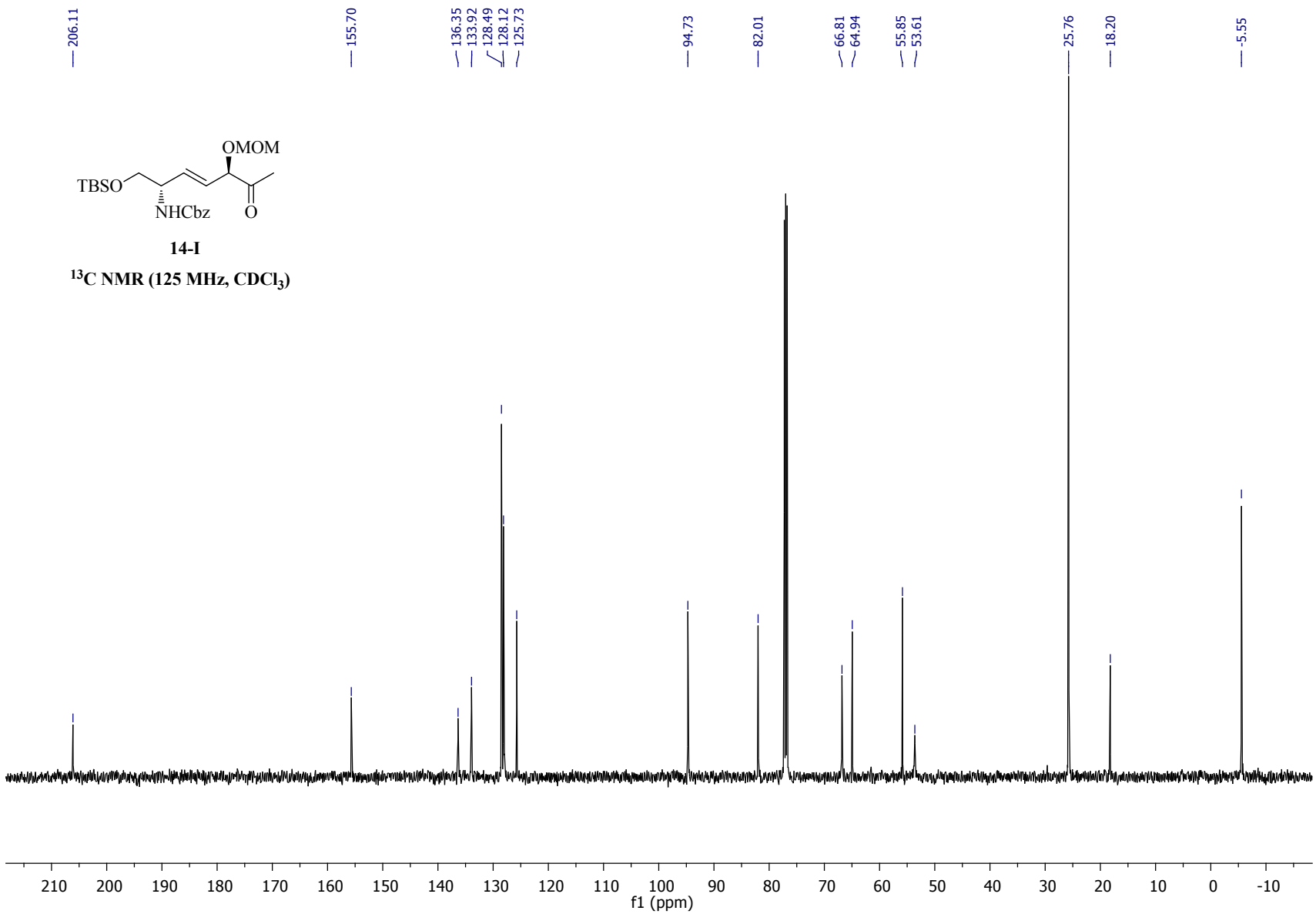

OMOM
TBSO
NHCbz
OH
14
^{1}H NMR (400 MHz, CDCl$_3$)
7.37
7.36
7.34
7.34
7.32
7.31
5.77
5.76
5.73
5.72
5.52
5.50
5.48
5.46
5.11
4.71
4.70
4.56
4.54
4.28
4.27
3.81
3.79
3.77
3.73
3.72
3.70
3.69
3.67
3.66
3.64
3.38
2.03
1.13
1.11
0.88
0.04
0.04
5.22
1.05
1.00
1.07
1.01
1.03
1.06
3.09
3.02
1.11
3.00
9.13
6.16
f1 (ppm)



14

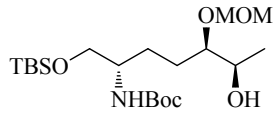
^{13}C NMR (100 MHz, $CDCl_3$)


OMOM
TBSO
NHCbz
O
14-I
1H NMR (500 MHz, CDCl3)
7.35
7.34
7.33
7.32
7.32
7.31
7.30
5.93
5.92
5.90
5.89
5.64
5.62
5.60
5.59
5.09
4.69
4.67
4.62
4.61
4.53
4.51
4.30
3.70
3.69
3.68
3.65
3.55
2.15
0.86
0.03
0.02
5.60
1.02
1.00
3.18
1.05
1.11
1.01
0.94
1.17
1.08
3.00
3.00
9.64
6.25
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)



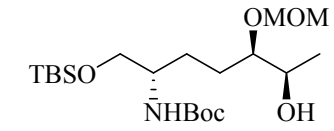
14-I

^{13}C NMR (125 MHz, $CDCl_3$)



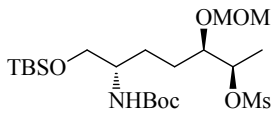
15

^{1}H NMR (400 MHz, $CDCl_3$)



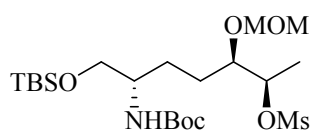
15

^{13}C NMR (100 MHz, $CDCl_3$)



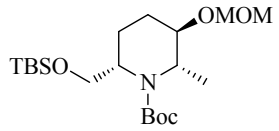
16

^{1}H NMR (400 MHz, $CDCl_3$)



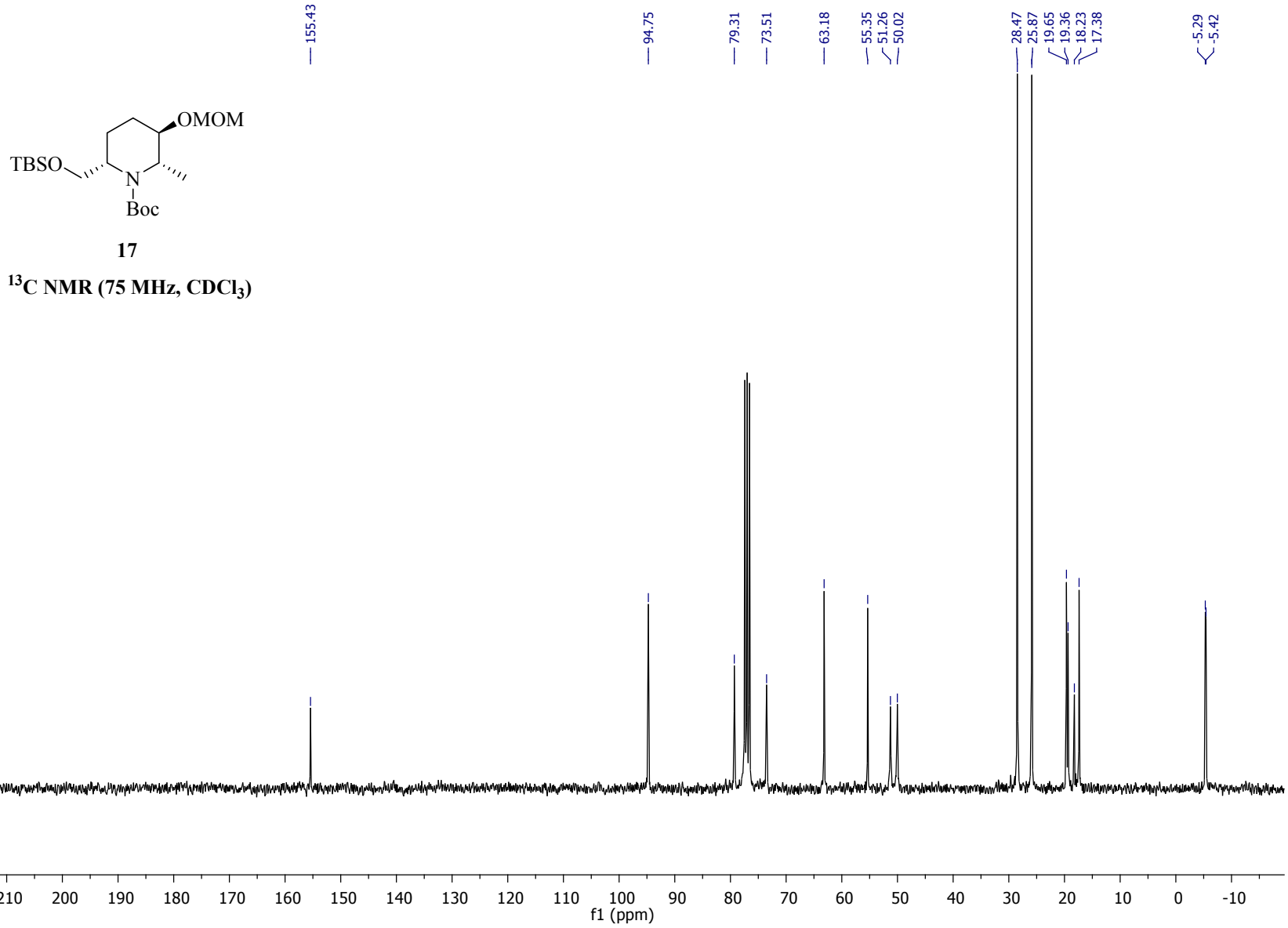
16

^{13}C NMR (100 MHz, $CDCl_3$)



17

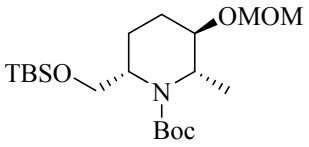
^{1}H NMR (300 MHz, $CDCl_3$)



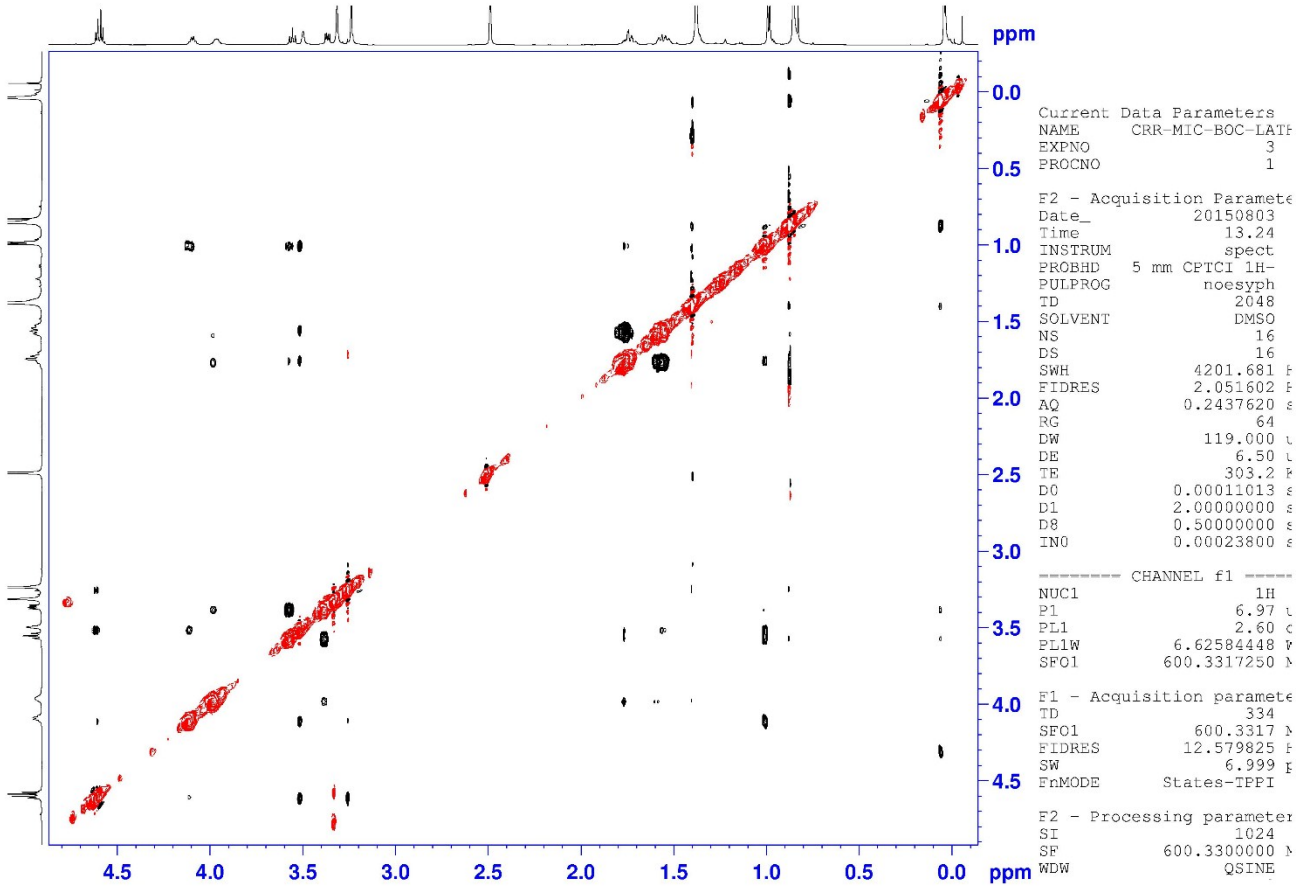
17

^{13}C NMR (75 MHz, $CDCl_3$)

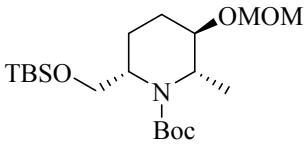
2D NOESY (Nuclear Overhauser effect spectroscopy) spectrum of compound **17** in DMSO-d6 recorded on 600 MHz spectrometer.



17



Expansions of 2D NOESY spectrum of compound **17** in DMSO-d6 recorded on 600 MHz.



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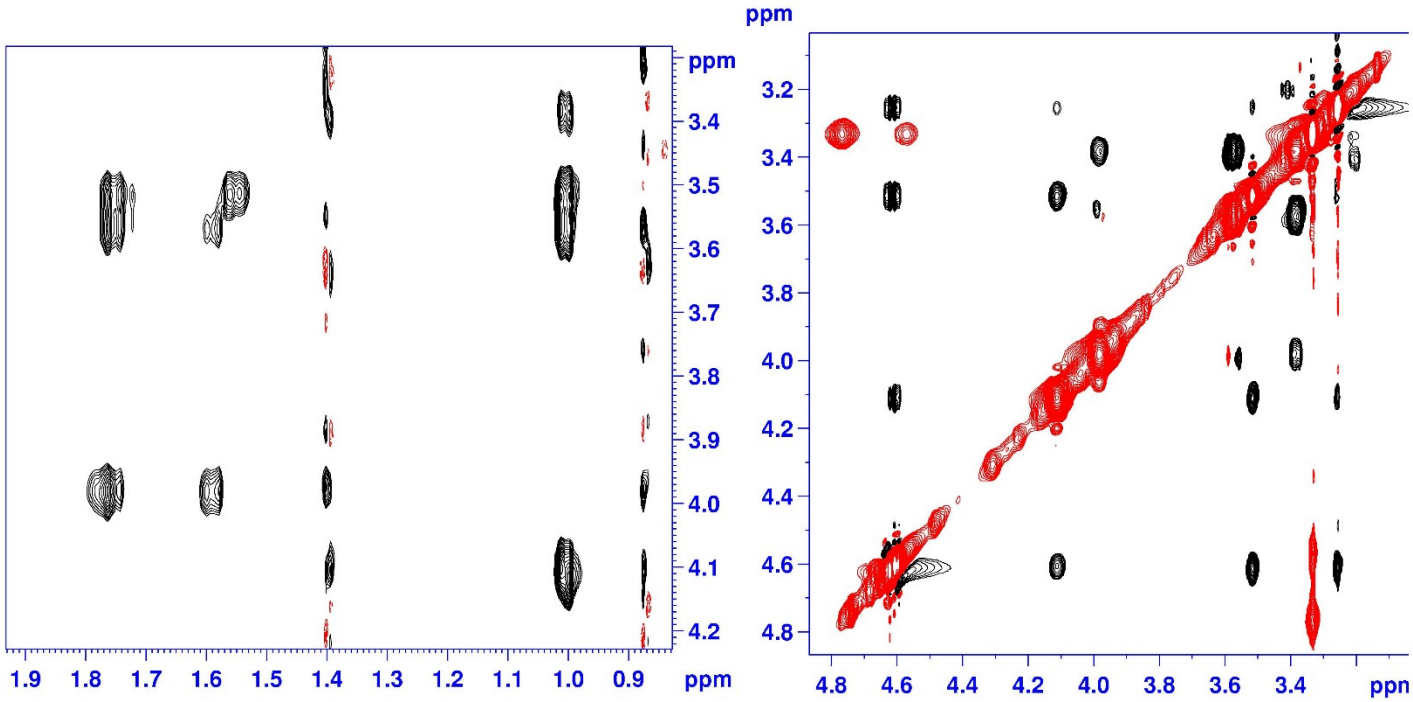
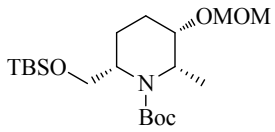
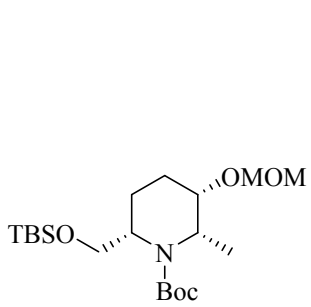




17a

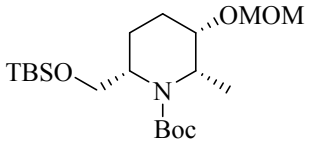
^{1}H NMR (300 MHz, $CDCl_3$)



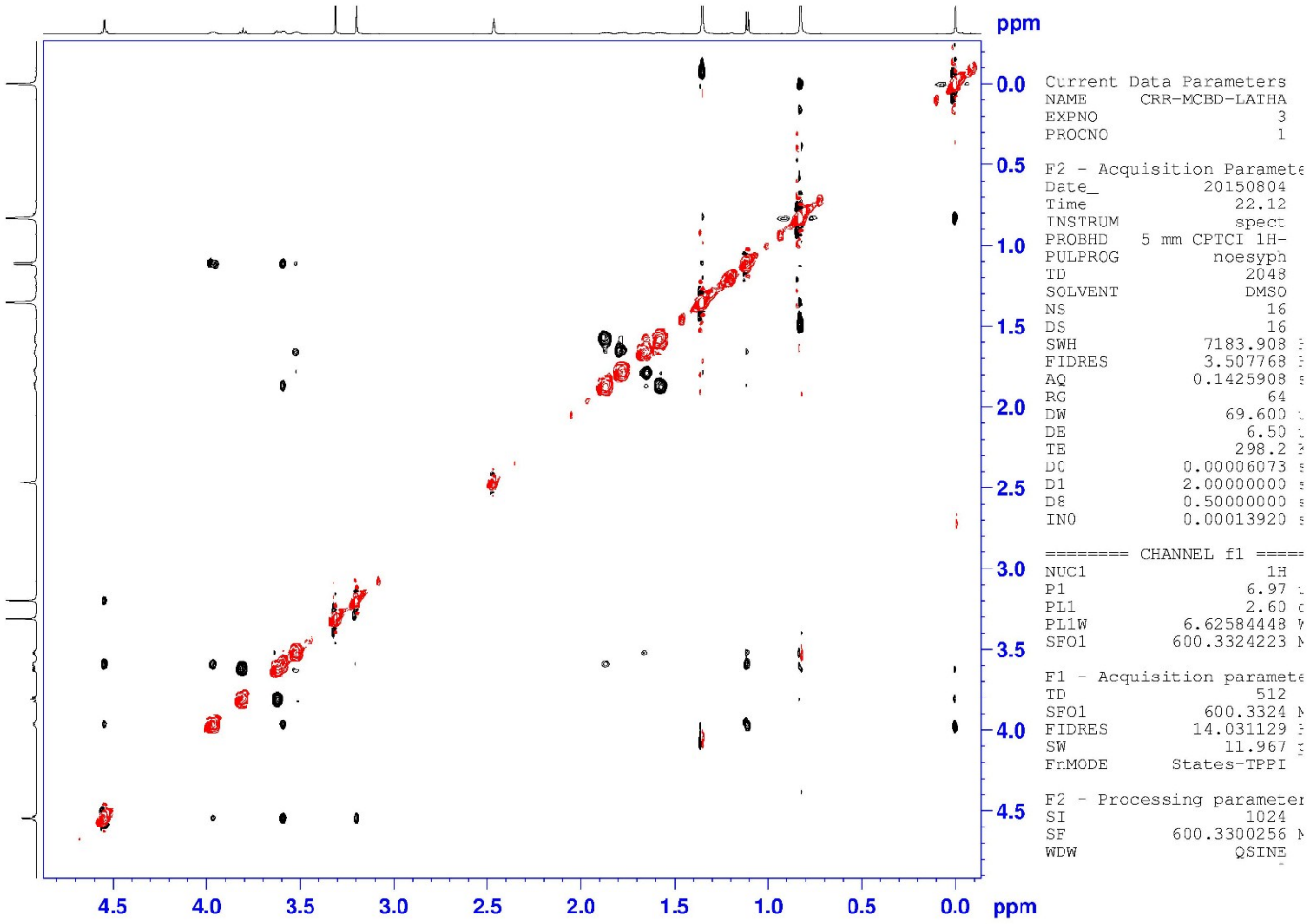
17a

^{13}C NMR (75 MHz, $CDCl_3$)

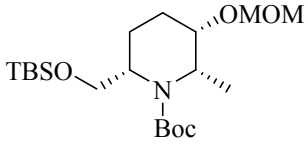
2D NOESY (Nuclear Overhauser effect spectroscopy) spectrum of compound **17a** in DMSO-d6 recorded on 600 MHz spectrometer.



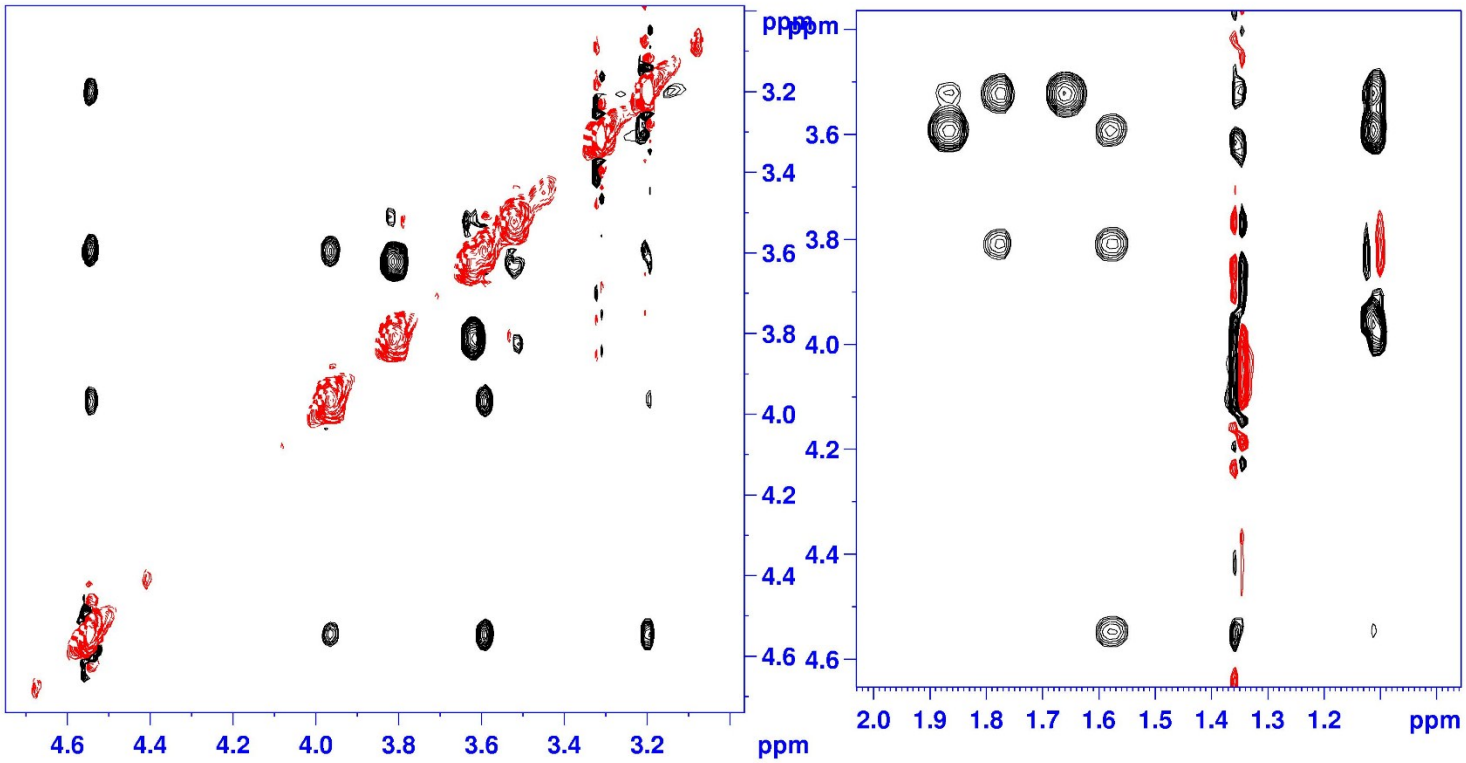
17a

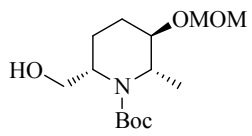


Expansions of 2D NOESY spectrum of compound **17** in DMSO-d6 recorded on 600 MHz.



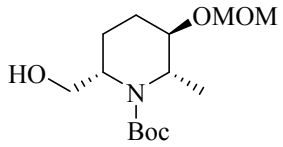
17a





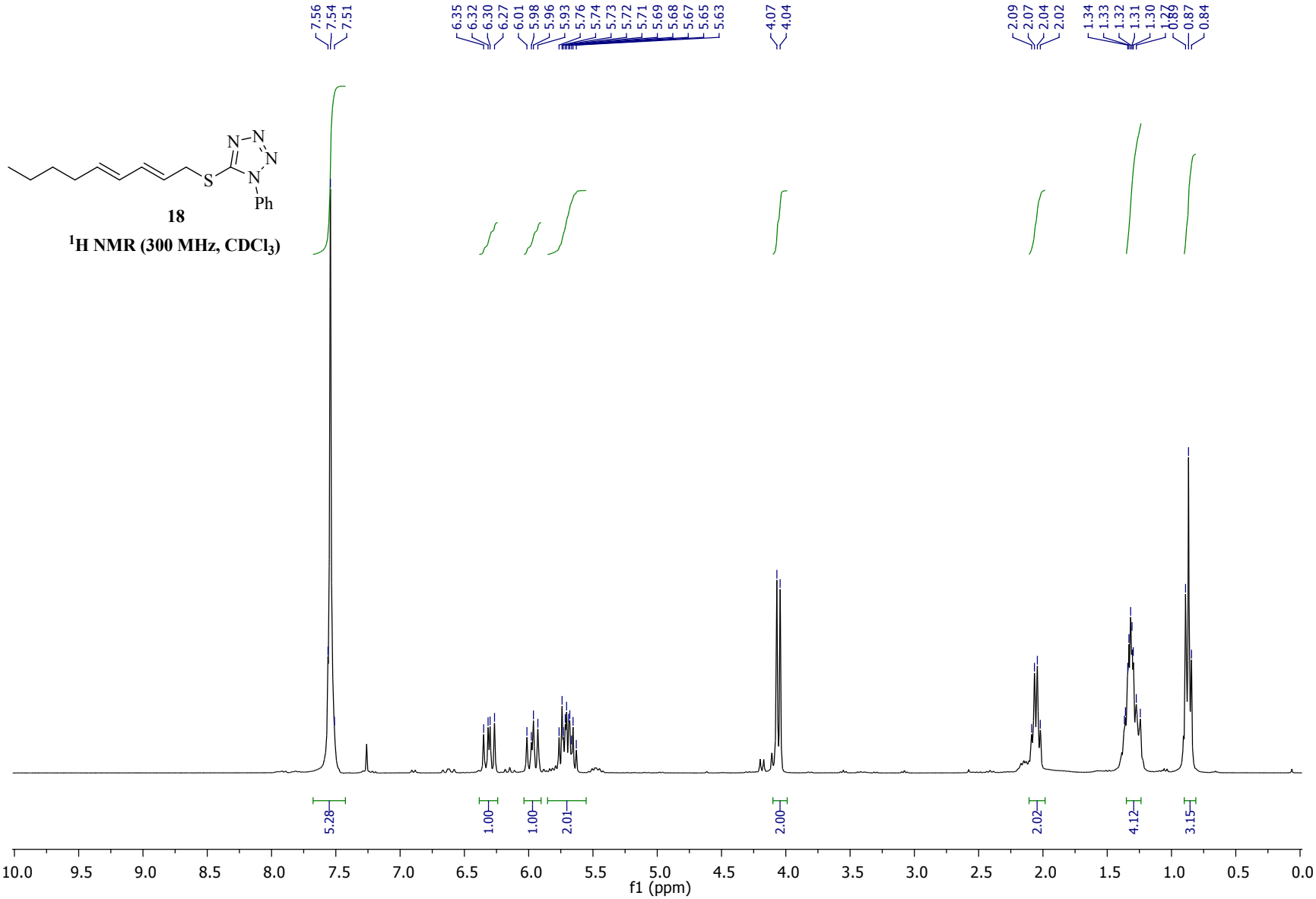
4

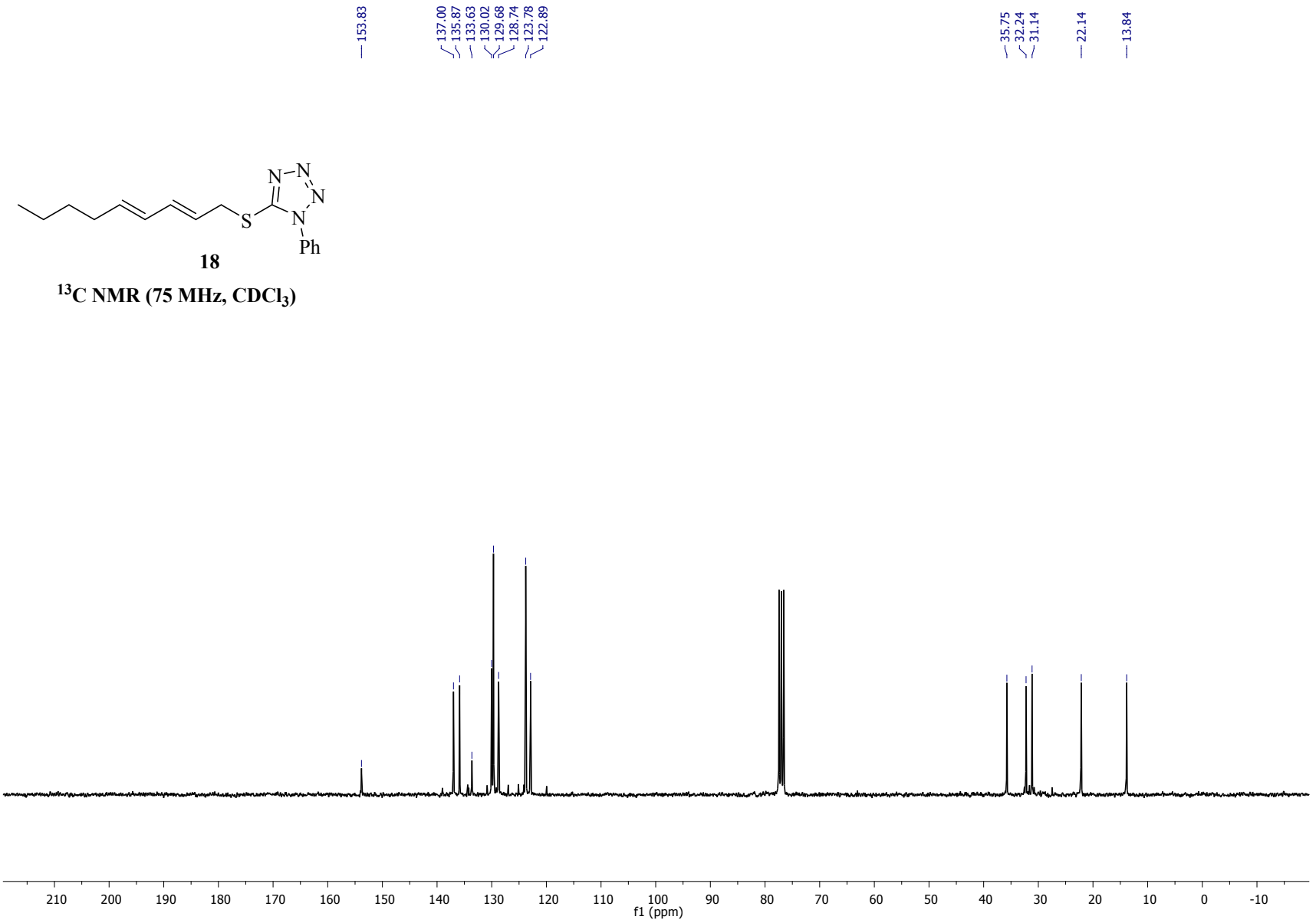
^{1}H NMR (300 MHz, $CDCl_3$)



4

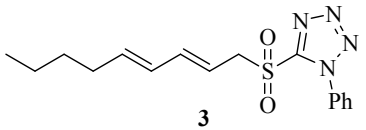
^{13}C NMR (75 MHz, $CDCl_3$)


7.56
7.54
7.51
6.35
6.32
6.30
6.27
6.01
5.98
5.96
5.93
5.76
5.74
5.73
5.72
5.71
5.69
5.68
5.67
5.65
5.63
4.07
4.04
2.09
2.07
2.04
2.02
1.34
1.33
1.32
1.31
1.30
0.89
0.87
0.84
N
N
N
N
S
Ph
18
1H NMR (300 MHz, CDCl3)
5.28
1.00
1.00
2.01
2.00
2.02
4.12
3.15
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



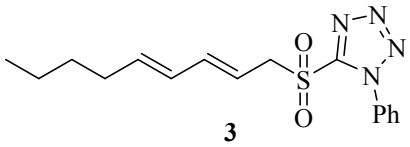
18

^{13}C NMR (75 MHz, $CDCl_3$)



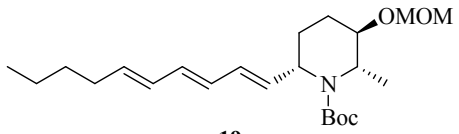
3

^{1}H NMR (500 MHz, $CDCl_3$)



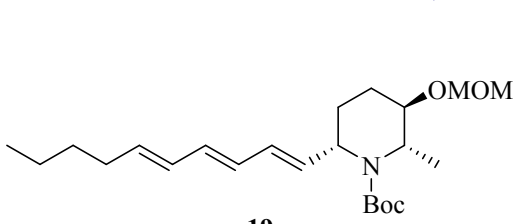
3

^{13}C NMR (125 MHz, $CDCl_3$)



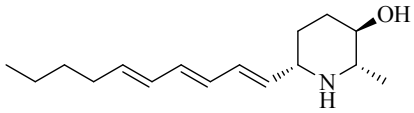
19

^{1}H NMR (300 MHz, $CDCl_3$)



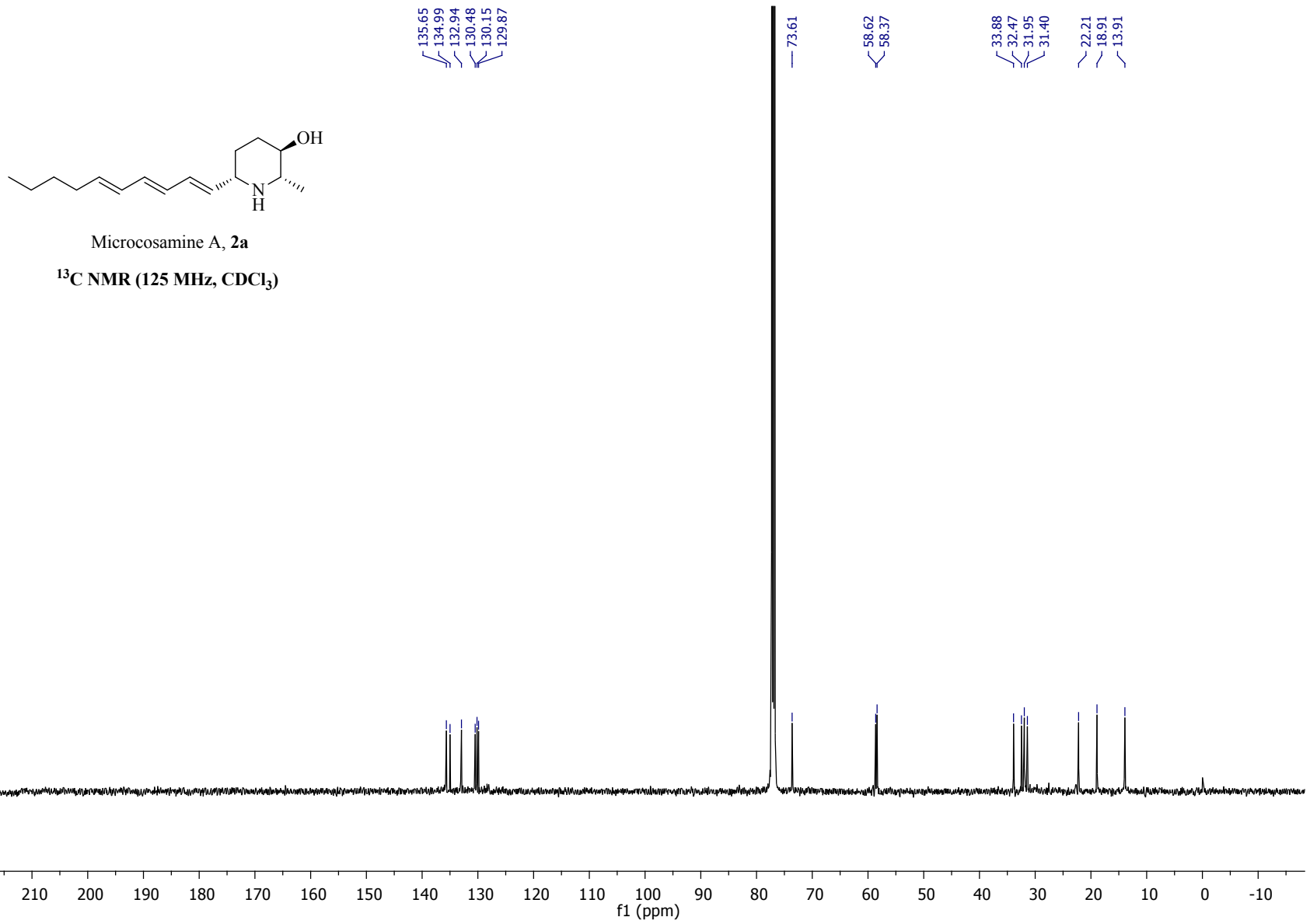
19

^{13}C NMR (75 MHz, $CDCl_3$)



Microcosamine A, **2a**

^{1}H NMR (500 MHz, $CDCl_3$)



Microcosamine A, **2a**

^{13}C NMR (125 MHz, $CDCl_3$)