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SUPPORTING INFORMATION

Highly Convergent Total Synthesis of (+)-Anaferine and (–)-Dihydrocuscohygrine.

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Contents

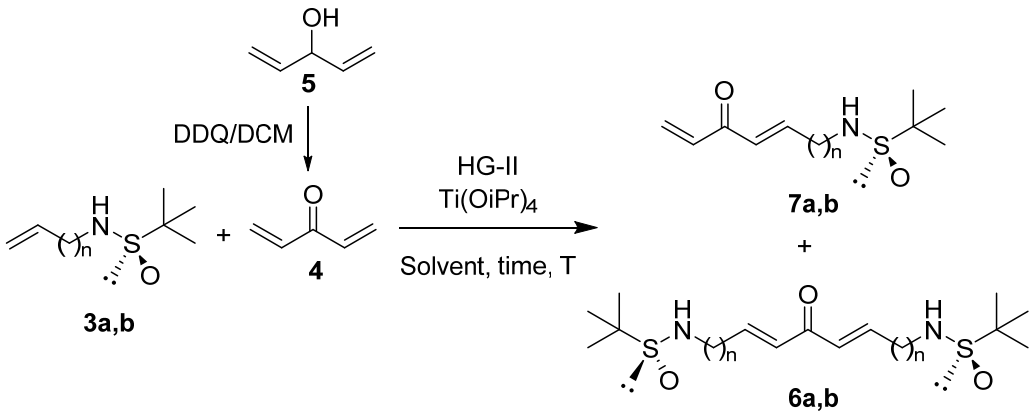
GENERAL REMARKS

Reactions involving moisture-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under nitrogen atmosphere. The following solvents were purified prior to use: THF, diethyl ether and toluene were distilled from sodium/benzophenone, CH_2Cl_2 was distilled from calcium hydride. All other solvents and reagents were used as received. The reactions were monitored with the aid of thin-layer chromatography (TLC) on 0.25 mm precoated silica gel plates. Visualization was carried out with UV light and aqueous ceric ammonium molybdate solution or potassium permanganate stains. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size 0.040-0.063 mm). ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz or 500MHz spectrometer. Chemical shifts are given in ppm (δ), with reference to the residual proton resonances of the solvents. Coupling constants (J) are given in Hertz (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet and quartet, respectively. The letters br indicate that the signal is broad. High-resolution mass spectra were carried out on VGmAutospec (VG Analytical, Micromass Instruments) by the Universidad de Valencia Mass Spectrometry Service.

Synthesis of starting sulfinyl amines **3a,b** were carried out following procedures described in the literature.[1,2]

[1] S. Fustero, S. Monteagudo, M. Sánchez-Roselló, S. Flores, P. Barrio and C. del Pozo, *Eur. J. Chem.*, 2010, **16**, 9835.
[2] S. F. Reed, *J. Org. Chem.*, 1962, **27**, 4116.

Synthesis of the Cross Metathesis products 6a,b and 7a,b



Preparation of a solution of divinyl ketone 4.

To a solution of divinyl alcohol **5** (500 mg, 6.0 mmol) in ethyl ether (6 mL) was added DDQ (1.49 g, 6.6 mmol). The resulting solution was stirred at rt 24h. The resulting mixture was poured into pentane (7 mL) (to precipitate the $DDQH_2$) and the flask washed out with additional pentane (2 x 5 mL). The resulting solid was filtered off and washed with pentane (2 x 5 mL) and then, the combined filtrates were carefully concentrated under reduced pressure (800 mm Hg) at rt to reduce the volume to 5 mL approximately.

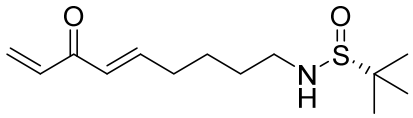
Optimization of the cross metathesis reactions

To a solution of the corresponding sulfonamide **3** (3 mmol) in the corresponding solvent (0,1 M), $Ti(OiPr)_4$ (10 mol %) was added and the mixture was stirred for 5 minutes under N_2 atmosphere. Then, divinyl ketone **4** (the solution previously prepared as indicated above) and 2º generation Hoveyda-Grubbs catalyst (10 mol %) were added in one portion, and the reaction mixture was stirred at room temperature (monitored by TLC). The reaction mixture was concentrated under reduced pressure and the residue was chromatographed on silica gel, employing dichloromethane:ethyl acetate mixtures (from 5:1 to ethyl acetate). The results for the optimization of this reaction are shown in the table below.

Entry	Equiv. 4	Equiv. 3a	Cat.	Temperature	Solvent	Time	R(%) 7a+6a
1	1	2	HG-II	rt	DCM	4h	8+10
2	1	1	HG-II	rt	DCM	4h	17+28
3	2	1	HG-II	rt	DCM	4h	20+61
4	2	1	HG-II	rt	DCM	16h	7+78
5	3	1	HG-II	rt	DCM	4h	32+50
6	3	1	HG-II	rt	DCM	16h	27+53
7	2	1	HG-II	rt	Tol	16h	7+38
8	2	1	HG-II	Δ (reflux)	DCM	4h	30+21
9	2	1	HG-II	Δ (reflux)	Tol	4h	16+12
10	2	1	HG-II	rt	DCM	48h	11+47
11	2	1	Grubbs-II	rt	DCM	16h	21+53

Optimized conditions (entry 4) involved the use of DCM as solvent and a 2:1 ratio between divinyl ketone **4** and sulfonamide **3** at rt for 16 h.

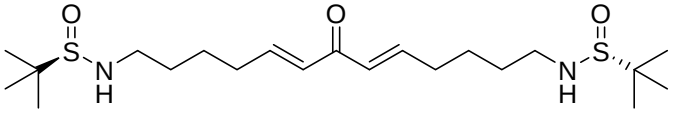
(E)-(S_R)-2-Methyl-*N*-(7-oxonona-5,8-dien-1-yl)-2-propane sulfinamide (7a)



7a

By means of the general procedure described above, single-cross sulfonamide **7a** was obtained as a brown oil (54 mg, 7%) after flash chromatography with 2:1 dichloromethane:ethyl acetate (the product is unstable and must be stored at low temperature and it should be used in a short period of time). $[\alpha]_D^{25}$= -25,2 (c 2.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.89 (dt, *J* = 15.5, 6.9 Hz, 1H), 6.57 (dd, *J* = 17.4, 10.6 Hz, 1H), 6.35 (d, *J* = 15.7 Hz, 1H), 6.26 (dd, *J* = 17.4, 1.1 Hz, 1H), 5.80 (dd, *J* = 10.6, 1.1 Hz, 1H), 3.24 – 3.01 (m, 3H), 2.26 (dd, *J* = 13.2, 6.8 Hz, 2H), 1.65 – 1.48 (m, 4H), 1.18 (s, 9H). ^{13}C NMR (75,5 MHz, $CDCl_3$) δ (ppm): 189.7, 148.1, 135.0, 128.6, 128.5, 55.7, 45.4, 32.3, 30.6, 25.3, 22.6. HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{13}H_{24}NO_2S$: 258,1522; found: 258,1525.

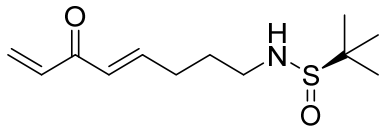
(S_R,S_R)-*N*,*N*'-[(5E,8E)-7-Oxotrideca-5,8-diene-1,13-diyl]bis(2-methyl-2-propane sulfinamide) (6a)



6a

By means of the general procedure described above, double-cross sulfonamide **6a** (1.01 g, 78%) was obtained as a brown oil after flash chromatography with ethyl acetate (the product is unstable and must be stored at low temperature and it should be used in a short period of time). $[\alpha]_D^{25}$= -12,5 (c 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.87 (dt, *J* = 15.5, 6.9 Hz, 2H), 6.31 (d(br), *J* = 15.7 Hz, 2H), 3.23 – 3.12 (m, 4H), 3.1 – 3.02 (m, 2H), 2.26 (dd, *J* = 13.2, 6.6 Hz, 4H), 1.66 – 1.48 (m, 8H), 1.20 (s, 18H). ^{13}C NMR (75,5 MHz, $CDCl_3$) δ (ppm): 189.3, 147.2, 129.1, 55.7, 45.5, 32.2, 30.6, 25.4, 22.7. HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{21}H_{40}N_2O_3S_2$: 433,2553; found: 433,2553.

(S_R)-(E)-2-Methyl-N-(6-oxoocta-4,7-dien-1-yl)-2-propane sulfinamide (7b)

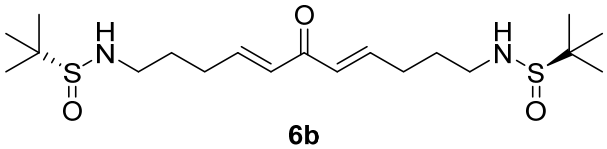


7b

By means of the general procedure described above, single-cross sulfonamide **7b** was obtained as a brown oil (87 mg, 12%) after flash chromatography with 2:1 dichloromethane:ethyl acetate (the product is very unstable and must be used freshly prepared). $[\alpha]_D^{25}$= -21,2 (c 1.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): δ 6.92 (dt, *J* = 15.7, 6.9 Hz, 1H), 6.59 (dd, *J* = 17.4, 10.6 Hz, 1H), 6.43 – 6.23 (m, 2H), 5.89 – 5.82 (m, 1H), 3.26 – 3.02 (m, 3H), 2.38 – 2.30 (m, 2H),

1.83 – 1.73 (m, 2H), 1.22 (s, 9H). Only ^{1}H-NMR data is available due to the instability of the product.

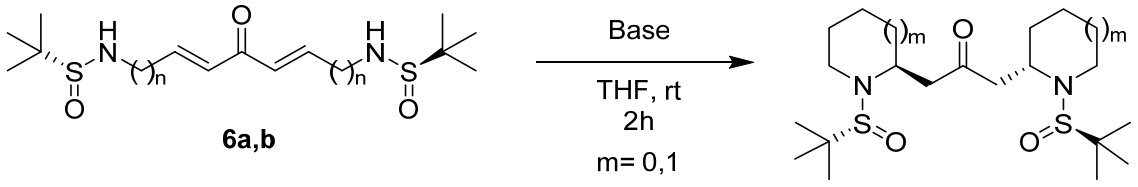
(S_R-S_R)-*N*,*N*'-[(4E,7E)-6-Oxoundeca-4,7-diene-1,11-diyl]bis(2-methyl-2-propane sulfinamide) (6b)



6b

By means of the general procedure described above, double-cross sulfonamide **6b** (788 mg, 65%) was obtained as a brown oil after flash chromatography with 1:3 dichloromethane:ethyl acetate (the product is very unstable and must be used freshly prepared). $[\alpha]_D^{25}$= -11,3 (c 2.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.91 – 6.85 (m, 2H), 6.34 (d, *J* = 15.7 Hz, 2H), 3.24 – 3.05 (m, 6H), 2.36 – 2.28 (m, 4H), 1.80 – 1.72 (m, 4H), 1.21 (s, 18H). ^{13}C NMR (75,5 MHz, $CDCl_3$) δ (ppm): δ 189.1, 146.7, 129.3, 55.8, 45.2, 29.9, 23.8, 22.7. HRMS (ESI/Q-TOF): m/z $[M + H]^+$ calcd for $C_{19}H_{37}N_2O_3S_2$: 405,2246; found: 405,2235.

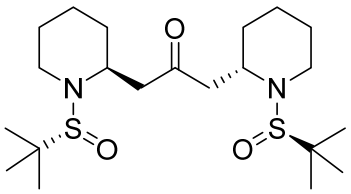
Synthesis of the IMAMR products 8a,b and 9a,b



6a,b **8a,b**

To a solution of the corresponding conjugated bis-sulfinamide **6a,b** (0.1 mmol) in dry THF (0,1M), the corresponding base (2.2 equiv) was added and the reaction mixture was stirred for 2 hours under N_2 atmosphere. Then, when the reaction is finished (monitored by TLC), a small portion of Silica Gel was added, the mixture was concentrated under reduced pressure and was chromatographed on silica gel, employing ethyl acetate:methanol mixtures (from ethyl acetate to 20:1).

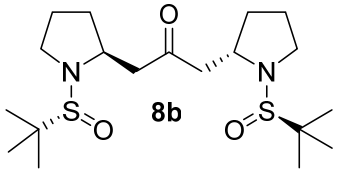
(S_R,S_R)-1,3-Bis[(2S)-1-(*tert*-butylsulfinyl)piperidin-2-yl]-2-propanone (8a)



8a

By means of the general procedure described above, starting from **6a** (86 mg) employing KH as a base, bis-piperidine **8a** (84 mg, 97%) was obtained as a pale brown oil after flash chromatography with ethyl acetate. $[\alpha]_D^{25}$= -12,1 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): δ 3.95 (dq, *J* = 8.8, 4.4 Hz, 2H), 3.19 – 3.04 (m, 4H), 2.91 (dd, *J* = 16.7, 4.8 Hz, 2H), 2.85 (dd, *J* = 16.7, 8.1 Hz, 2H), 1.87 – 1.71 (m, 4H), 1.60 – 1.57 (m, 6H), 1.52 – 1.45 (m, 2H), 1.15 (s, 18H). ^{13}C NMR (75,5 MHz, $CDCl_3$) δ (ppm): 206.0, 68.1, 58.4, 52.9, 46.0, 43.5, 30.3, 26.2, 23.6, 20.6. HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{21}H_{41}N_2O_3S_2$: 433,2553; found: 433,2553.

(S_R,S_R)-1,3-Bis[(2S)-1-(*tert*-butylsulfinyl)pyrrolidin-2-yl]-2-propanone (8b)



8b

By means of the general procedure described above, starting from **6b** (81 mg) employing NaH as a base, IMAMR product **8b** (73 mg, 90%) was obtained as a brown solid after flash chromatography with ethyl acetate. $[\alpha]_D^{25}$= -108,3 (c 2.2, $CHCl_3$).Mp= 134-137°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): δ 3.94 (dtd, *J* = 8.5, 6.7, 5.4 Hz, 2H), 3.65 (ddd, *J* = 10.3, 8.4, 4.4 Hz, 2H), 2.73 – 2.65 (m, 4H), 2.38 (dd, *J* = 16.5, 8.6 Hz, 2H), 2.06 (td, *J* = 12.2, 6.9 Hz, 2H), 1.82 – 1.67 (m, 4H), 1.33 (ddt, *J* = 12.5, 8.5, 6.9 Hz, 2H), 1.11 (s, 18H). ^{13}C NMR (75,5 MHz, $CDCl_3$) δ (ppm): δ 206.3, 61.6, 57.4, 50.4, 41.3, 32.0, 26.0, 24.0. HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{19}H_{37}N_2O_3S_2$: 405,2246; found: 405,2236.

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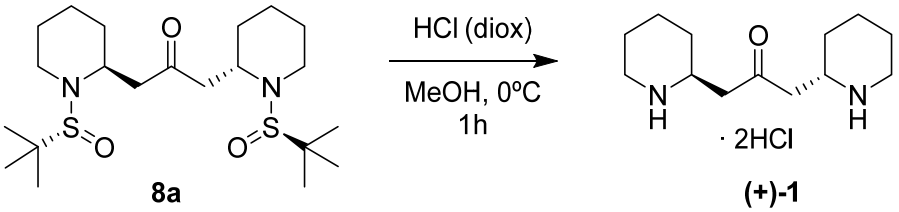
Synthesis of (+)-anaferine (1)

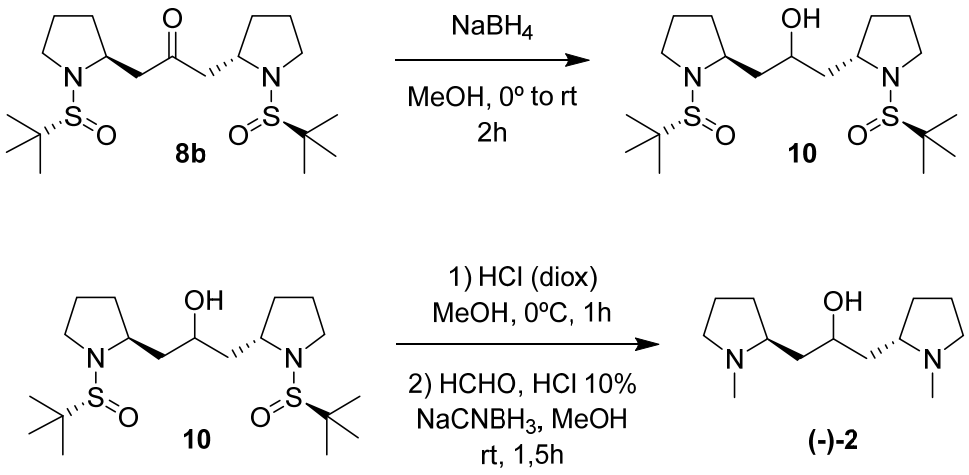


8a **(+)-1**

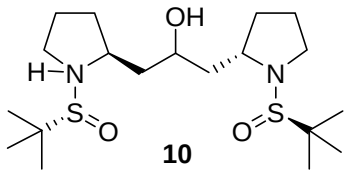
To a solution of IMAMR product **8a** (37 mg, 0,086 mmol) in dry methanol (0,05 M) at 0°C, hydrogen chloride (4,0 M in dioxane; 0,21 mL; 10,0 equiv) was added dropwise and the reaction mixture was stirred for 1 hour under N_2 atmosphere (monitored by TLC). The reaction mixture was concentrated under reduced pressure. (+)-Anaferine dihydrochloride **1** was obtained (25mg, 99%) as a white solid without further purification. $[\alpha]_D^{25}$= +48,7 (c 0.5, MeOH/H_2O 1:1). $[\alpha]_{D,lit}^{20}$= -49,8 ± 2 (c 0.529 MeOH/H_2O 1:1)[3]. ^{1}H NMR (300 MHz, CD_3OD) δ (ppm): δ 3.57 (s, 2H), 3.41 – 3.35 (m, 2H), 3.08 – 2.97 (m, 6H), 1.96 – 1.87 (m, 6H), 1.76 – 1.53 (m, 6H). These data are in agreement with the ones showed in the literature.[4]

[3] *(a)* A. Rother, J. M. Bobbitt and A. E. Schwarting, *Chem. Ind. (London)*, 1962, 654; *(b)* A. E. Schwarting, J. M. Bobbitt, A. Rother, C. K. Atal, K. L. Khanna, J. D. Leary and W. G. Walter, *Lloydia*, 1963, **26**, 258.
[4] S. Blechert and C. Stapper, *Eur. J. Org. Chem.*, 2002, 2855.

Synthesis of (-)-dihydrocuscohygrine 2.

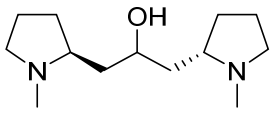


(S_R,S_R)-1,3-Bis[(2S)-1-(*tert*-butylsulfinyl)pyrrolidin-2-yl]-2-propanol (10)



To a solution of IMAMR product **8b** (78 mg, 0,19 mmol) in dry methanol (0,05 M) at 0°C, sodium borohydride (22 mg; 3,0 equiv) was added and the reaction mixture was stirred for 30 minutes at 0°C under N_2 atmosphere. After this time, the reaction mixture was stirred at room temperature for 1,5 h. Then, when the reaction is finished (monitored by TLC), a small portion of Silica Gel was added, the mixture was concentrated under reduced pressure and was chromatographed on silica gel, employing ethyl acetate:methanol mixtures (from ethyl acetate to 15:1). The product was obtained (71 mg, 90%) as a white solid. $[\alpha]_D^{25}$= -102,4 (c 2.0, $CHCl_3$). Mp= 134-137°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): δ 3.87 – 3.67 (m, 5H), 2.79 – 2.71 (m, 2H), 2.55 (s, 1H), 2.04 (tq, *J* = 12.0, 6.8 Hz, 3H), 1.89 – 1.66 (m, 7H), 1.62 – 1.49 (m, 2H), 1.46 – 1.35 (m, 2H), 1.21 (s, 9H), 1.19 (s, 9H). ^{13}C NMR (75,5 MHz, $CDCl_3$) δ (ppm): δ 67.4, 63.5, 63.5, 57.7, 57.3, 44.7, 44.6, 41.6, 41.5, 32.0, 31.5, 26.3, 26.1, 24.2, 24.1. HRMS (ESI/Q-TOF): m/z [M + H]$^+$ calcd for $C_{19}H_{39}N_2O_3S_2$: 407,2402; found: 407,2404.

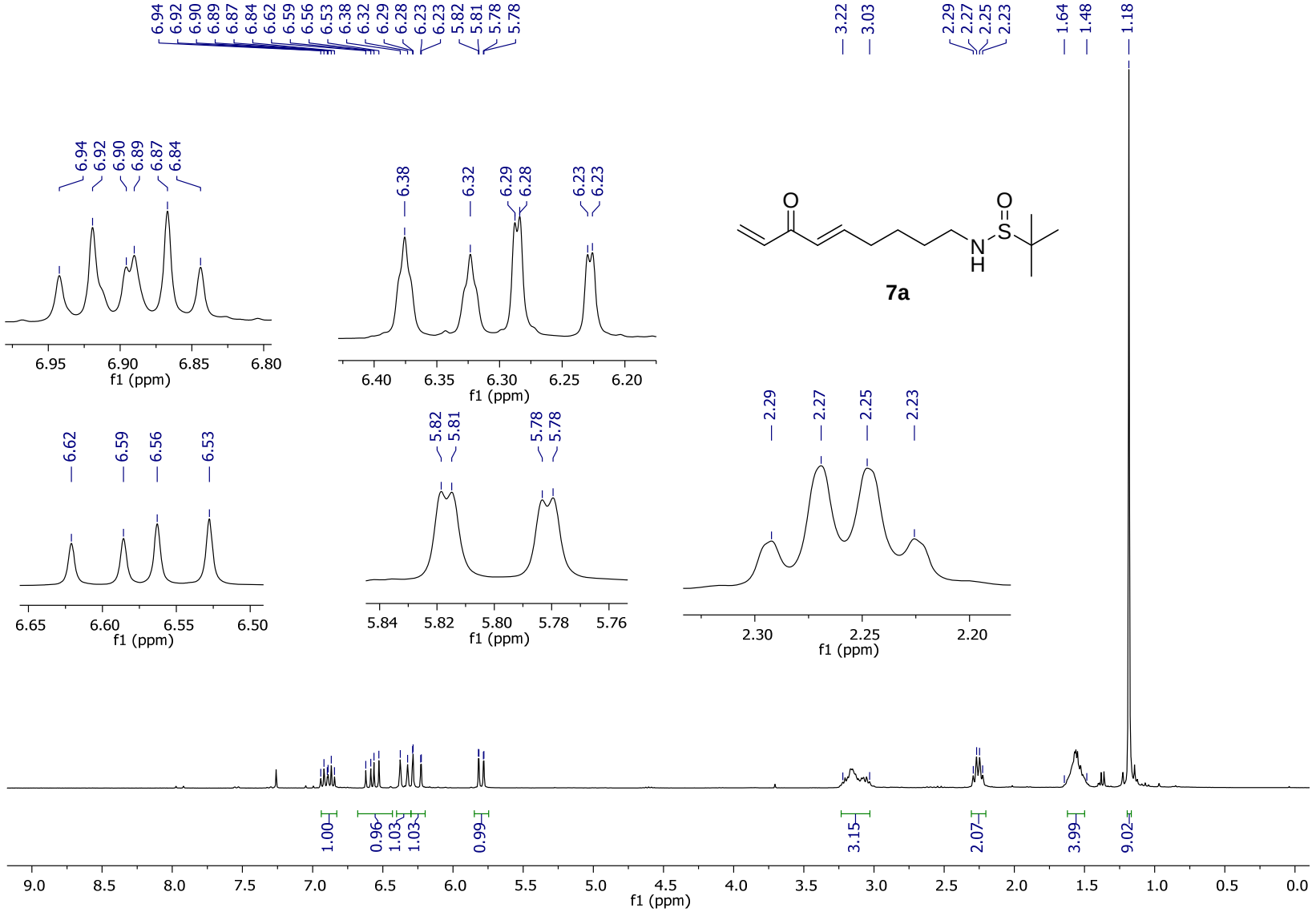
(-)-Dihydrocuscohygrine (2)



(-)-2

To a solution of **10** (71 mg, 0,17 mmol) in dry methanol (0,05 M) at 0°C, hydrogen chloride (4,0 M in dioxane; 0,44 mL; 10,0 equiv) was added dropwise and the reaction mixture was stirred for 1 h under N_2 atmosphere (monitored by TLC). The reaction mixture was concentrated under reduced pressure. Then, NaOH 1M was added (10 mL) and the dihydrochloride was stirred with the NaOH solution for 30 minutes. The solution was extracted six times with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated. Free diamine was redisolved in methanol (0,05 M), and a solution of formaldehyde (37%, 0,42 mL, 30 equiv) and HCl 10% (10%, 0,4 mL, 15 equiv) in methanol was added dropwise. The reaction mixture was stirred for 1h, and then sodium ciannoborohydride (160 mg, 15 equiv) was added. After 30 minutes, the reaction mixture was quenched with water (5 mL). The aqueous layer was extracted twice with diethyl ether. Finally, NaOH 1M (10 mL) was added to the aqueous layer, and it was extracted six times with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated. The crude mixture was purified by flash chromatography with 10:4:1 hexane:dichloromethane:diethylamine as eluent to afford pure dihydrocuscohygrine (34 mg; 86%) as a colorless oil. $[\alpha]_D^{25}$= -101,2 (c 2.2, acetone). $[\alpha]_{D,lit}^{20}$= -105,5 (c 1.67, acetone)[5]. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.03 (tt, *J* = 10.1, 2.5 Hz, 1H), 3.12 – 3.05 (m, 2H), 2.60 – 2.56 (m, 1H), 2.36 (s, 3H), 2.35 (s, 3H), 2.23 – 2.06 (m, 3H), 1.94 – 1.71 (m, 8H), 1.45 (dt, *J* = 14.6, 2.5 Hz, 1H), 1.31 – 1.20 (m, 4H). These data are in agreement with the ones showed in the literature.[6]

[5] T. Yamauchi, S. Hagiwara and K. Higashiyama, *J. Org. Chem.*, 2008, **73**, 9787.
[6] C. Stapper and S. Blechert, *J. Org. Chem.*, 2002, **67**, 6456.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6.92
6.90
6.89
6.87
6.84
6.62
6.59
6.56
6.53
6.38
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6.29
6.28
6.23
6.23
5.82
5.81
5.78
5.78
3.22
3.03
2.29
2.27
2.25
2.23
1.64
1.48
1.18
O
O
S
N
H
7a
f1 (ppm)
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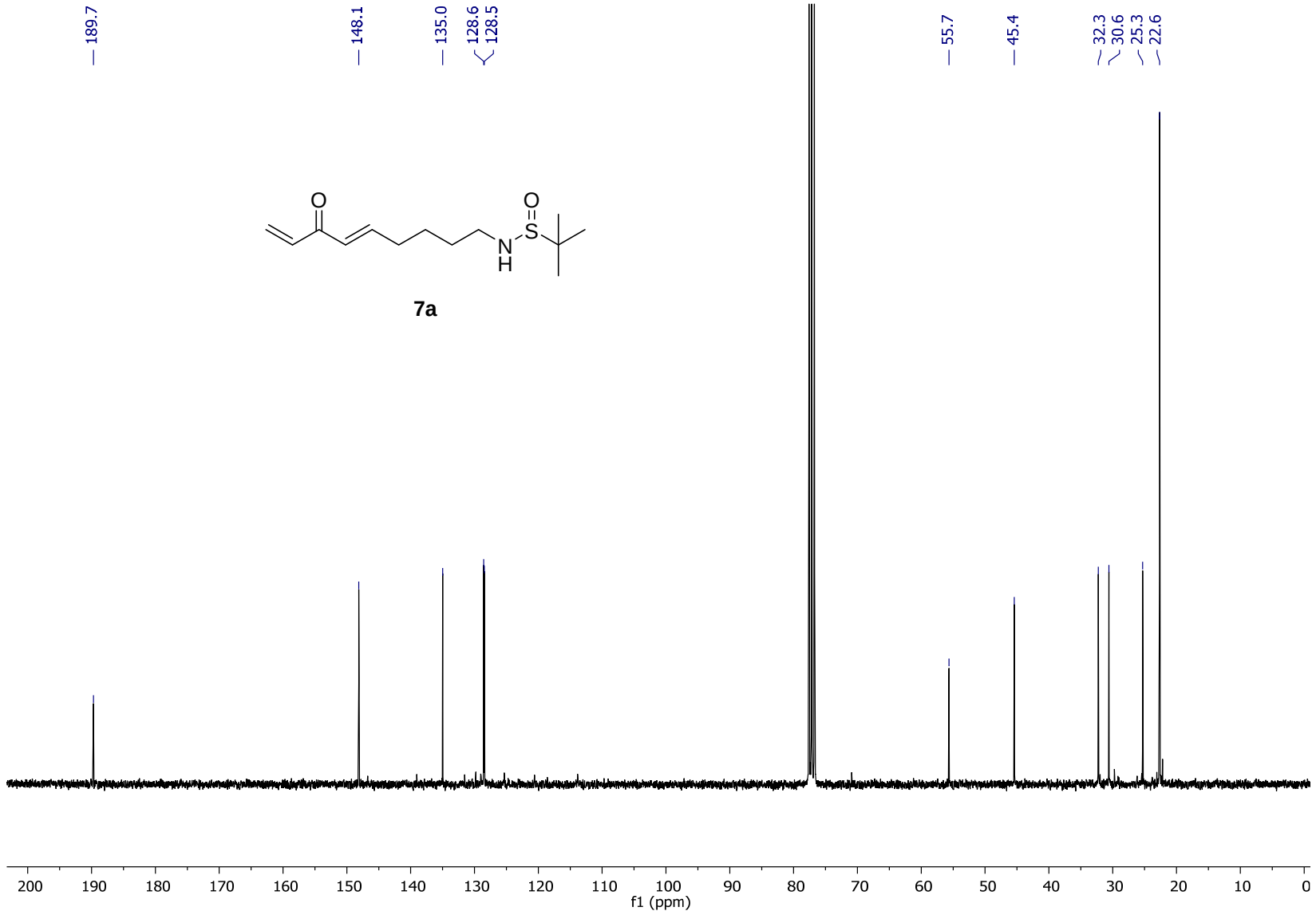
0.96
1.03
1.03
0.99
3.15
2.07
3.99
9.02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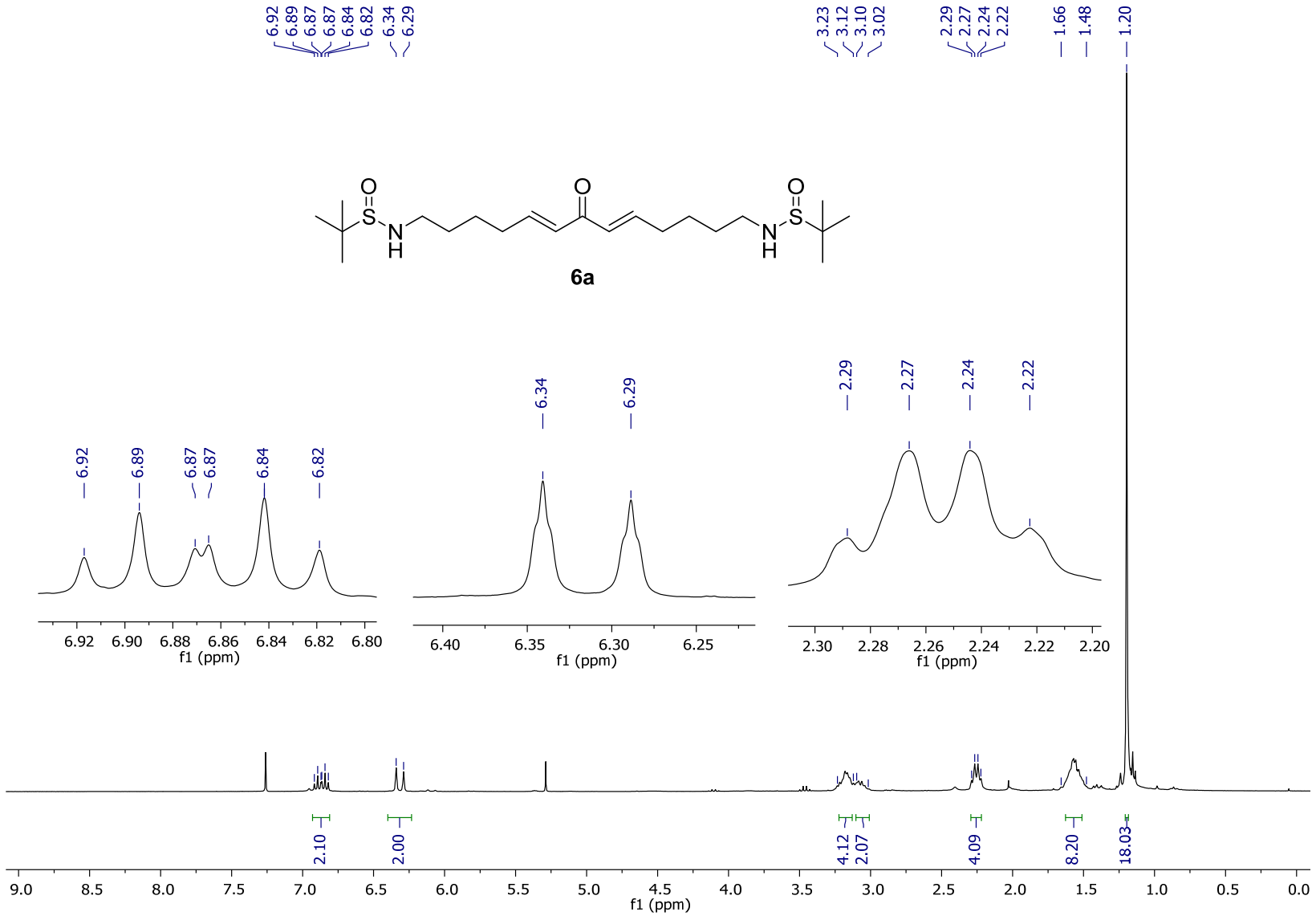
148.1
135.0
128.6
128.5
55.7
45.4
32.3
30.6
25.3
22.6
O
O
S
N
H
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

7a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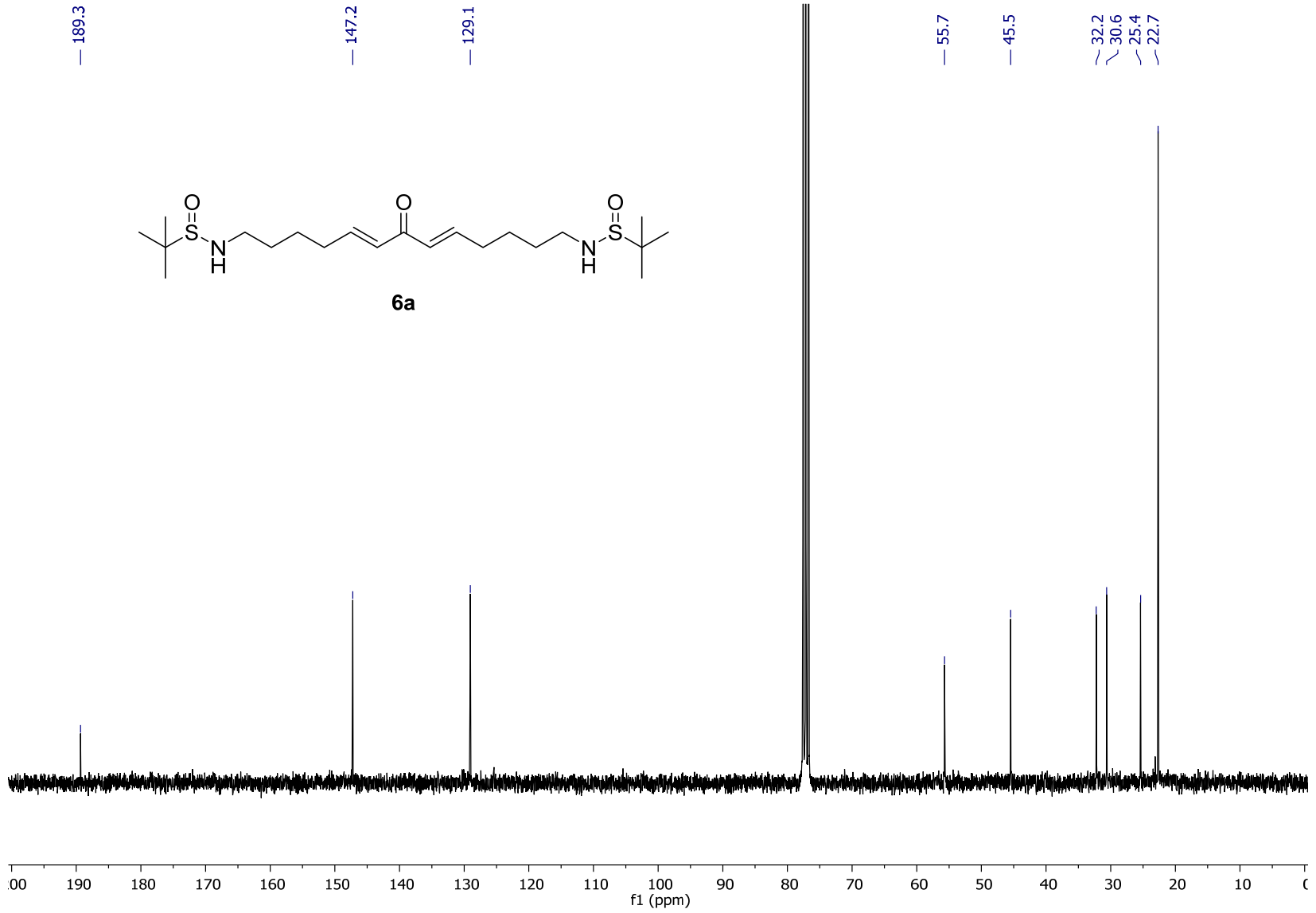
3.23
3.12
3.10
3.02
2.29
2.27
2.24
2.22
1.66
1.48
1.20
6a
f1 (ppm)
2.10
2.00
4.12
2.07
4.09
8.20
18.03


189.3
147.2
129.1
55.7
45.5
32.2
30.6
25.4
22.7
O
S
N
H
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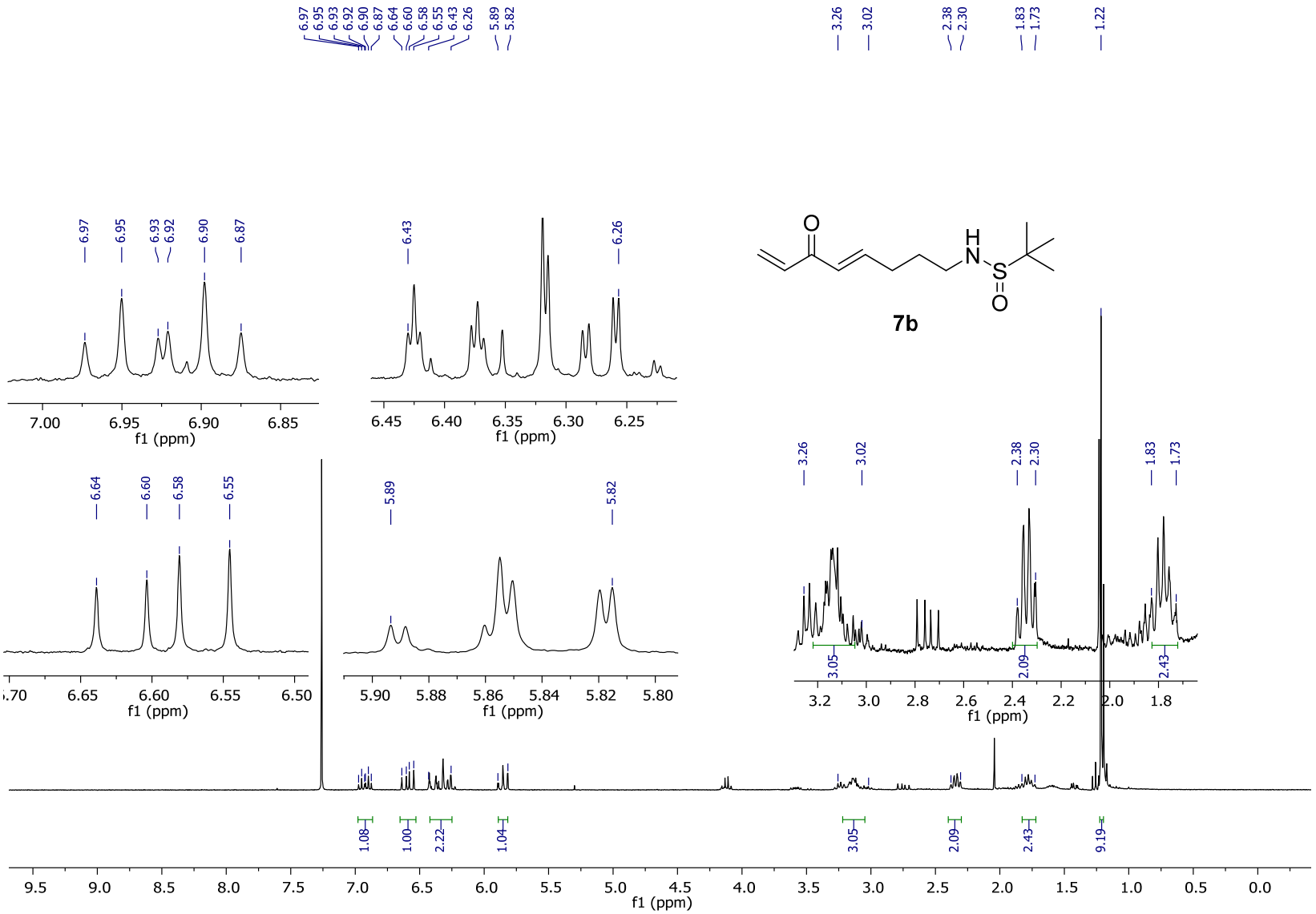
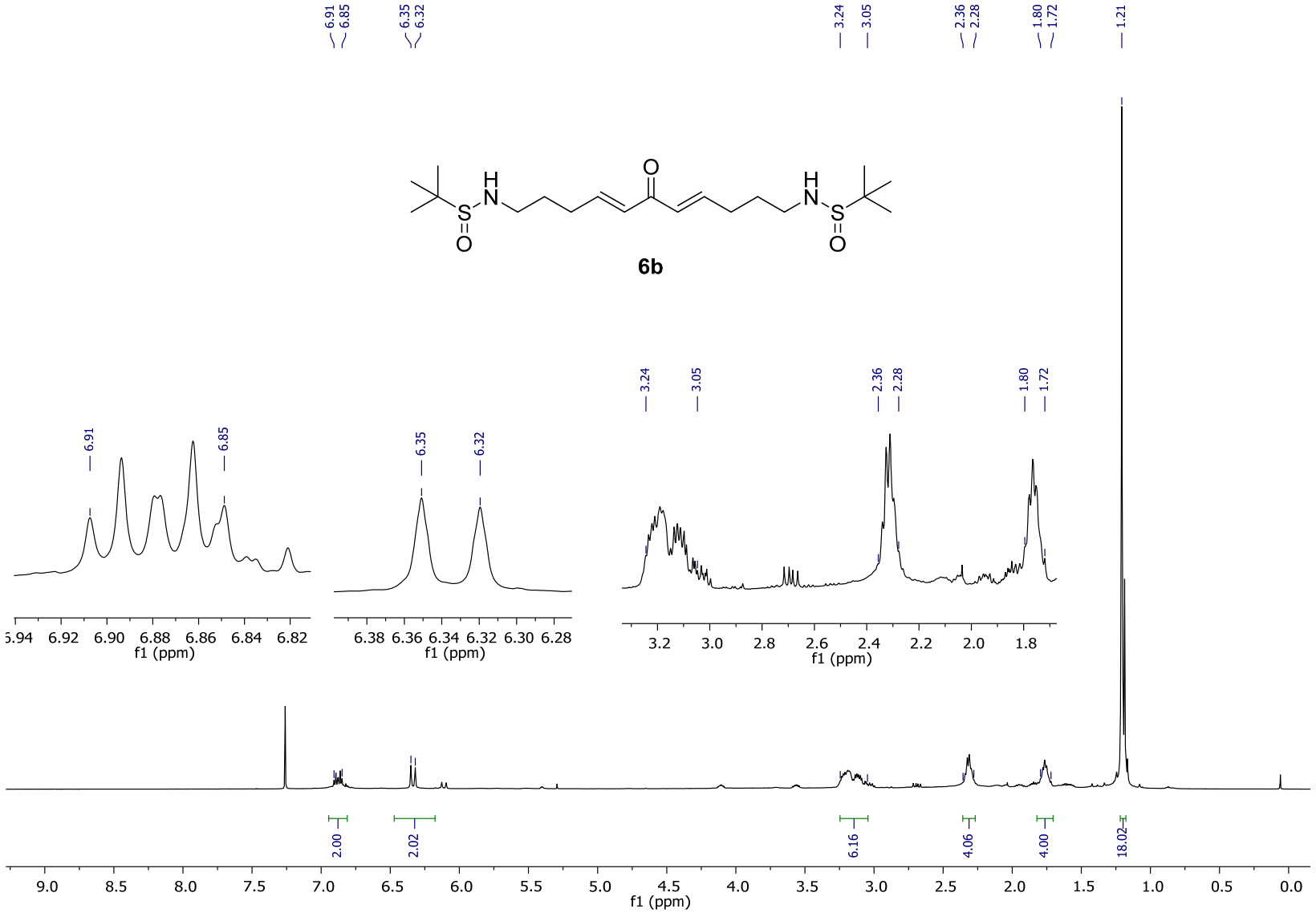
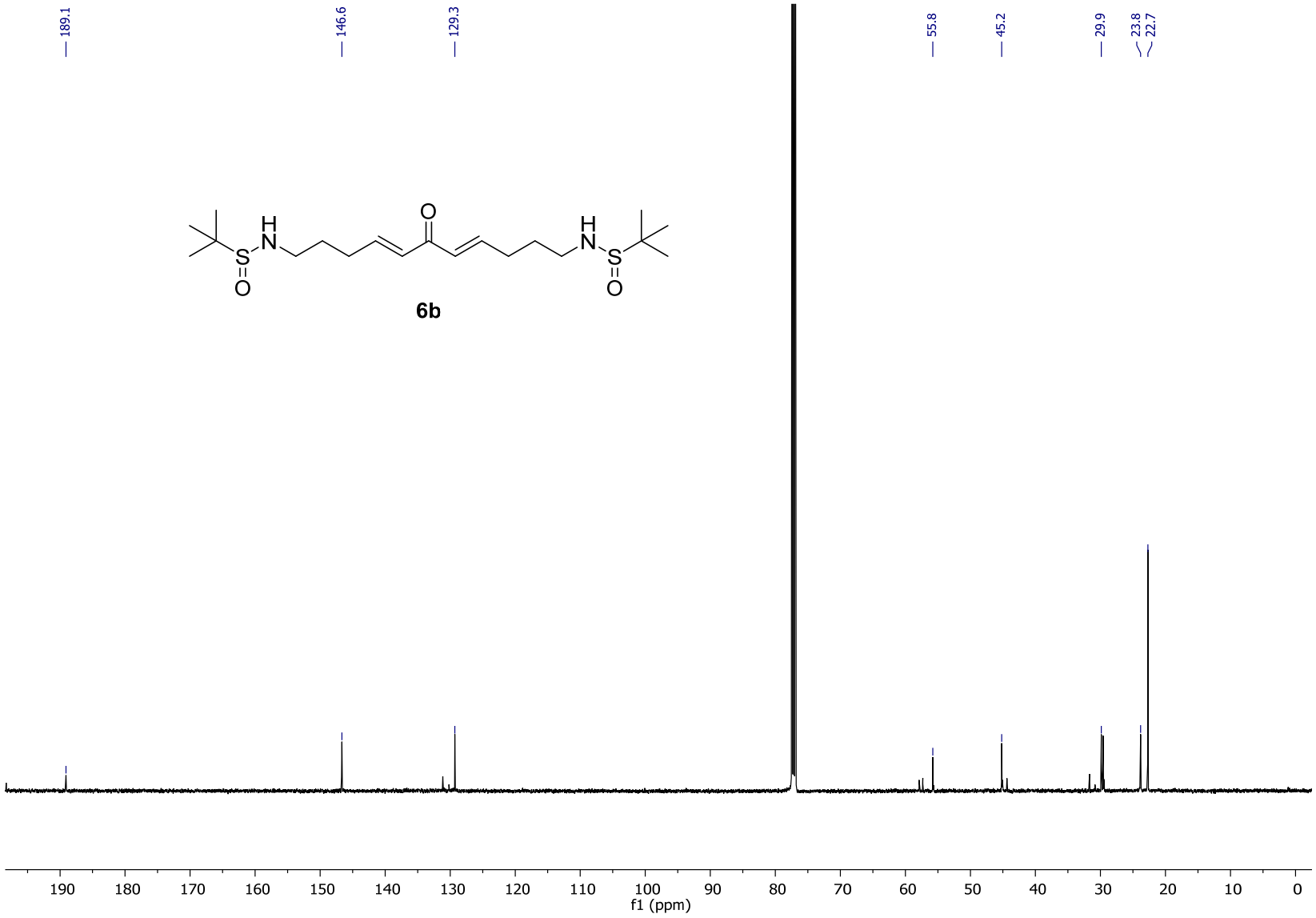
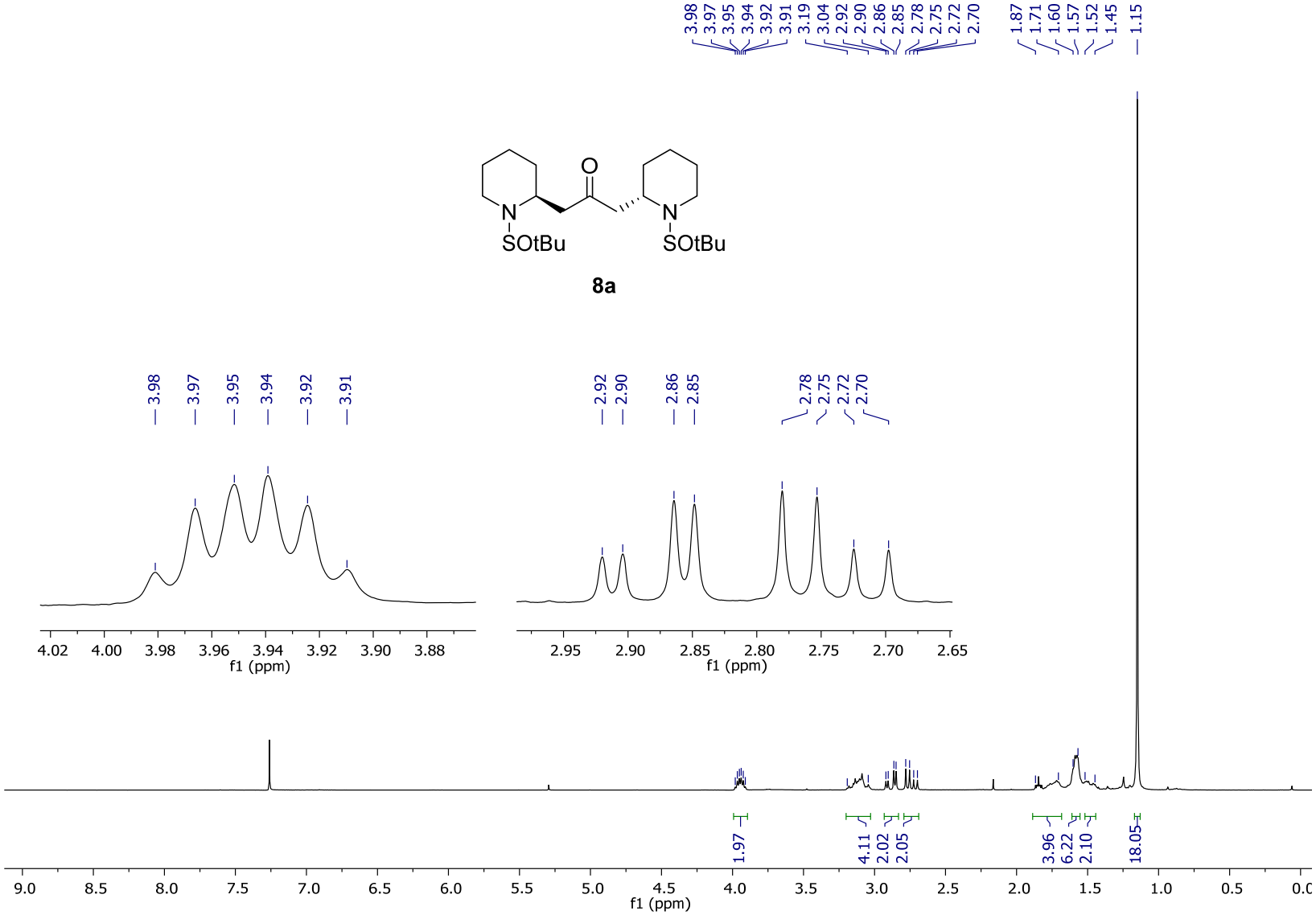
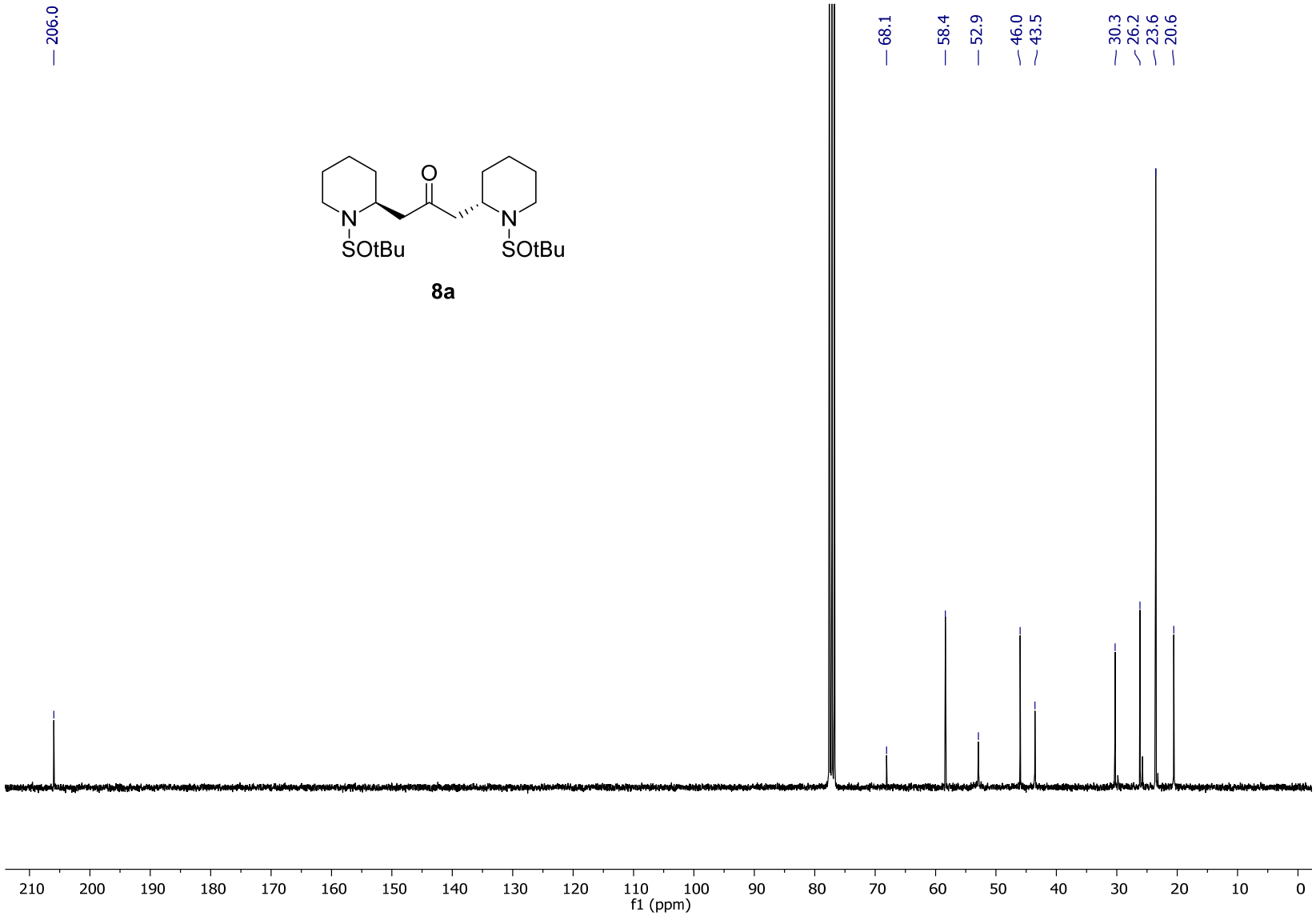
O
S
N
H
6a
f1 (ppm)

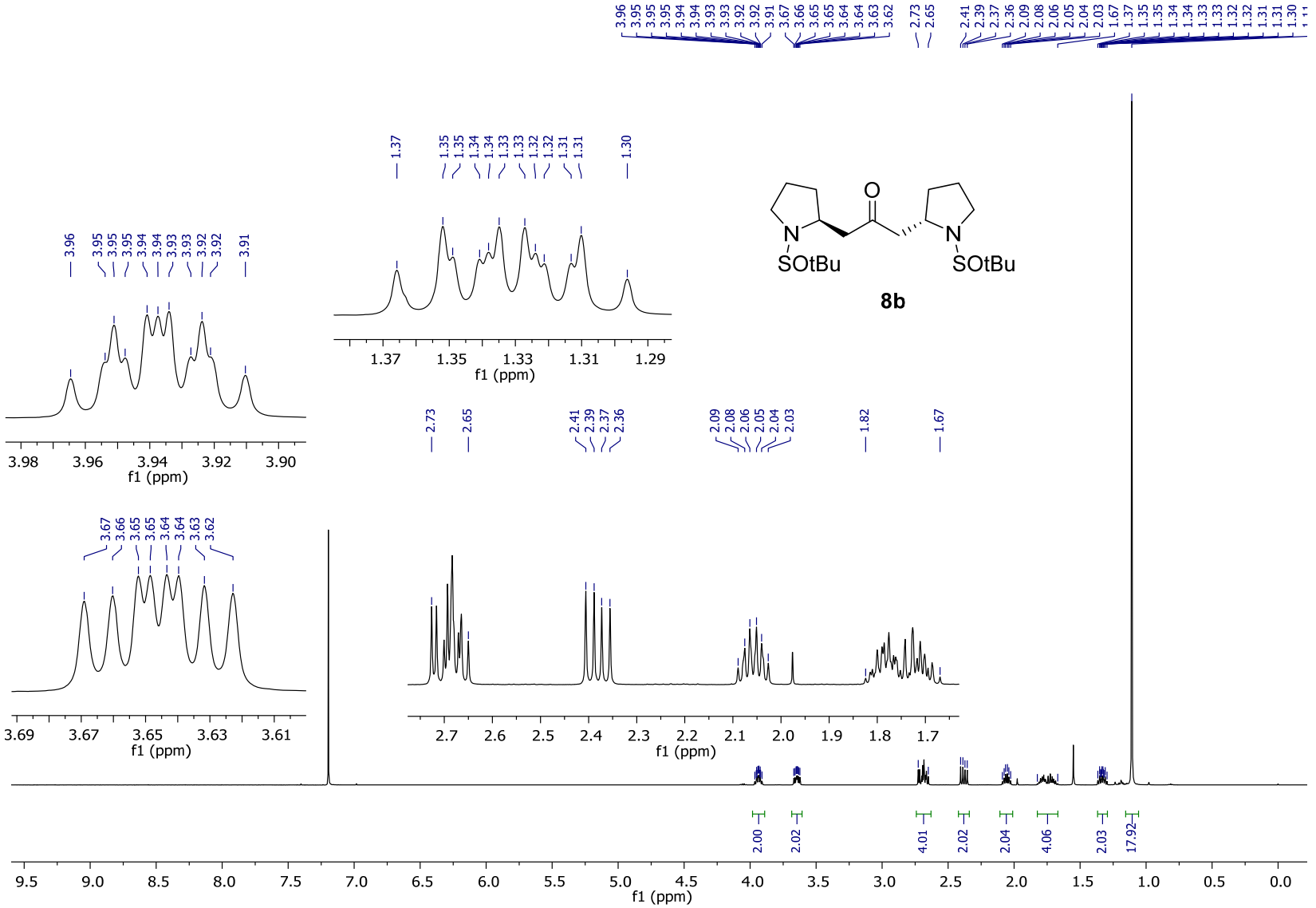

6.97
6.95
6.93
6.92
6.90
6.87
6.64
6.60
6.58
6.55
6.43
6.26
5.89
5.82
3.26
3.02
2.38
2.30
1.83
1.73
1.22
O
H
N
S
O=O
7b
f1 (ppm)
1.08
1.00
2.22
1.04
3.05
2.09
2.43
9.19

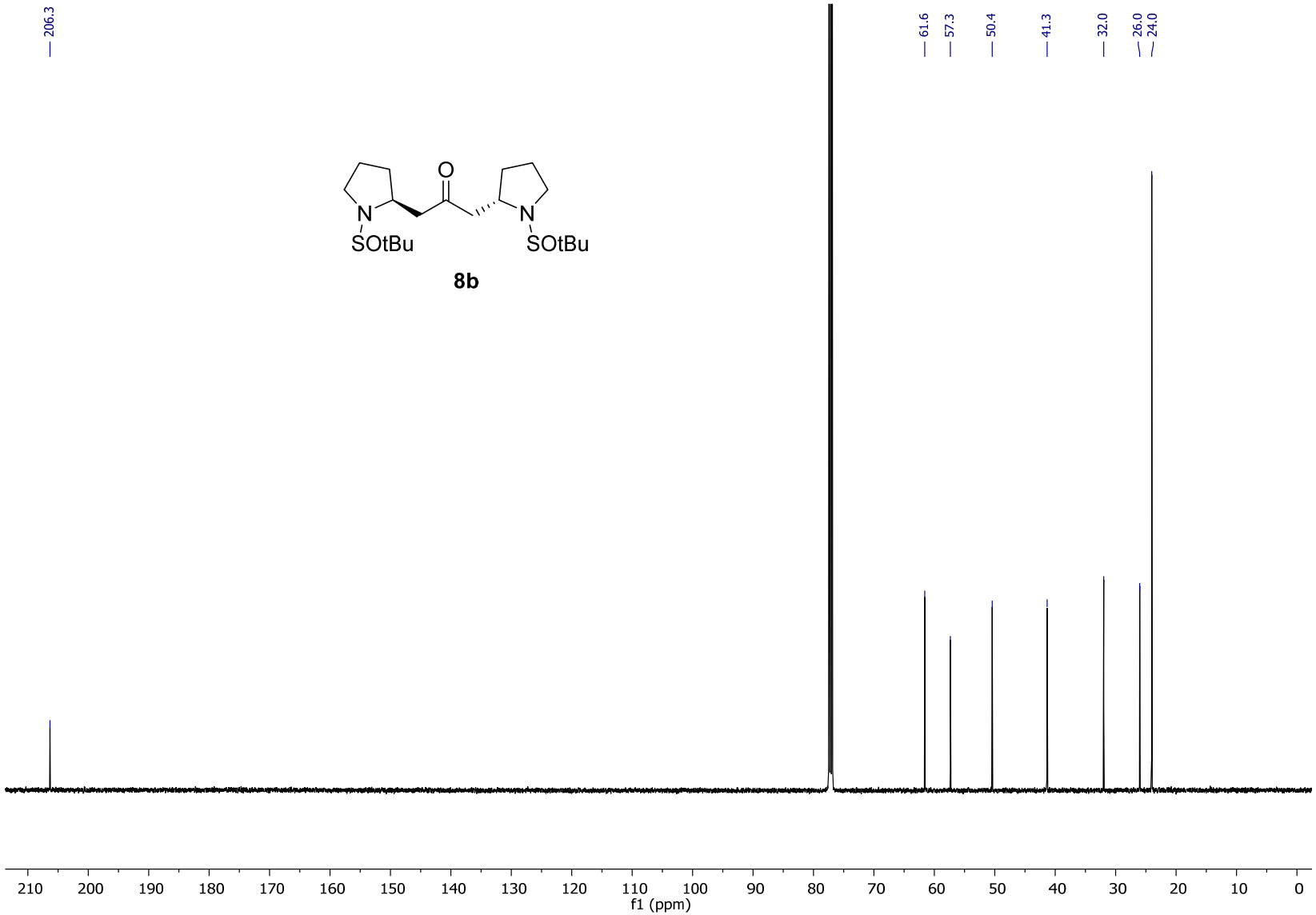

6.91
6.85
6.35
6.32
3.24
3.05
2.36
2.28
1.80
1.72
1.21
6b
f1 (ppm)
2.00
2.02
6.16
4.06
4.00
18.02

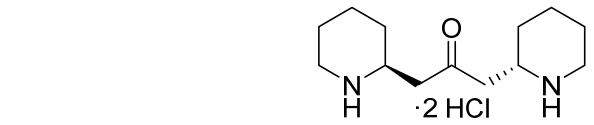

189.1
146.6
129.3
55.8
45.2
29.9
23.8
22.7
O
H
N
S
O
H
N
S
O
6b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


3.98
3.97
3.95
3.94
3.92
3.91
3.19
3.04
2.92
2.90
2.86
2.85
2.78
2.75
2.72
2.70
1.87
1.71
1.60
1.57
1.52
1.45
1.15
O
N
SOtBu
N
SOtBu
8a
f1 (ppm)
f1 (ppm)
1.97
4.11
2.02
2.05
3.96
6.22
2.10
18.05
f1 (ppm)


206.0
68.1
58.4
52.9
46.0
43.5
30.3
26.2
23.6
20.6
O
N
SOtBu
N
SOtBu
8a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

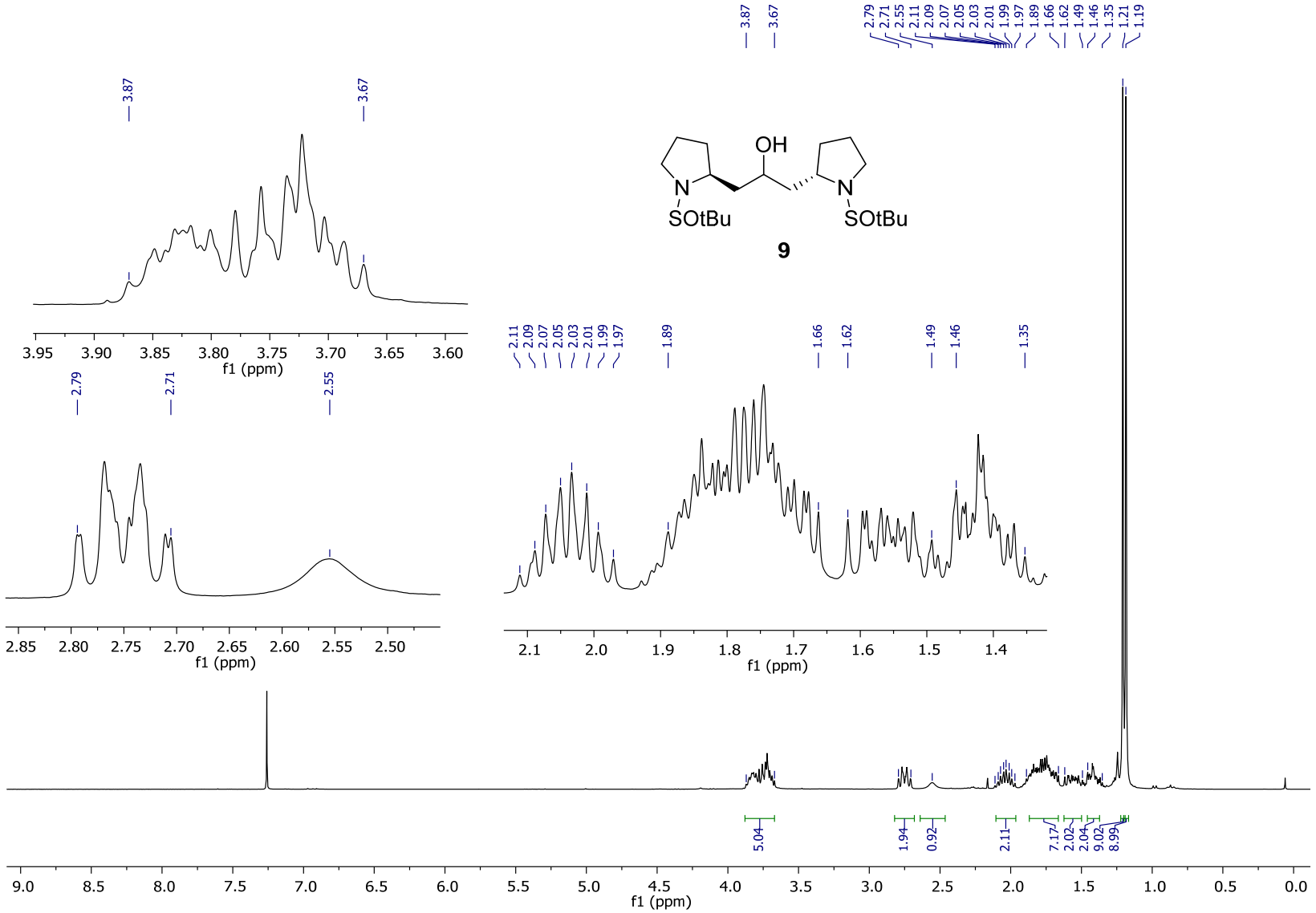

3.96 3.95 3.95 3.95 3.94 3.94 3.93 3.93 3.92 3.92 3.91 3.67 3.66 3.65 3.65 3.64 3.64 3.63 3.62 2.73 2.65 2.41 2.39 2.37 2.36 2.09 2.08 2.06 2.05 2.04 2.03 1.67 1.37 1.35 1.35 1.34 1.34 1.33 1.33 1.32 1.32 1.31 1.31 1.30
O
N
SOtBu
N
SOtBu
8b
f1 (ppm)
2.00 2.02 4.01 2.02 2.04 4.06 2.03 17.92

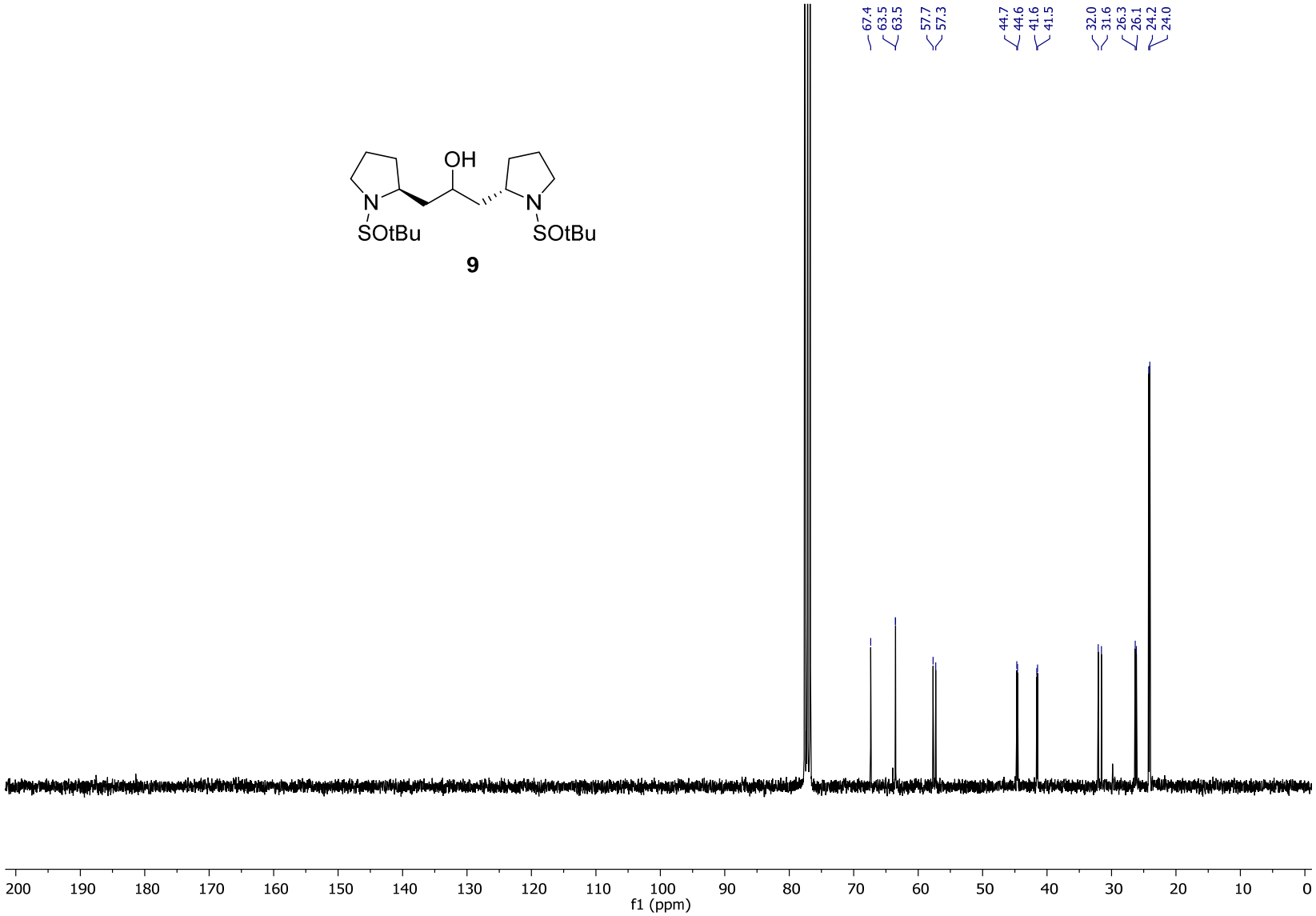

206.3
61.6
57.3
50.4
41.3
32.0
26.0
24.0
O
N
SOtBu
N
SOtBu
8b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

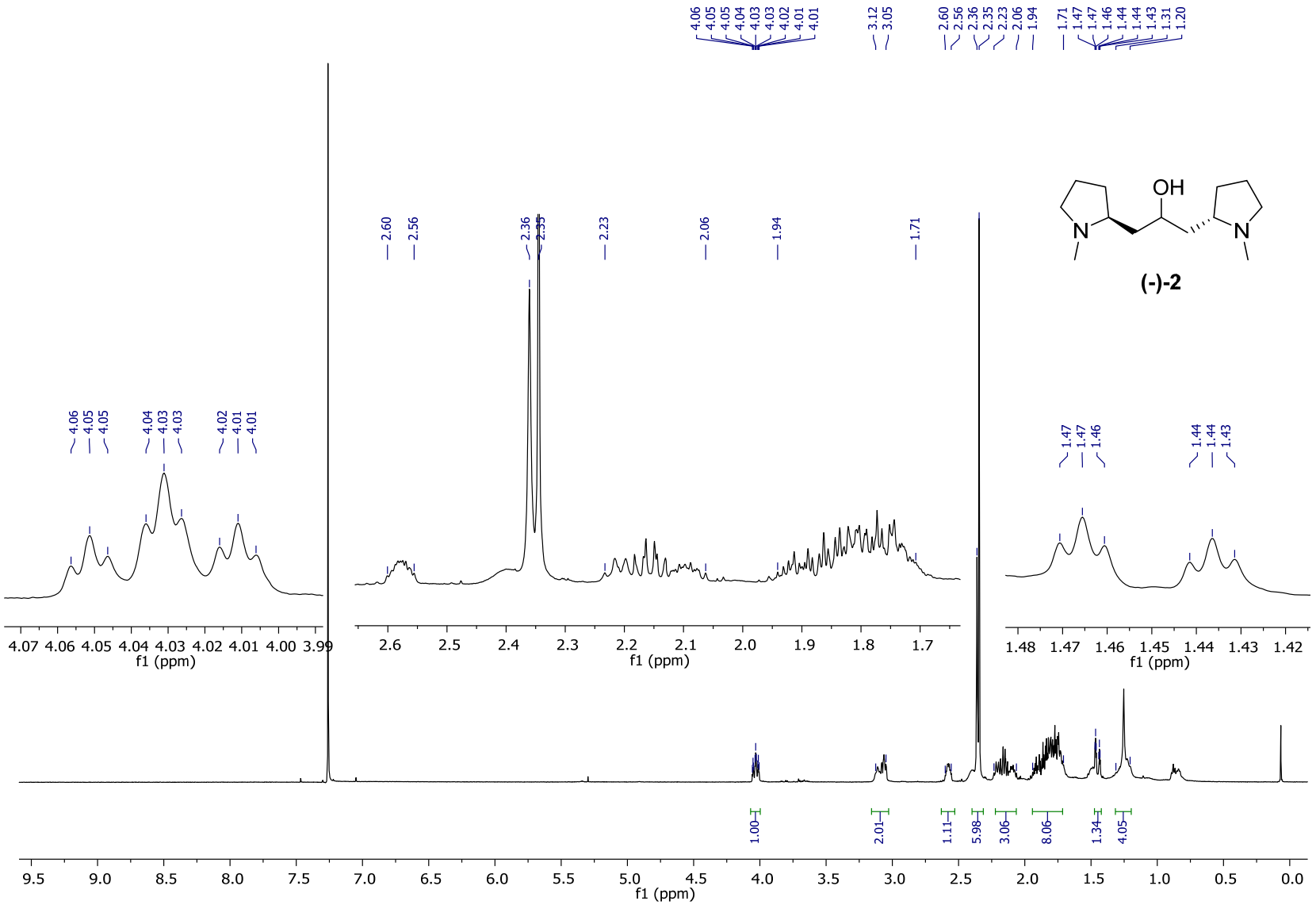

O
N
H
·2 HCl
N
H

(+)-1

3.57
3.41
3.35
3.08
2.97
1.96
1.87
1.76
1.53
2.01
2.07
5.90
6.01
6.10
f1 (ppm)


3.87
3.67
2.79
2.71
2.55
2.11
2.09
2.07
2.05
2.03
2.01
1.99
1.97
1.89
1.66
1.62
1.49
1.46
1.35
1.21
1.19
OH
N
SOtBu
N
SOtBu
9
f1 (ppm)
5.04
1.94
0.92
2.11
7.17
2.02
2.04
9.02
8.99


OH
N
SOtBu
N
SOtBu
9
67.4
63.5
63.5
57.7
57.3
44.7
44.6
41.6
41.5
32.0
31.6
26.3
26.1
24.2
24.0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


4.06 4.05 4.05 4.04 4.03 4.03 4.02 4.01 4.01 3.12 3.05 2.60 2.56 2.36 2.35 2.23 2.06 1.94 1.71 1.47 1.47 1.46 1.44 1.44 1.43 1.31 1.20
OH
N
N
(-)-2
4.07 4.06 4.05 4.04 4.03 4.02 4.01 4.00 3.99
f1 (ppm)
2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7
f1 (ppm)
1.48 1.47 1.46 1.45 1.44 1.43 1.42
f1 (ppm)
1.00 2.01 1.11 5.98 3.06 8.06 1.34 4.05
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)