Electronic Supporting Information (ESI)

A Formal [3+3]-Annulation-based Approach to Pancratistatins: Total Synthesis of (+/-)-7-Deoxy-pancratistatin and its 2-*epi* and 2,4-di-*epi* analogues

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Contents:

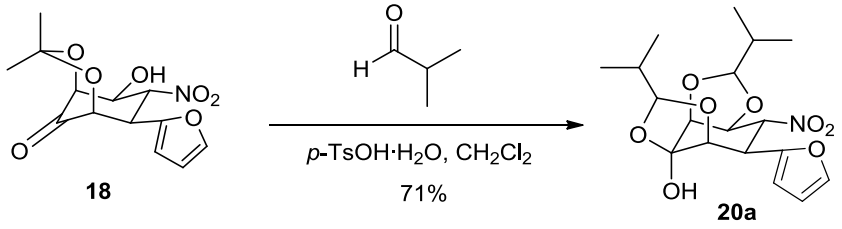
General Remarks

Solvents for moisture-sensitive reactions were distilled and dried according to standard procedures. Anhydrous Na_2SO_4 was used to dry organic solutions during workups. Reagents were purchased in the highest available commercial quality and used as supplied except where noted. Reactions were monitored by TLC with pre-coated silica gel 60 F254 aluminum plates (Merck KGaA, Darmstadt) using UV light as the visualizing agent and by dipping the plate into a solution of $(NH_4)_6Mo_7O_{24}.4\,H_2O$ (12.5 g) and $Ce(SO_4)_2.4\,H_2O$ (5 g) in 10% aqueous H_2SO_4 (500 mL), followed by heating. Flash column chromatography was performed with silica gel (0.035-0.070 mm, 60 Å) from Merck. Concentrations were carried out in a rotary evaporator. ^1H, ^{13}C, DEPT and 2D NMR were recorded using either Bruker DPX-250, AMX-300 and WM-500 spectrometers, or Varian Mercury 300 and Inova 400 spectrometers, as indicated; chemical shifts are reported in ppm and coupling constants in Hz; multiplicities are given as follows: s (singlet), br s (broad singlet), br d (broad doublet), d (doublet), t (triplet), and m (multiplet). Mass spectra were recorded on Micromass Autospec, TRACE MS and HP-5988-A spectrometers using Electronic Impact (EI, 70 eV), Electrospray (ESI) or Chemical Ionization (CI). IR spectra were recorded on BIO RAD FTS135 and MATTSON CYGNUS-100 spectrometers. Melting points were determined on a Büchi apparatus (Dr. Tottoli, Flawil, Switzerland).

Experimental procedures

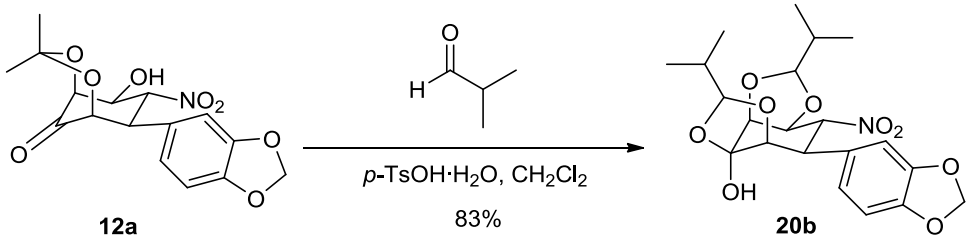
***Re* face-Reduction at C2: MODEL STUDIES on 18 and PRELIMINARY STUDIES with 12a**

Nitrocompound (+/-)-20a.



Isobutyraldehyde (550 µL, 6.05 mmol) and *p*-TsOH·H_2O (13 mg, 0.07 mmol) were added to a solution of **18**[1] (100 mg, 0.34 mmol), in dry CH_2Cl_2 (2.5 mL) under argon. After stirring for 1.5 h at rt, the pH of the mixture was adjusted to 7 by adding Et_3N and the volatiles were evaporated in vacuo. Chromatography (silica gel, 15% EtOAc/hexane) gave **20a** (91 mg, 71%) as a yellow oil: R_f = 0.44 (30% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33 (dd, J = 1.8, 0.8 Hz, 1H), 6.37-6.29 (m, 2H), 5.21 (dd, J = 12.5, 7.7 Hz, 1H), 4.98 (d, J = 5.3 Hz, 1H), 4.80-4.72 (m, 2H), 4.39 (d, J = 8.2 Hz, 1H), 3.34 (d, J = 3.4 Hz, 1H), 3.59 (dd, J = 12.5, 3.4 Hz, 1H), 3.28 (s, 1H), 2.05-1.92 (m, 2H), 1.10-0.96 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 147.3, 142.6, 110.8, 110.2, 109.4, 107.3, 101.8, 85.0, 80.4, 77.6, 76.6, 40.6, 31.6, 31.6, 17.3, 17.3, 17.1, 17.0; LRMS (CI) m/z (%): 384.2 [$(M+H)^+$, 5], 366.2 (25), 193.0 (100); HRMS [CI, $(M+H)^+$] m/z: calc. for ($C_{18}H_{26}NO_8$): 384.1658, found: 384.1658.

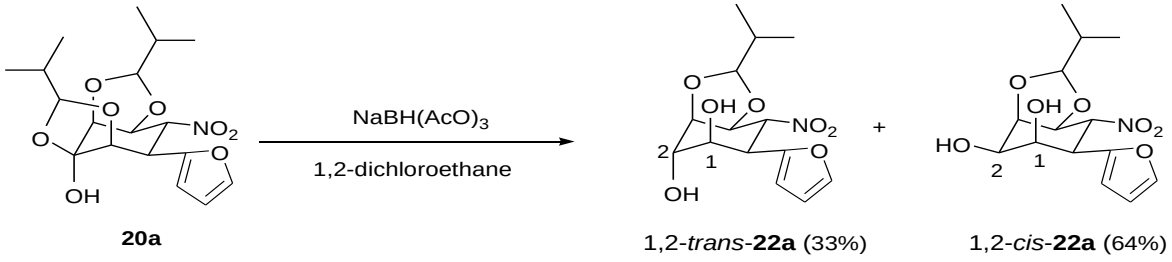
Nitrocompound (+/-)-20b.



[1] A multigram-scale detailed preparation of **18** from furfural, including a timetable, is described in the experimental section and the supporting information of: F. Cagide-Fagin and R. Alonso, *Eur. J. Org. Chem.*, 2010, **35**, 6741-6747.

Treatment of **12a**[2] (300 mg, 0.85 mmol) under the same conditions reported to convert **18** into **20a**, afforded **20b** (310 mg, 83%) as a white solid: R_f = 0.43 (30% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.80 (d, *J* = 1.6 Hz, 1H), 6.77-6.61 (m, 2H), 5.93 (s, 2H), 5.27 (dd, *J* = 12.5, 7.5 Hz, 1H), 4.95 (d, *J* = 5.5 Hz, 1H), 4.85-4.68 (m, 2H), 4.42 (d, *J* = 8.1 Hz, 1H), 4.20 (d, *J* = 3.2 Hz, 1H), 3.25 (dd, *J* = 12.5, 3.2 Hz, 2H**),** 2.06-1.94 (m, 2H), 1.10-0.97 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 147.8 (2C), 127.0, 123.0, 110.2, 109.5, 108.4, 107.3, 101.9, 101.3, 86.2, 82.2, 78.2, 77.0, 46.2, 31.7, 31.6, 17.5, 17.3 (2C), 17.0; LRMS (CI) m/z (%): 437.2 (M^+, 3); HRMS (CI, M^+) m/z: calc. for ($C_{21}H_{27}NO_9$): 438.1764, found: 438.1761.

Diols (+/-)-22a.



20a 1,2-*trans*-**22a** (33%) 1,2-*cis*-**22a** (64%)

A solution of **20a** (100 mg, 0.26 mmol) in dry 1,2-dichloroethane (1 mL) was added to a solution of $NaBH(AcO)_3$ (221 mg, 1.04 mmol) in the same solvent (4 mL) under argon. After stirring for 24 h at 45 ˚C, the solution was quenched with 30% aqueous hydrogen peroxide (106 µL), neutralized with 5% aqueous KOH (pH = 7) and extracted with CH_2Cl_2 (3 x 1 mL). Chromatography (20% EtOAc/hexane) afforded 1,2-*trans*-**22a** [27 mg, 33%, R_f = 0.30 (40% EtOAc/hexane)] and 1,2-*cis*-**22a** [52.65 mg, 64%, R_f = 0.23 (40% EtOAc/hexane)] as white solids.

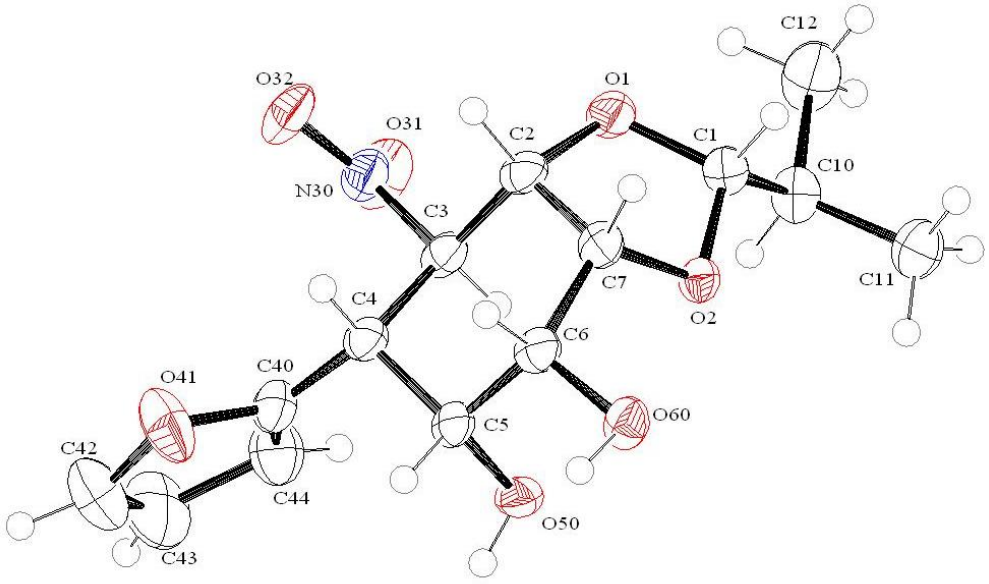
1,2-*trans*-**22a**: ^{1}H NMR ($CDCl_3$, 250 MHz) *δ*: 7.39 (d, *J* = 1.0 Hz, 1H), 6.38 – 6.22 (m, 2H), 5.06 (dd, *J* = 12.2, 8.5 Hz, 1H), 4.85-4.72 (m, 2H), 4.52-4.38 (m, 1H), 4.33-4.22 (m, 1H), 4.20-4.12 (m, 1H), 3.84 (dd, *J* = 12.2, 2.7 Hz, 1H), 2.45 (d, *J* = 5.4 Hz, 1H), 2.20 (m, 1H), 2.02-1.85 (m, 1H), 1.07-0.97 (m, 6H); ^{13}C

[2] A detailed preparation procedure and full characterization data for **12a** can be found in: J. C. Ortiz, L. Ozores, F. Cagide-Fagin and R. Alonso, *Chem. Comm.*, 2006, 4239-4241

NMR ($CDCl_3$, 100 MHz) δ: 143.0, 110.8, 109.7, 109.0, 88.0, 79.9, 75.0, 72.4, 68.5, 39.3, 32.1, 17.0, 16.7; LRMS (CI) m/z (%): 314.2 [$(M+H)^+$, 40], 267.2 (27), 249.2 (11); HRMS [CI, $(M+H)^+$] m/z: calc. for ($C_{14}H_{20}NO_7$): 314.1239, found: 314.1227.

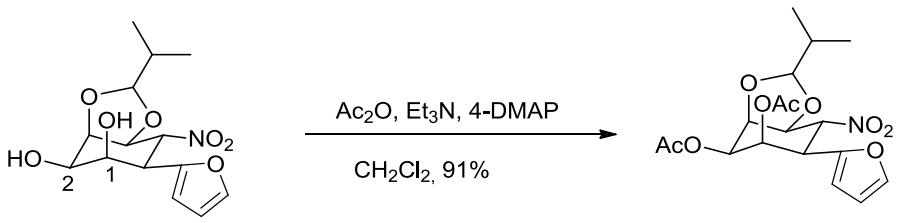
1,2-*cis*-**22a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36 (dd, J = 4.9, 4.3 Hz, 1H), 6.37-6.23 (m, 2H), 5.07 (dd, J = 12.6, 8.3 Hz, 1H), 4.82 (d, J = 4.5 Hz, 1H), 4.64 (dd, J = 8.3, 5.5 Hz, 1H), 4.43 (t, J = 5.5 Hz, 1H), 4.32-4.24 (m, 1H), 4.08-3.97 (m, 1H), 3.36 (dd, J = 12.6, 1.6 Hz, 1H), 3.01 (d, J = 8.1 Hz, 1H), 2.61 (d, J = 4.6 Hz, 1H), 2.02-1.91 (m, 1H), 1.07-0.9; (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 149.1, 142.8, 110.6, 109.9, 108.5, 87.0, 78.1, 75.9, 71.1, 68.4, 41.6, 31.9, 16.9, 16.5; LRMS (CI) m/z (%): 314.2 [$(M+H)^+$, 100], 267.2 (40), 249.2 (37); HRMS [CI, $(M+H)^+$] m/z: calc. for ($C_{14}H_{20}NO_7$): 314.1239, found: 314.1239.

X Ray for 1,2-*cis*-**22a**



Compound reference	1,2-*cis*-**22a**	Temperature/K	90(2)
Chemical formula	$C_{14}H_{19}NO_7$	Space group	$P1,^{-}$
Formula Mass	313.30	No. of formula units per unit cell, Z	2
Crystal system	Triclinic	No. of reflections measured	8754
a/Å	13.063(2)	No. of independent reflections	8754
b/Å	13.707(2)	R_{int}	0.0000
c/Å	13.950(2)	Final R_1 values ($I > 2\sigma(I)$)	0.0501
α/°	99.713(2)	Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.1423
β/°	99.524(2)	Final R_1 values (all data)	0.1024
γ/°	99.393(2)	Final $wR(F^2)$ values (all data)	0.1755
Unit cell volume/Å^3	2380.8(7)		

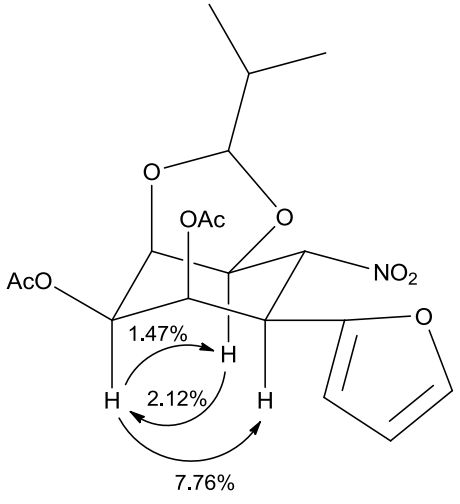
Acetate (+/-)-23.



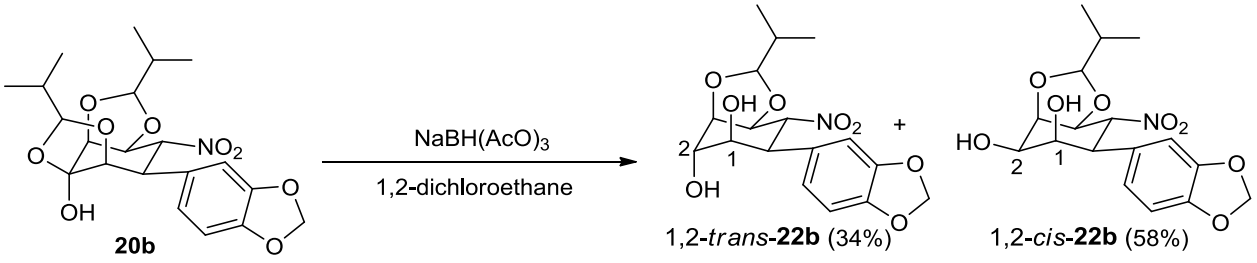
1,2-*cis*-**22a** 1,2-*cis*-**23**

To a solution of the diol 1,2-*cis*-**22a** (10 mg, 0.032 mmol) in dry CH_2Cl_2 (1 mL) under argon, Et_3N (22 μL, 0.16 mmol), Ac_2O (7.5 μL, 0.080 mmol) and 4-DMAP (1 mg, 0.006 mmol) were added. After stirring for 30 min at rt, the solution was neutralized with 0.1 M $HCl_{(aq)}$ (0.8 mL) and extracted (CH_2Cl_2, 3 x 1 mL). Chromatography (30% EtOAc/hexane) gave 1,2-*cis*-**23** (11 mg, 91%) as a yellow solid: R_f = 0.38 (30% EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.31 (dd, J = 1.8, 0.8 Hz, 1H), 6.26 (dd, J = 3.3, 1.8 Hz, 1H), 6.16 (dd, J = 3.3, 0.8 Hz, 1H), 5.56-5.53 (m, 1H), 5.36-5.25 (m, 1H), 5.11 (dd, J = 12.6, 8.4 Hz, 1H), 4.88 (d, J = 3.9 Hz, 1H), 4.67 (dd, J = 8.4, 5.4 Hz, 1H), 4.46-4.37 (m, 1H), 3.63 (dd, J = 12.6, 2.3 Hz, 1H), 2.11 (s, 3H), 2.09-2.00 (m, 4H), 1.13-103 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.1, 169.6, 147.5, 143.2, 110.6, 110.4, 108.6, 87.1, 76.0, 75.9, 68.6, 68.0, 40.0, 31.8, 20.8 (2C), 17.0, 16.3; LRMS (EI) m/z (%): 398.3 [$(M+H)^+$, 3].

Selected NOE data for 1,2-*cis*-**23**

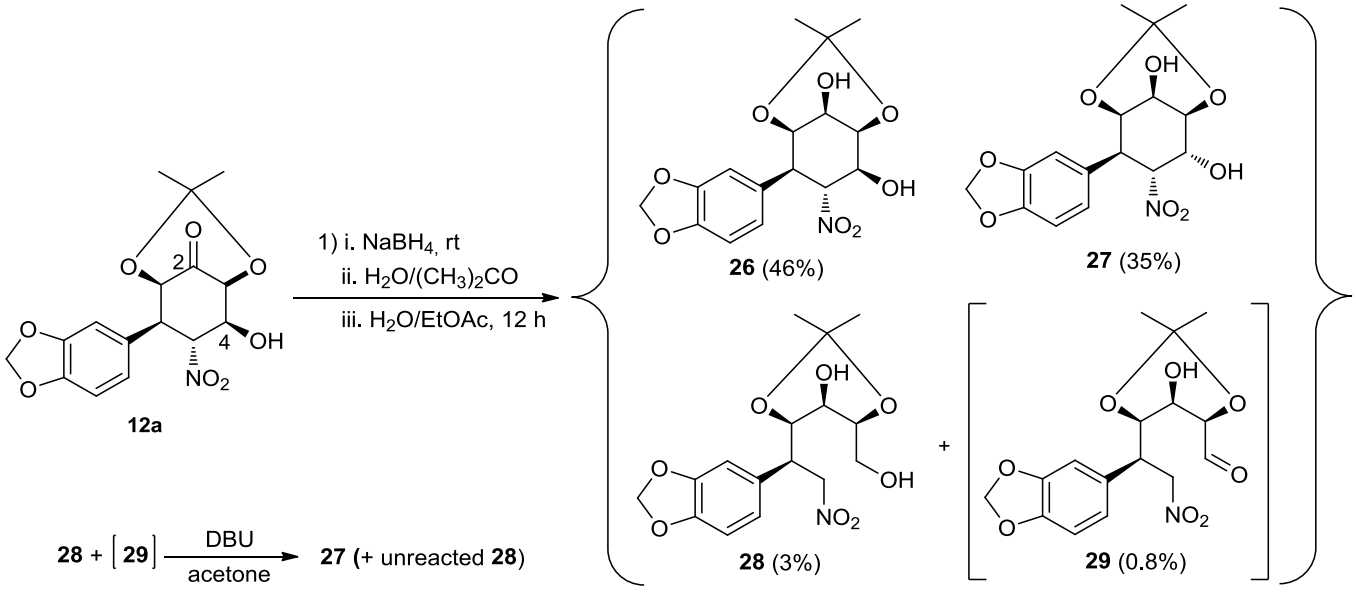


Diols (+/-)-22b.



Treatment of **20b** (30 mg, 0.07 mmol) with $NaBH(AcO)_3$, as reported for **20a**, afforded a mixture of 1,2-*trans*-**22b** (8.4 mg, 0.02 mmol, 34%) and 1,2-*cis*-**22b** (14.5 mg, 0.04 mmol, 58%). Yields were determined by ^1H NMR integration with 1,4-dichlorobenzene as internal standard. ^1H NMR ($CDCl_3$, 250 MHz) δ: 6.89 (s, $1H_{cis}$, $1H_{trans}$), 6.74 (s, $2H_{cis}$, $2H_{trans}$), 5.94 (s, $2H_{cis}$, $2H_{trans}$), 5.18-5.02 (m, $1H_{cis}$, $1H_{trans}$), 4.90-4.73 (m, $1H_{cis}$, $2H_{trans}$), 4.71-4.60 (m, $1H_{cis}$), 4.50-4.35 (m, $1H_{cis}$, $1H_{trans}$), 4.31-4.24 (m, $1H_{trans}$), 4.04 (br s, $2H_{cis}$), 3.95 (br s, $1H_{trans}$), 3.52 (dd, J = 12.7, 2.0 Hz, $1H_{trans}$), 3.02 (br d, J = 12.6 Hz, $1H_{cis}$), 2.08-1.88 (m, $1H_{cis}$, $1H_{trans}$), 1.11-0.97 (m, $6H_{cis}$, $6H_{trans}$).

Diols (+/-)-26-28.



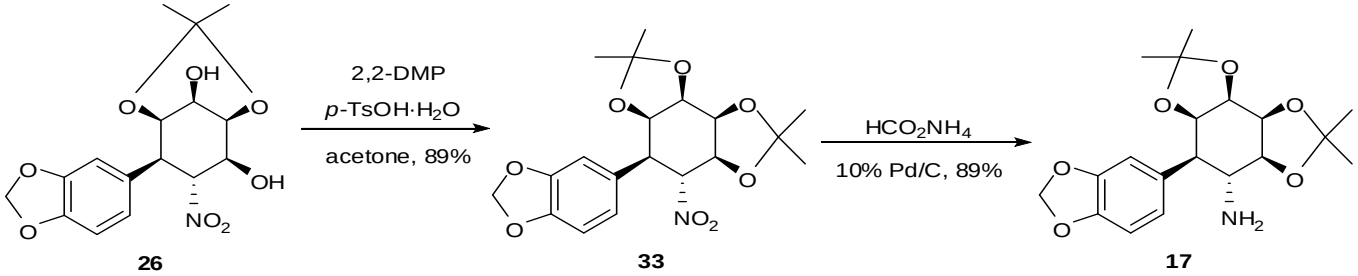
$NaBH_4$ (300 mg, 7.94 mmol) was added to a solution of **12a** (2.59 g, 7.38 mmol) in MeOH (50 mL) under argon and the mixture stirred for 15 min. A solution of H_2O/acetone (8:2, 50 mL) was then added. After stirring for 30 min, the volatiles were evaporated under vacuum, the crude dissolved in H_2O/EtOAc (1:1,

100 mL), and the mixture stirred for 12 h at rt and extracted with EtOAc (3 x 30 mL). Chromatography (50% EtOAc/hexane) afforded **26** (1,195 g, 3.39 mmol, 46%, R_f = 0.36) and **27** (0.916 g, 2.59 mmol, 35%, R_f = 0.5) as white solids, and a mixture of **28** and putative aldehyde **29** (0.104 g, R_f = 0.28) in a 3:0.8 ratio. A mixture of **28** (10 mg, 0.03 mmol) and **29** (10 mg, 0.03 mmol) was dissolved in dry acetone (1 mL), treated with DBU (10 µL, 0.07 mmol), stirred for 40 min, quenched with a saturated aqueous solution of NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). Chromatography (50% EtOAc/hexane) afforded **27** (10 mg, 100% from **29**) and unreacted **28** (10 mg) as white solids.

(+/-)-28: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (dd, J = 1.5, 0.7 Hz, 1H), 6.78-6.71 (m, 2H), 5.94 (s, 2H), 4.85 (dd, J = 13.0, 4.7 Hz, 1H), 4.62 (dd, J = 13.0, 9.5 Hz, 1H), 3.89 (dd, J = 9.5, 3.7 Hz, 1H), 3.80 (ddd, J = 9.5, 4.7, 3.5 Hz, 1H), 3.78-3.73 (m, 2H), 3.66 (td, J = 9.2, 3.7, 3.7 Hz, 1H), 3.50 (dt, J = 9.2, 4.6 Hz, 1H), 2.96 (d, J = 4.7 Hz, 1H), 2.49 (t, J = 5.2, 1H), 1.44 (s, 3H), 1.41 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 147.2, 132.0, 121.6, 108.5, 108.2, 101.1, 99.0, 77.0, 75.7, 73.2, 64.9, 62.4, 44.7, 29.0, 19.3.

Putative aldehyde intermediate (+/-)-29: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (s, 1H), 6.96-6.70 (m, 3H), 5.95 (s, 2H), 4.80 (dd, J = 13.1, 5.3 Hz, 1H), 4.69 (dd, J = 13.1, 9.5 Hz, 1H), 3.99 (d, J = 9.5 Hz, 1H), 3.93 (dd, J = 9.5, 2.9 Hz, 1H), 3.85 (ddd, J = 9.5, 5.3, 2.9 Hz, 1H), 3.53 (dt, J = 9.5, 9.5, 2.4 Hz, 1H), 2.82 (d, J = 2.4 Hz, 1H), 1.49 (s, 3H), 1.48 (s, 3H).

Amine (+/-)-17. B) From 12a in 3 steps (12a → 26 → 33 → 17) and 74% overall yield (Scheme 5) [3]

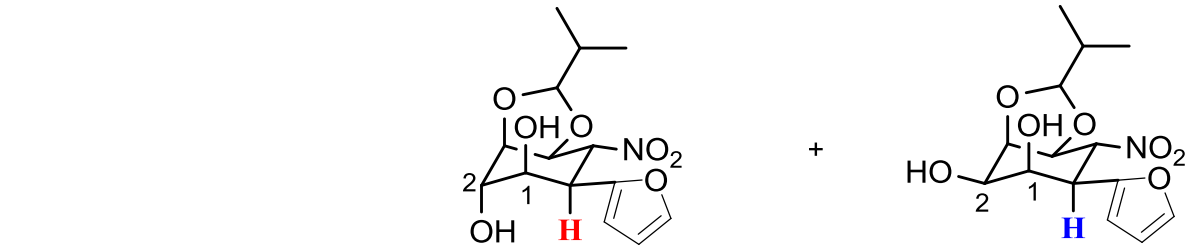


26 **33** **17**

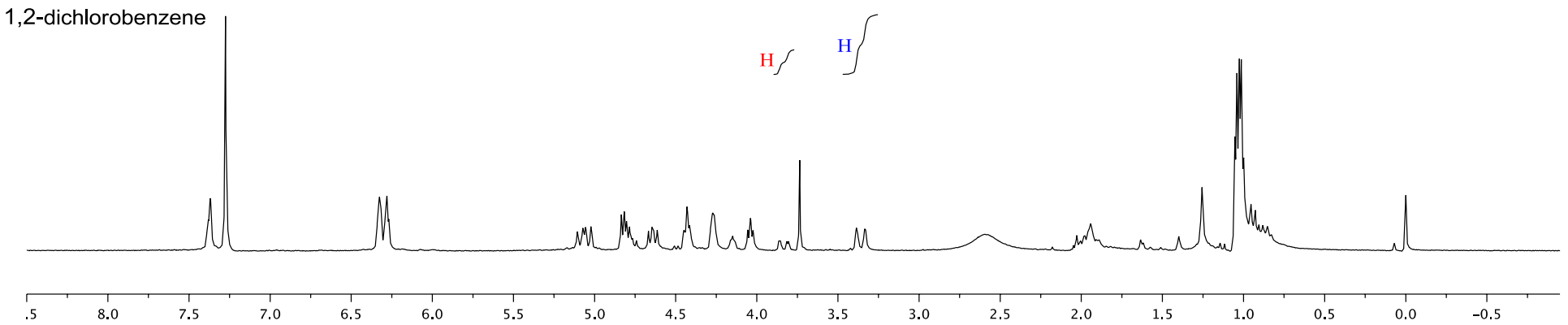
[3] Experimental details for the first step, the conversion of **12a** into **26**, are described in the experimental section of the article.

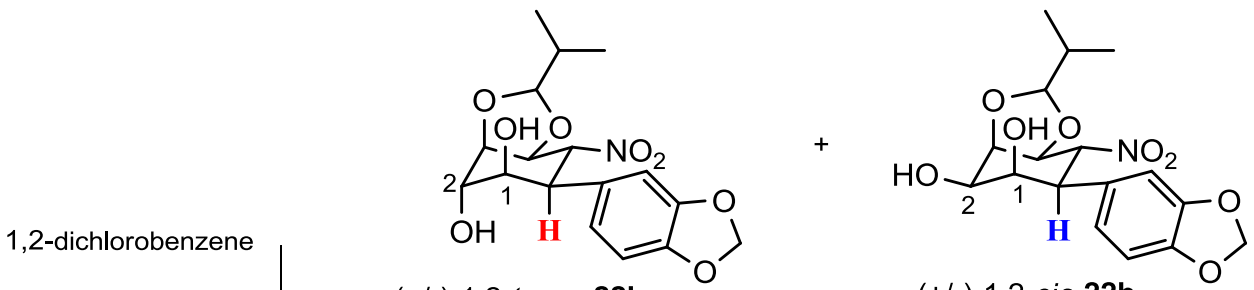
2,2-Dimethoxypropane (14 mL, 11.4 mmol) and *p*-TsOH.H_2O (544 mg, 2.86 mmol) were added to a solution of **26** (505 mg, 1.43 mmol) in distilled acetone (30 mL) at rt under argon. After stirring for 2 h, the pH was adjusted to 7 with a saturated aqueous solution of $NaHCO_3$ and Et_3N. Then, the solvent was partially concentrated and subsequently extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried and concentrated. Chromatography (silica gel, 20% EtOAc/hexane) afforded **33** (503 mg, 89%). Distilled MeOH (5 mL) was added to a mixture of **33** (223 mg, 0.57 mmol), 10% Pd/C (400 mg) and HCO_2NH_4 (429 mg, 6.80 mmol). The reaction mixture was stirred for 18 h and filtered over a Celite pad washing with MeOH (2 x 10 mL). Volatiles were completely removed in vacuo and the residue was purified by flash chromatography (silica gel, MeOH/EtOAc 1:9), which afforded **17** (185 mg, 89 %).

(+/-)-33: mp = 201-202 ºC (CH_2Cl_2/hexane); R_f = 0.54 (30% AcOEt/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.77 (s, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.26 (dd, *J* = 12.5, 7.5 Hz, 1H), 5.91 (s, 2H), 4.84 (t, *J* = 7.5 Hz, 1H), 4.60 (dd, *J* = 6.3, 4.3 Hz, 1H), 4.48 (dd, *J* = 7.5, 4.3 Hz, 1H), 4.41 (dd, *J* = 6.3, 2.8 Hz, 1H), 3.01 (dd, *J* = 12.5, 2.8 Hz, 1H), 1.62 (s, 3H), 1.57 (s, 3H), 1.36 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6, 147.5, 127.5, 122.7, 111.6, 109.7, 109.4, 108.2, 101.1, 87.1, 77.3, 75.6, 73.4, 73.0, 46.1, 26.2, 26.2, 25.5, 23.9; LRMS (ESI-TOF) m/z (%): 394.1507 (M+1, 21), 245.0772 (34), 177.0542 (51), 149.0241 (100); HRMS (ESI-TOF, M+1) m/z: calc. for ($C_{19}H_{24}NO_8$): 394.1496, found: 394.1507.

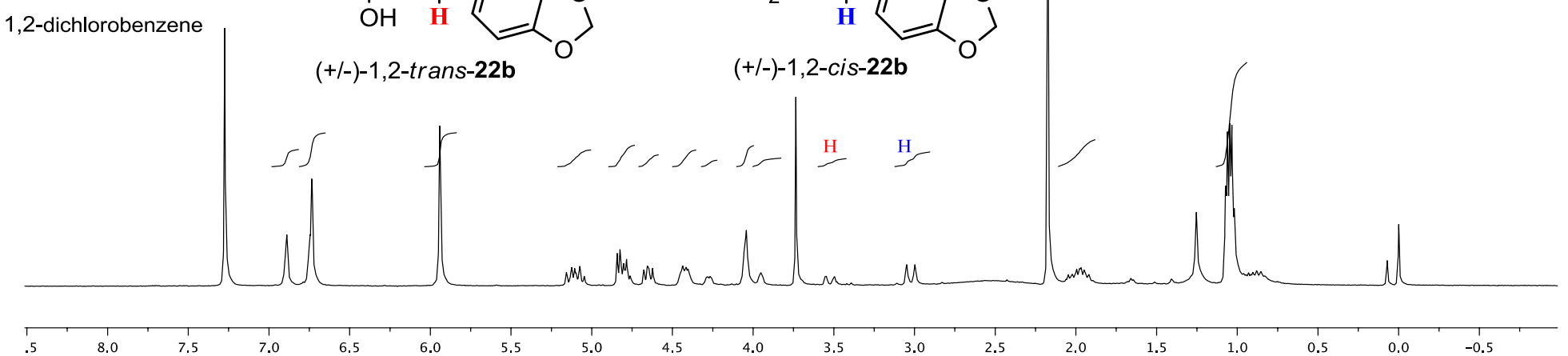


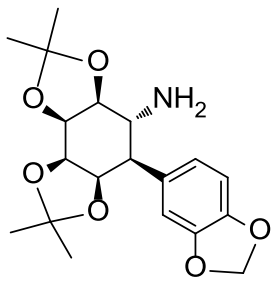
(+/-)-1,2-*trans*-**22a** (+/-)-1,2-*cis*-**22a**



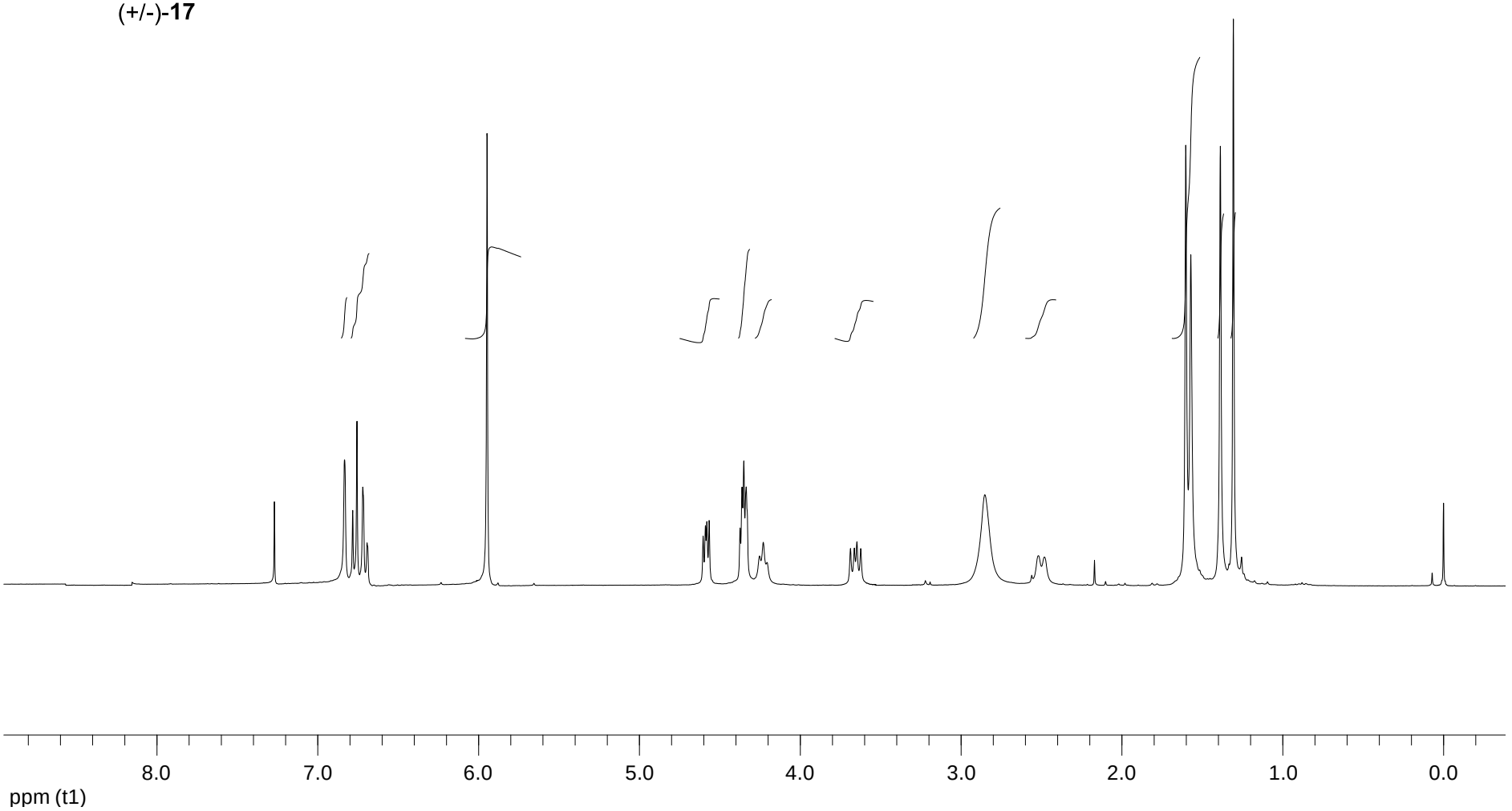


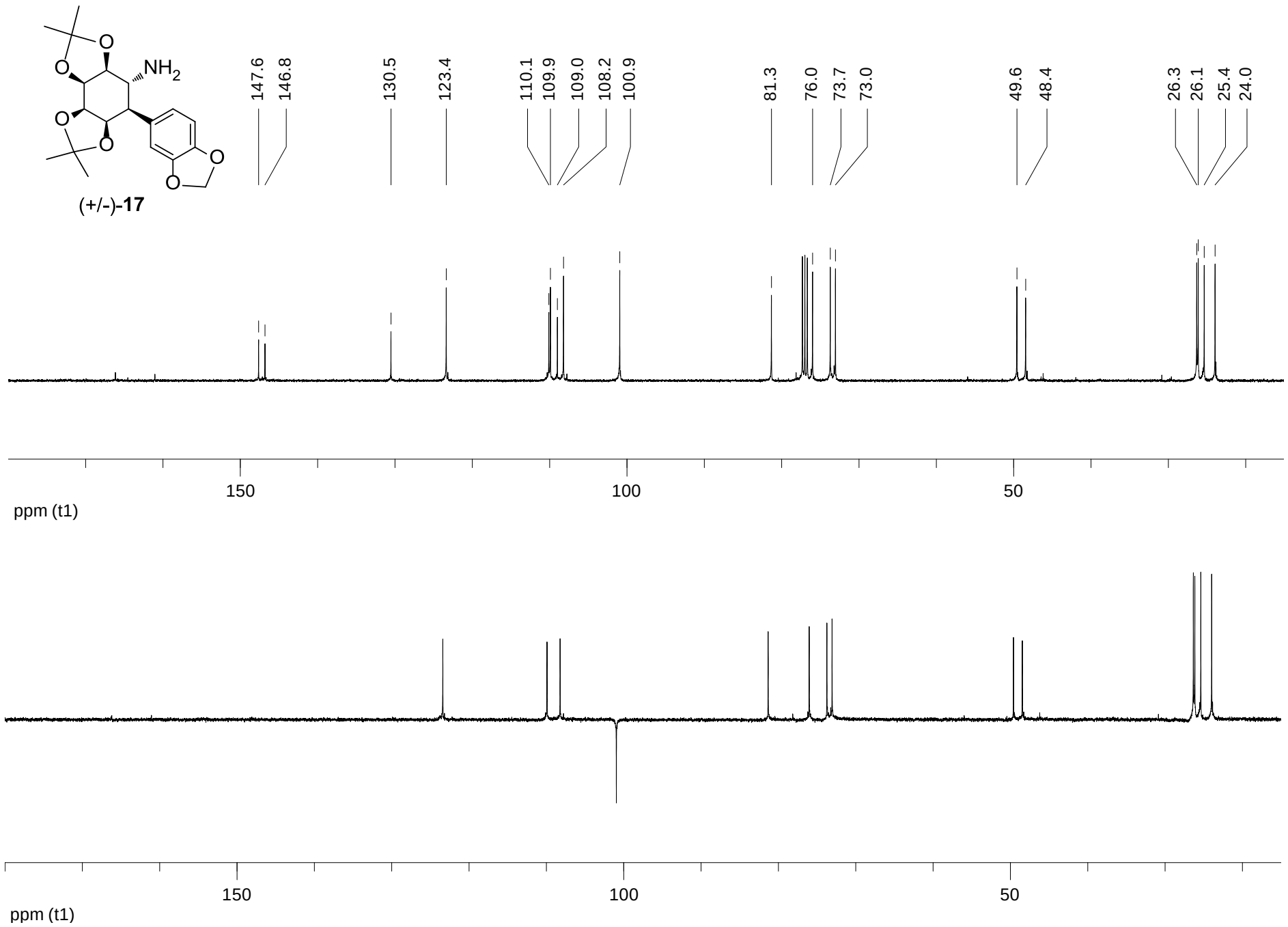
(+/-)-1,2-*trans*-**22b** (+/-)-1,2-*cis*-**22b**

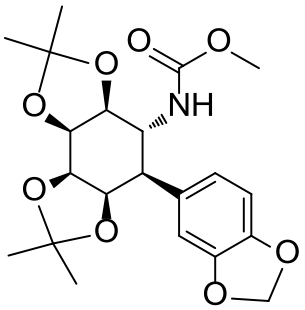




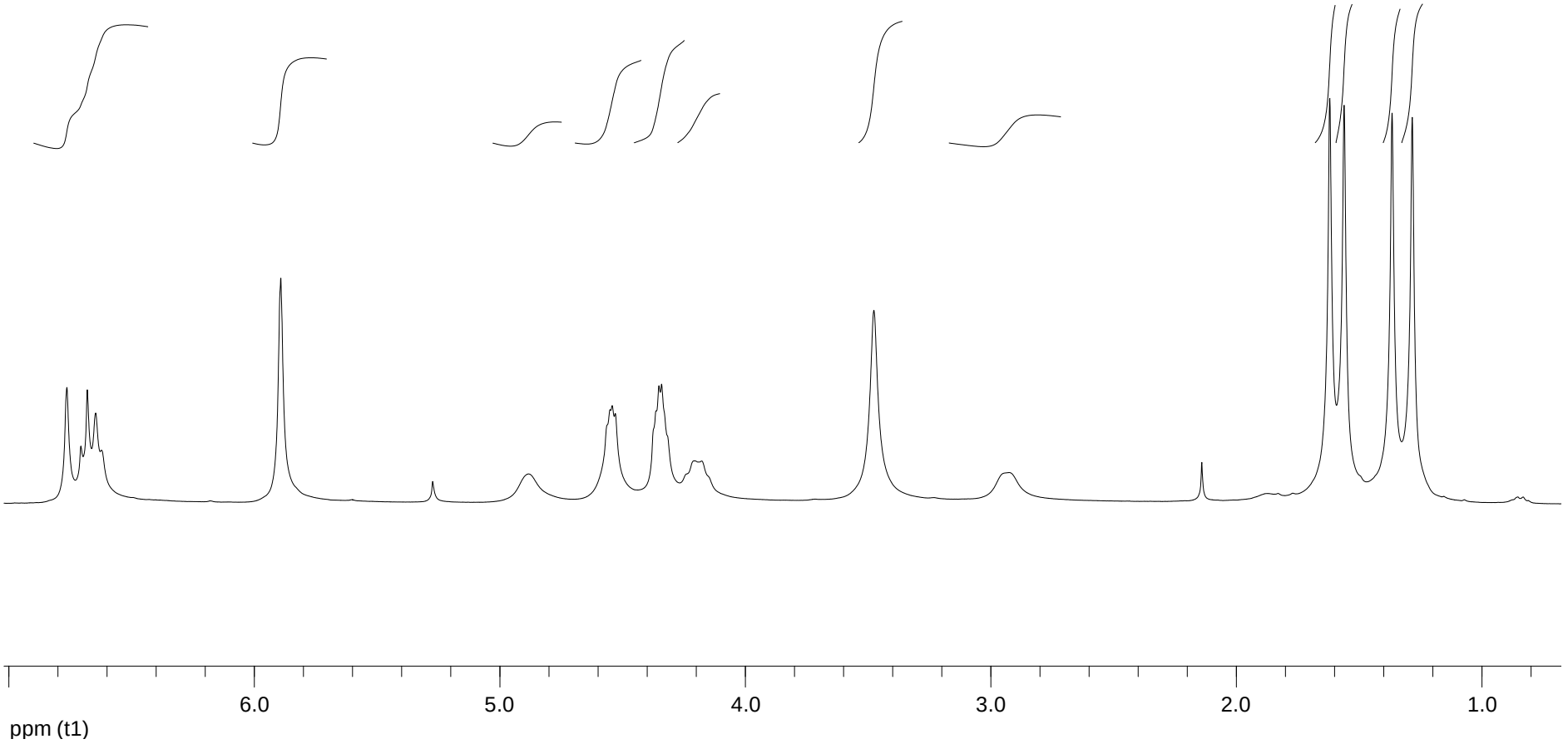
(+/-)-**17**

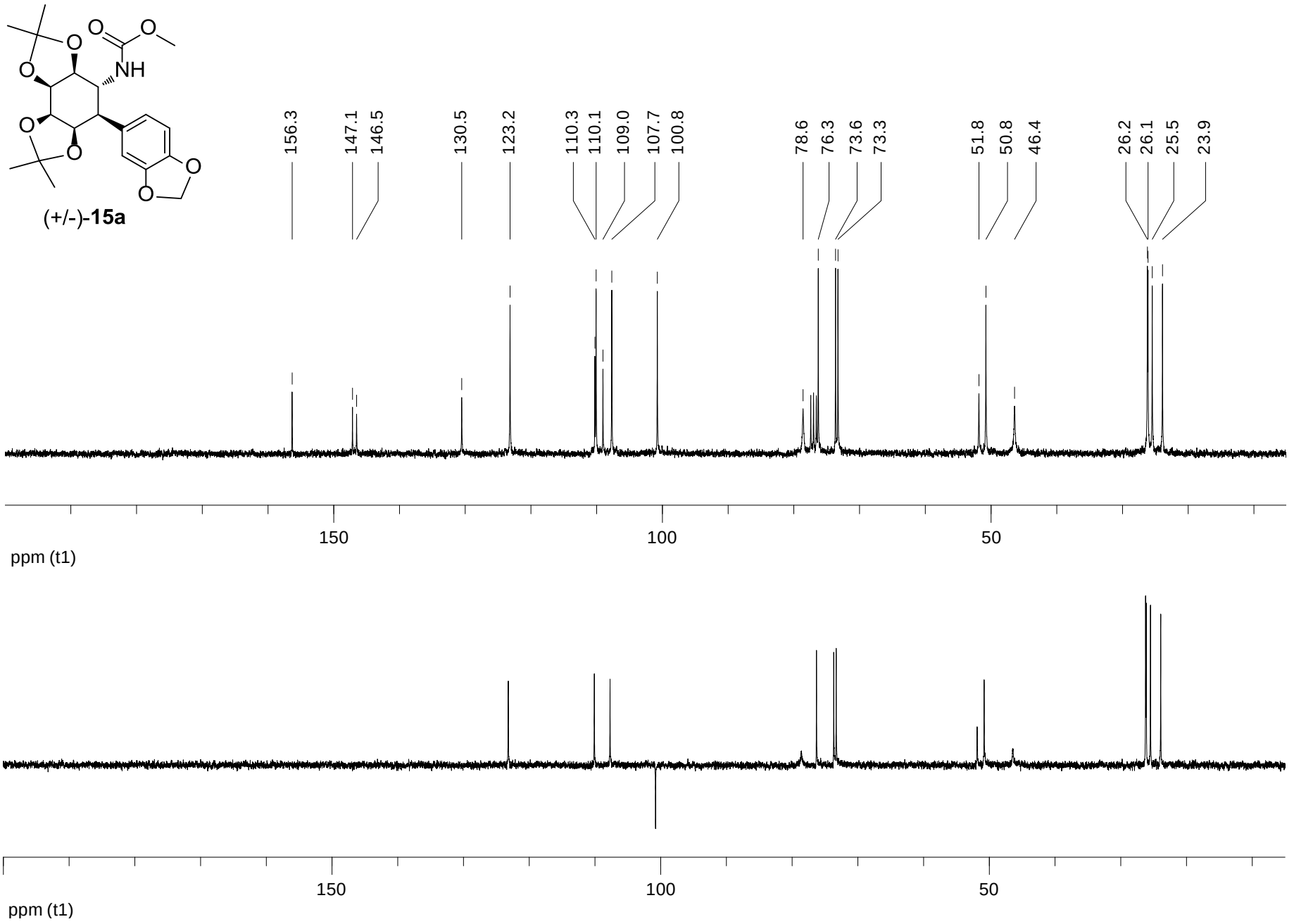


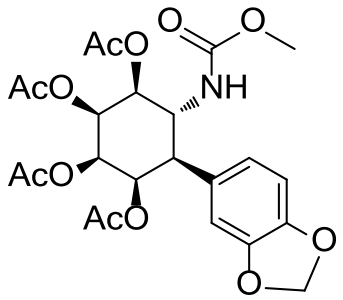

NH2
(+/-)-17
147.6
146.8
130.5
123.4
110.1
109.9
109.0
108.2
100.9
81.3
76.0
73.7
73.0
49.6
48.4
26.3
26.1
25.4
24.0
150
100
50
ppm (t1)
150
100
50
ppm (t1)



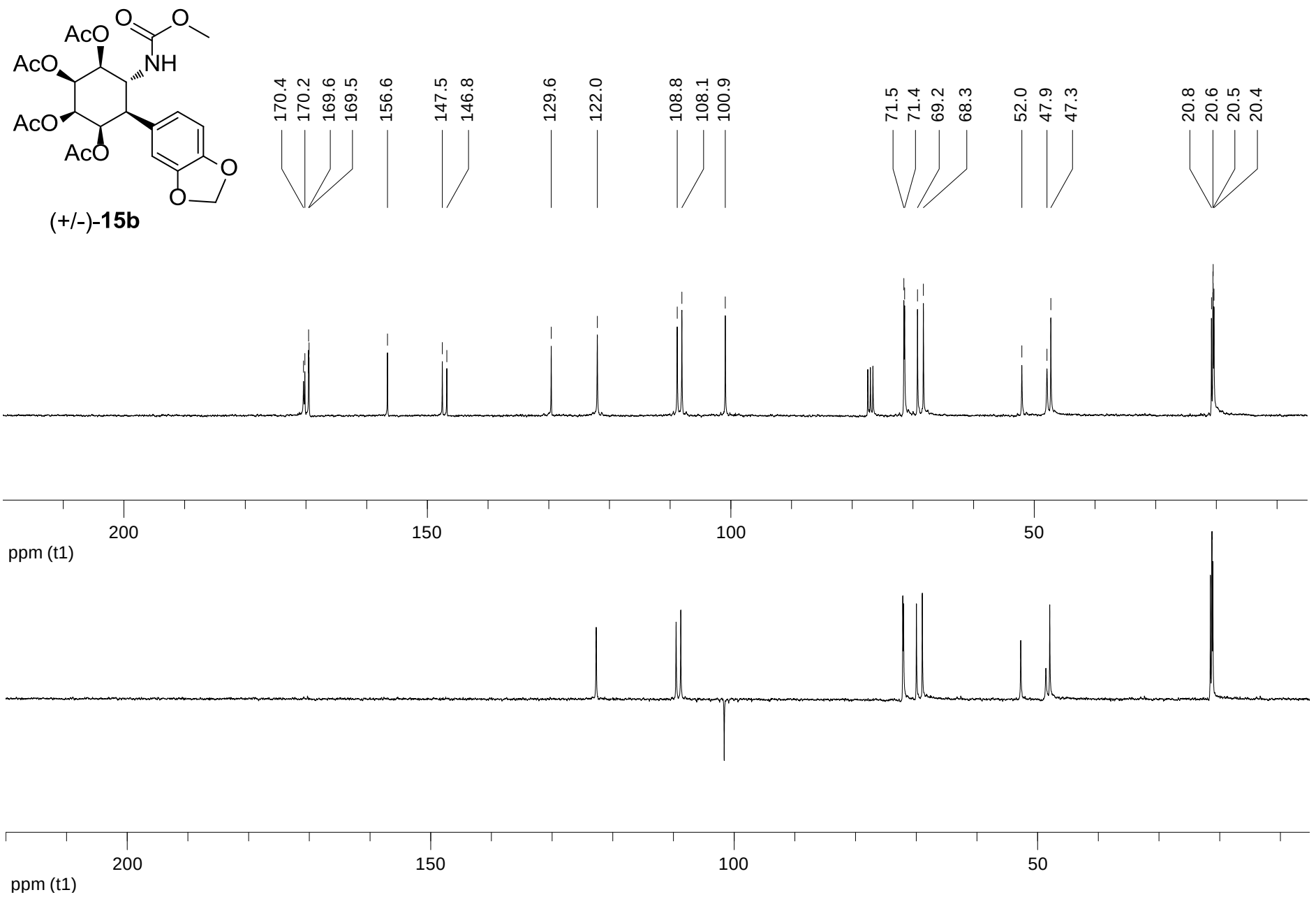
(+/-)-**15a**

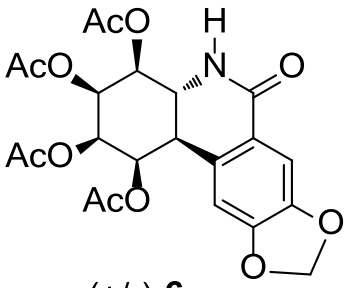



(+/-)-15a
156.3
147.1
146.5
130.5
123.2
110.3
110.1
109.0
107.7
100.8
78.6
76.3
73.6
73.3
51.8
50.8
46.4
26.2
26.1
25.5
23.9
150
100
50
ppm (t1)
150
100
50
ppm (t1)

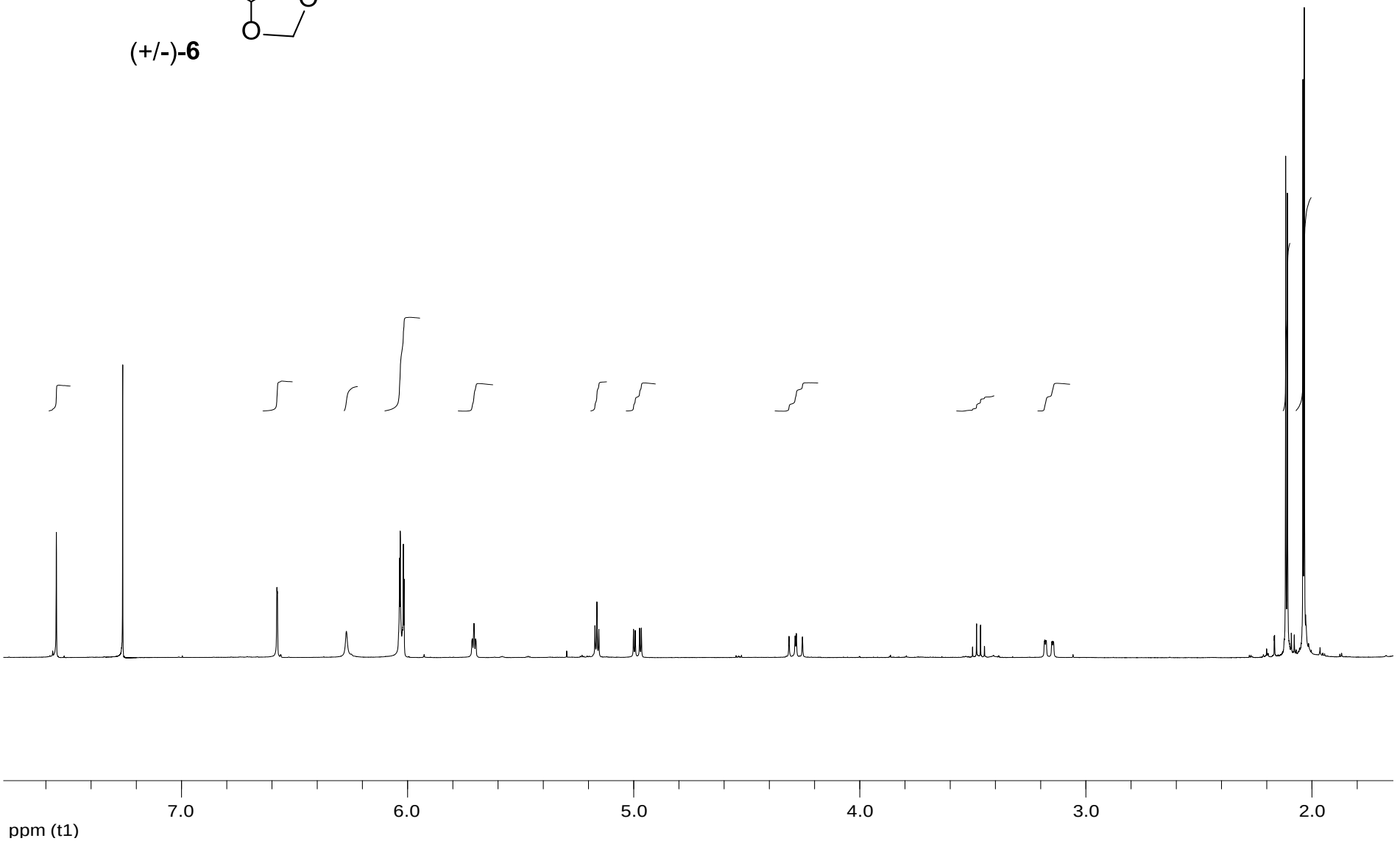


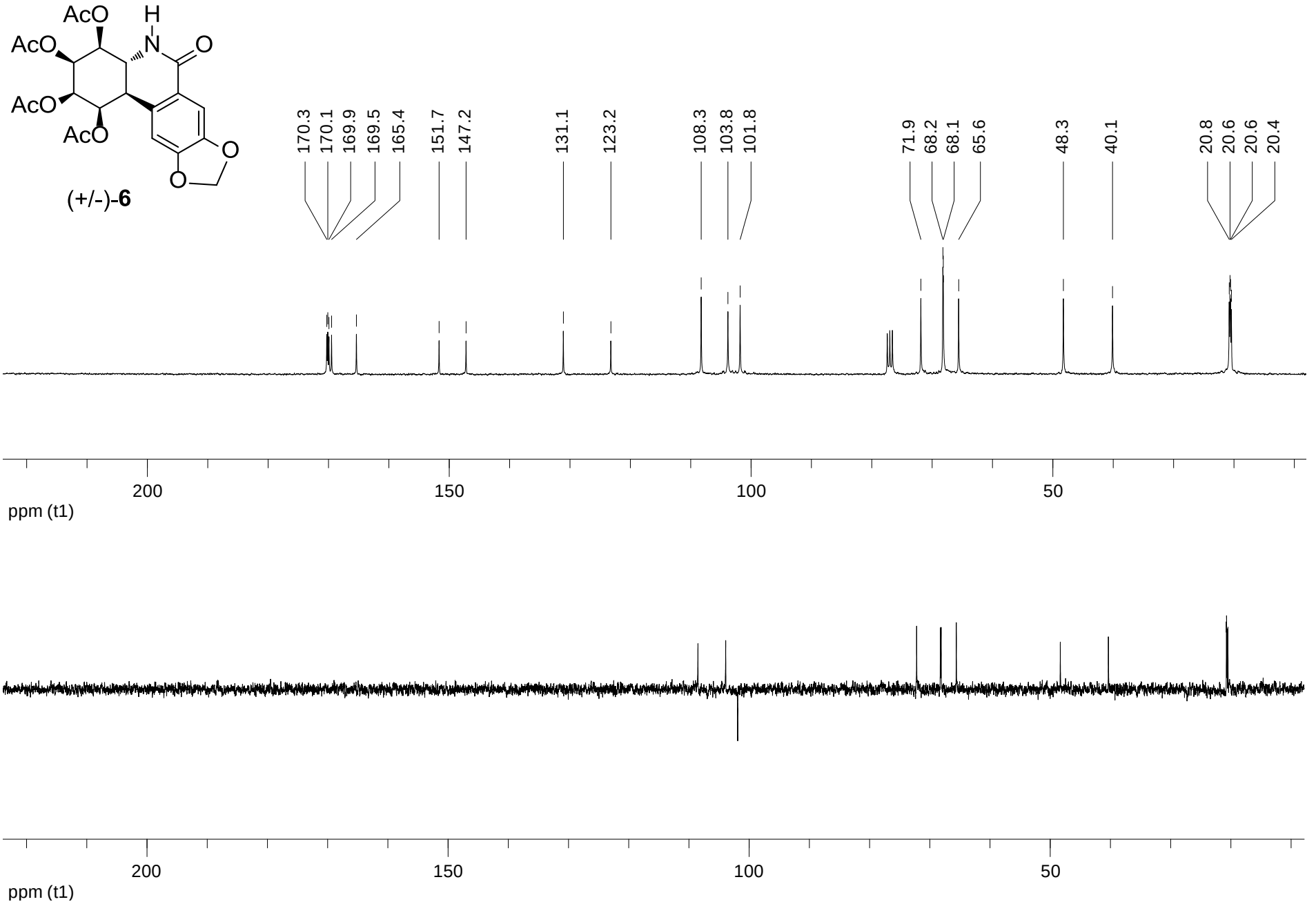
(+/-)-**15b**

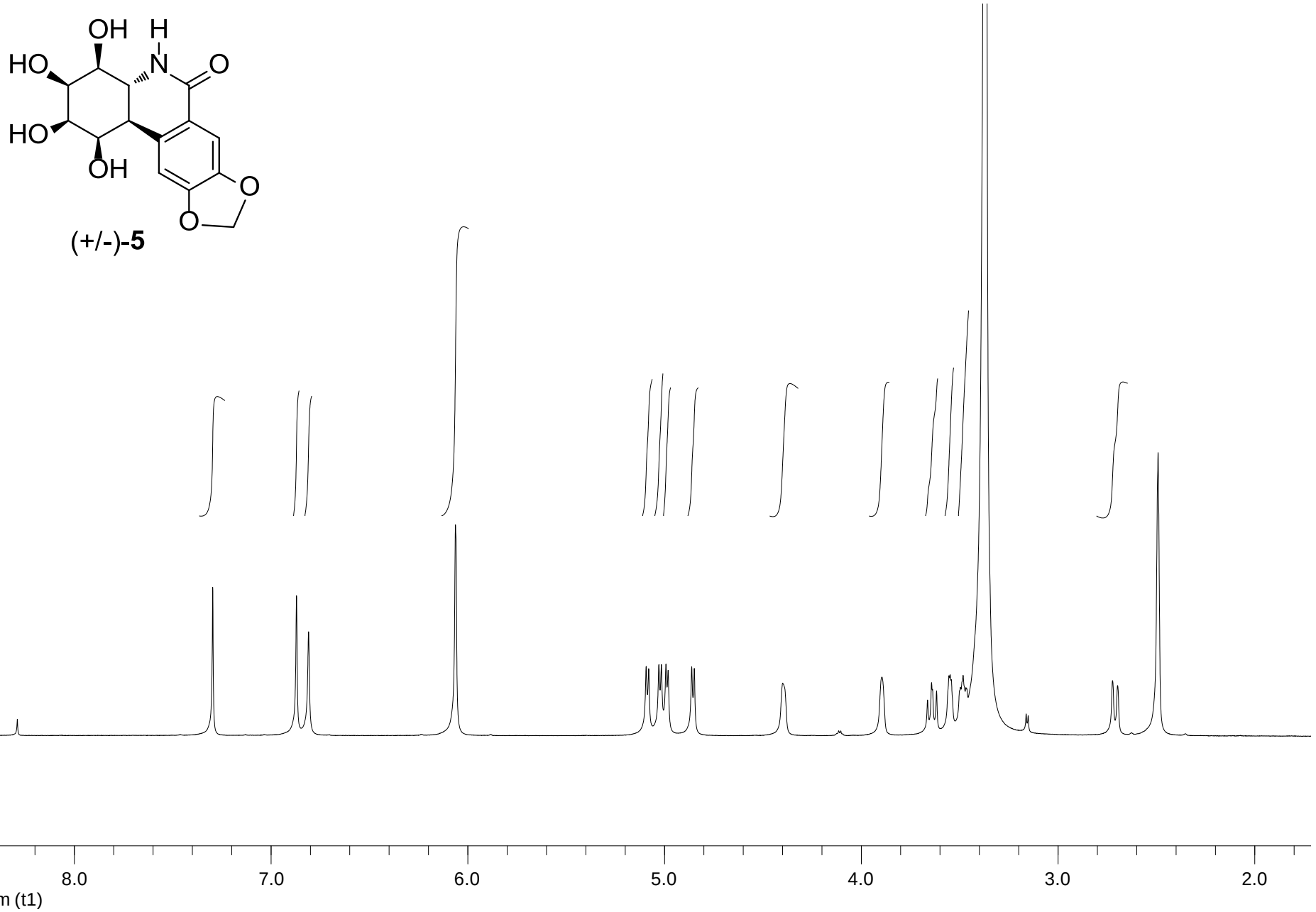

AcO
AcO
AcO
AcO
O
O
NH
O
O
(+/-)-15b
170.4
170.2
169.6
169.5
156.6
147.5
146.8
129.6
122.0
108.8
108.1
100.9
71.5
71.4
69.2
68.3
52.0
47.9
47.3
20.8
20.6
20.5
20.4
200
150
100
50
ppm (t1)
200
150
100
50
ppm (t1)

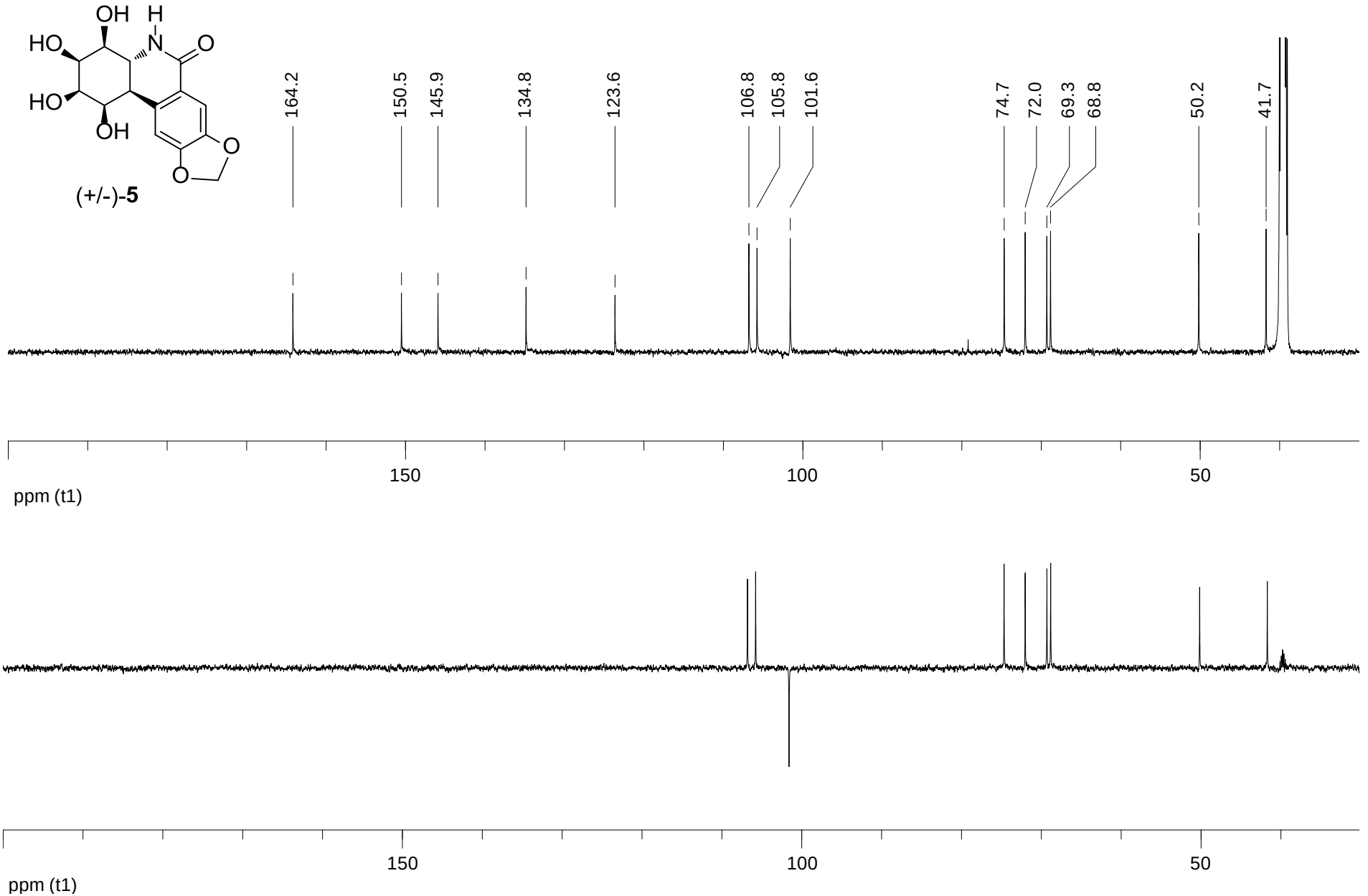


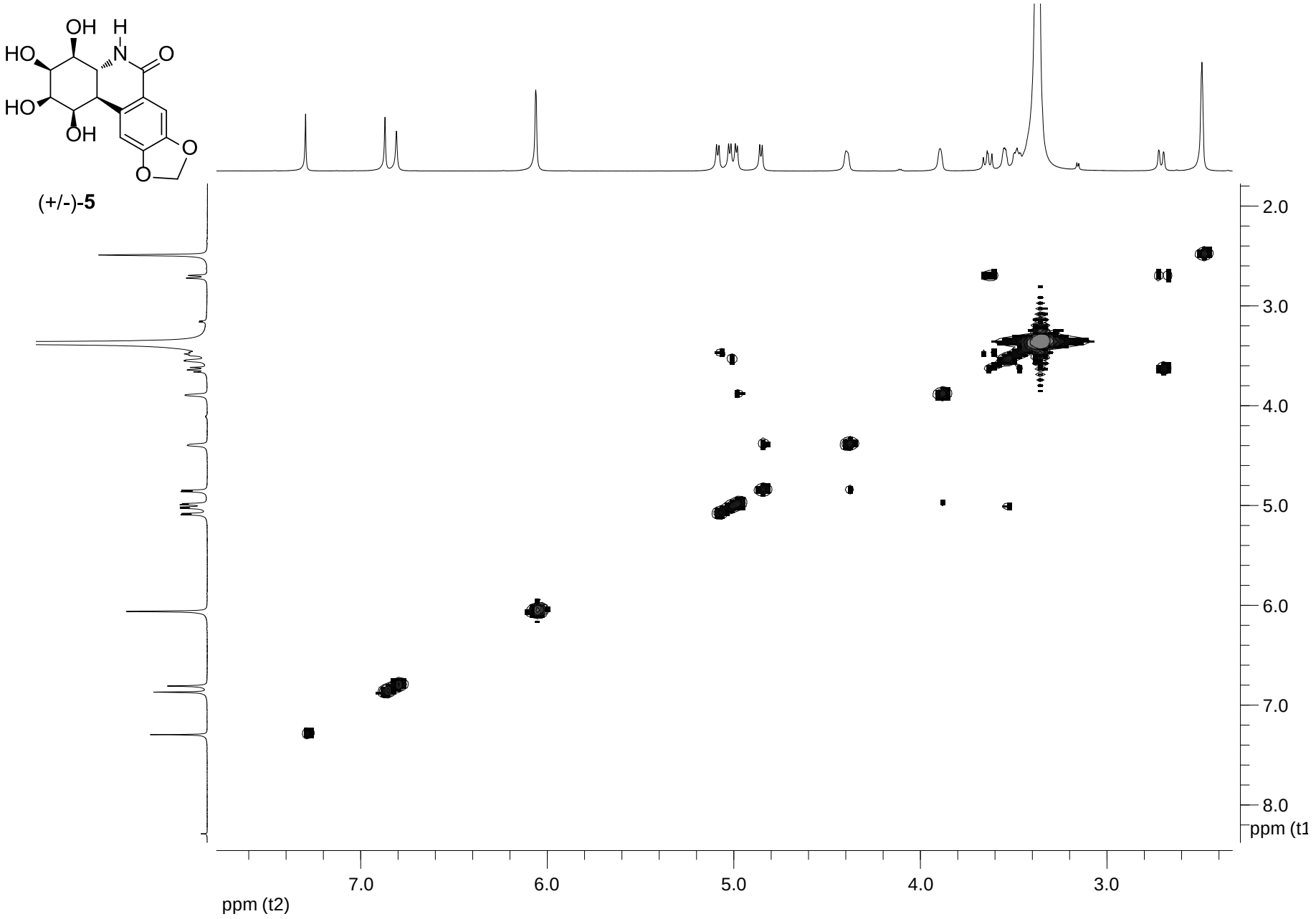
(+/-)-**6**

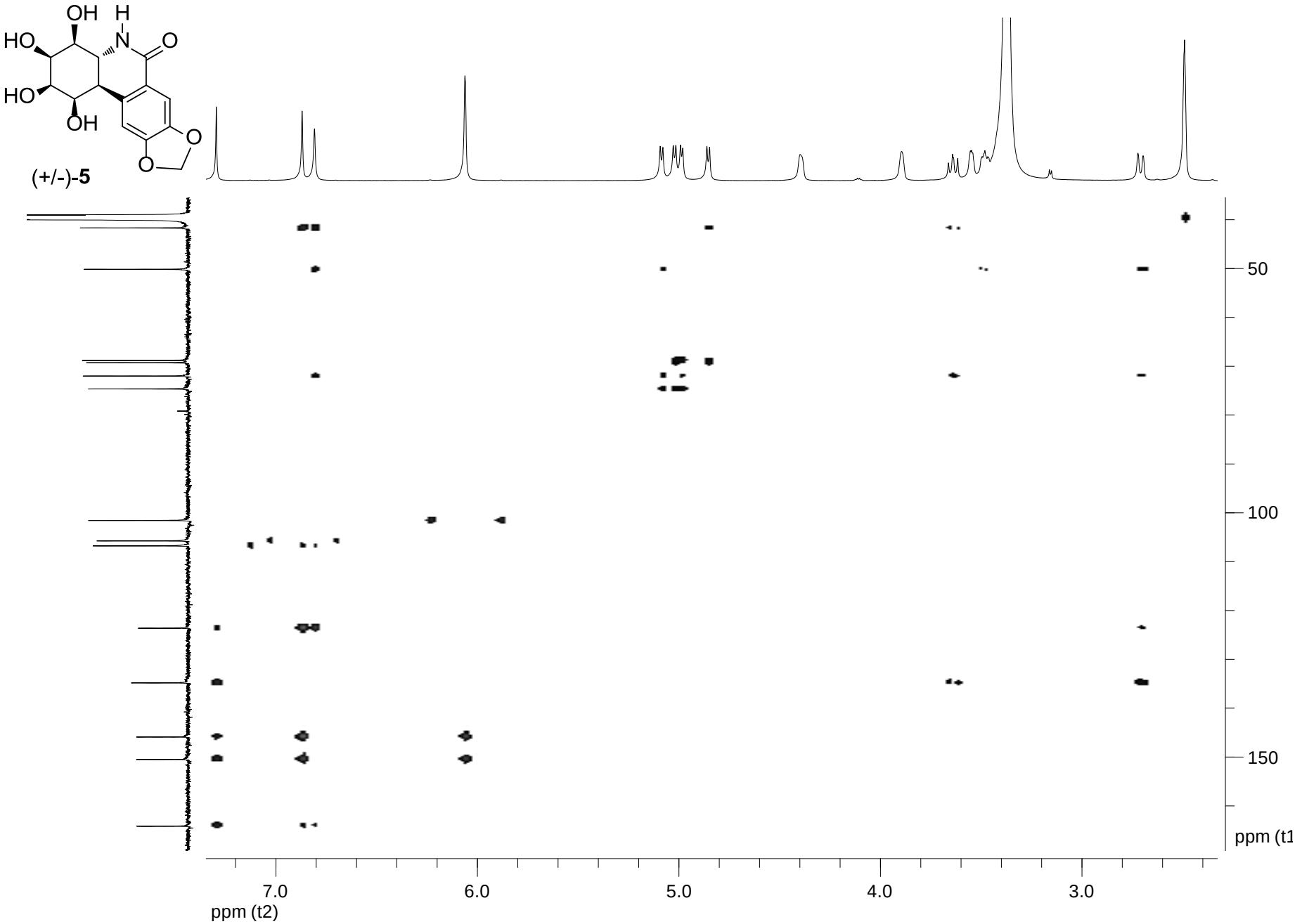


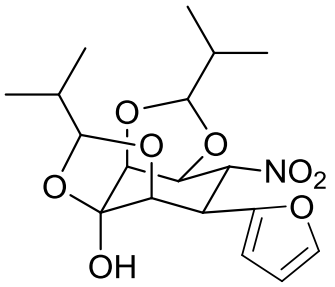

AcO
H
N
O
AcO
AcO
AcO
O
O
(+/-)-6
170.3
170.1
169.9
169.5
165.4
151.7
147.2
131.1
123.2
108.3
103.8
101.8
71.9
68.2
68.1
65.6
48.3
40.1
20.8
20.6
20.6
20.4
200
150
100
50
ppm (t1)
200
150
100
50
ppm (t1)


OH
H
HO
N
O
HO
OH
O
O
(+/-)-5
8.0
7.0
6.0
5.0
4.0
3.0
2.0
ppm (t1)

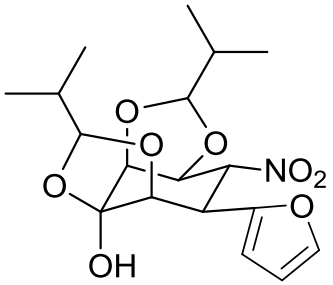

OH
H
HO
N
O
HO
OH
O
O
(+/-)-5
164.2
150.5
145.9
134.8
123.6
106.8
105.8
101.6
74.7
72.0
69.3
68.8
50.2
41.7
150
100
50
ppm (t1)
150
100
50
ppm (t1)


OH
H
HO
N
O
HO
OH
O
O
(+/-)-5
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1
7.0
6.0
5.0
4.0
3.0
ppm (t2)

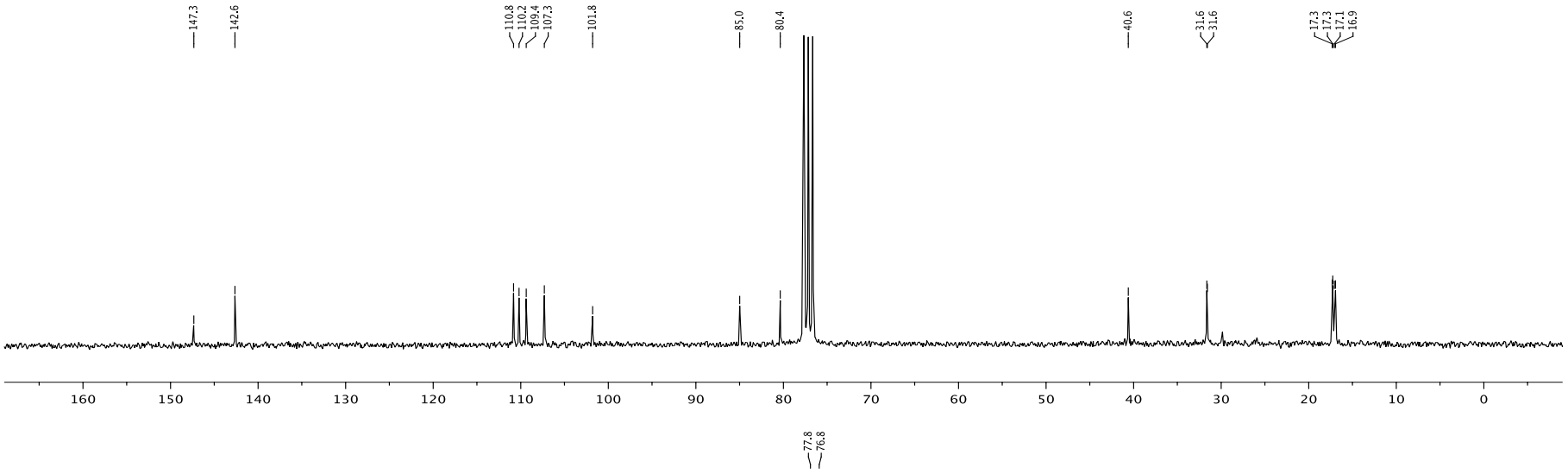

OH
H
HO
N
O
HO
OH
O
O
(+/-)-5
50
100
150
ppm (t1
7.0
6.0
5.0
4.0
3.0
ppm (t2)

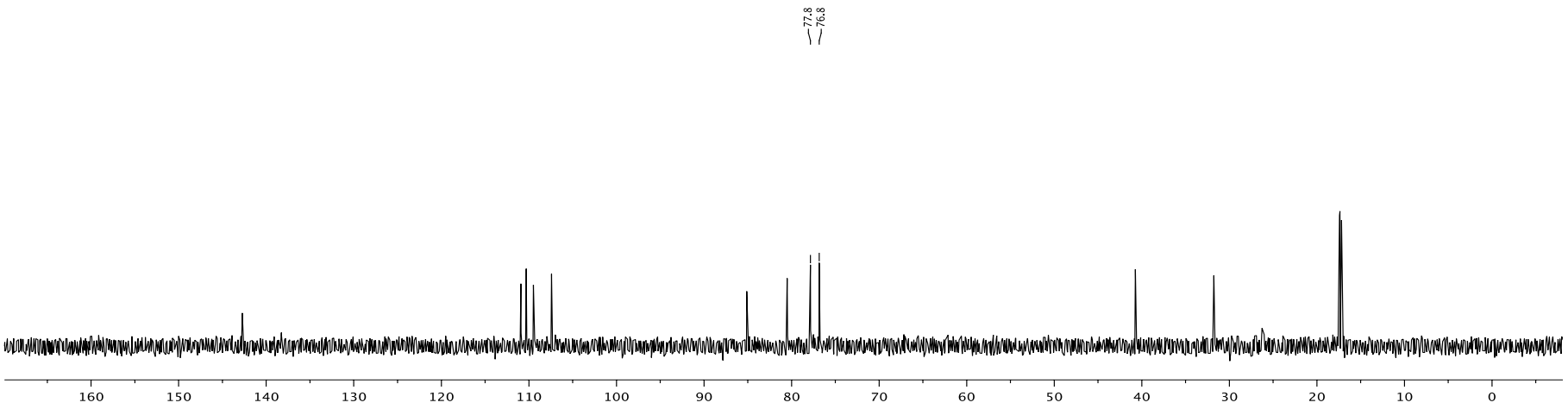


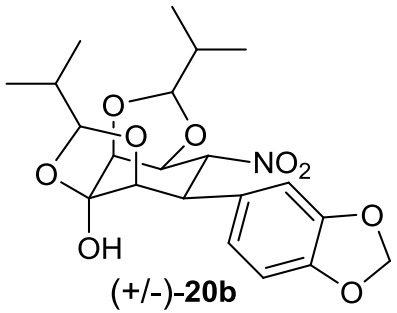
(+/-)-20a


O
O
O
O
NO2
O
OH

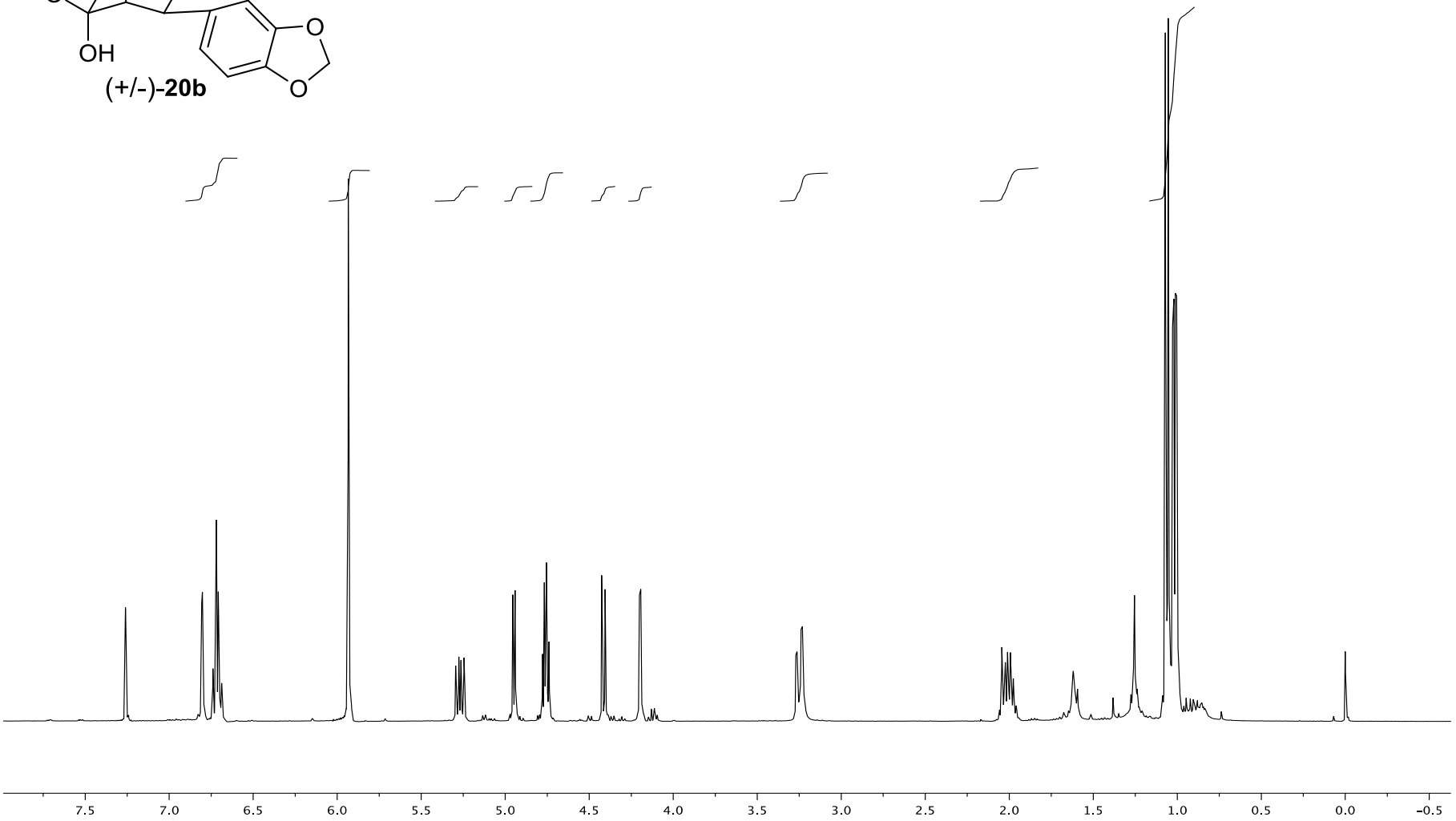
(+/-)-20a

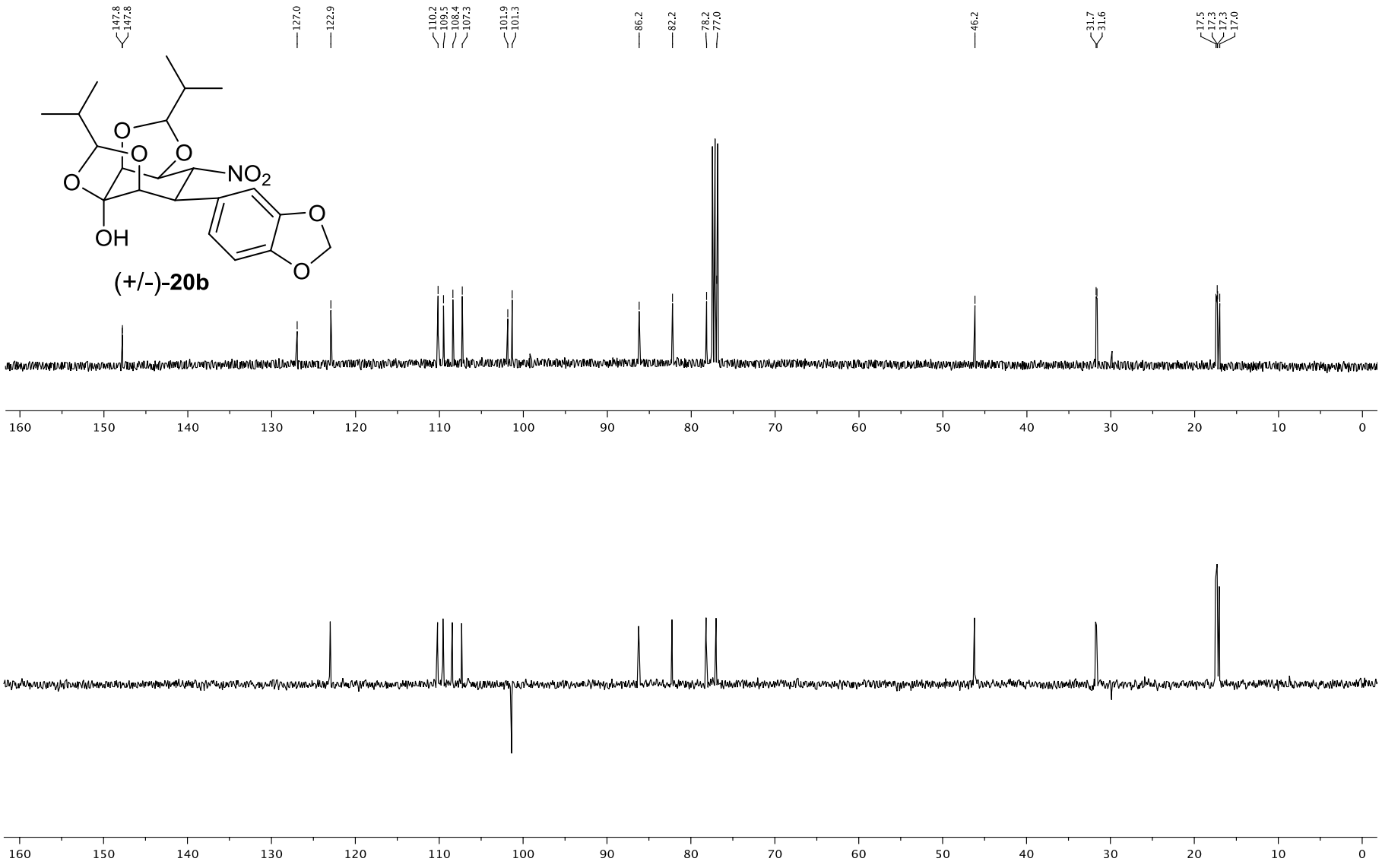

147.3
142.6
110.8
110.2
109.4
107.3
101.8
85.0
80.4
40.6
31.6
31.6
17.3
17.3
17.1
16.9
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

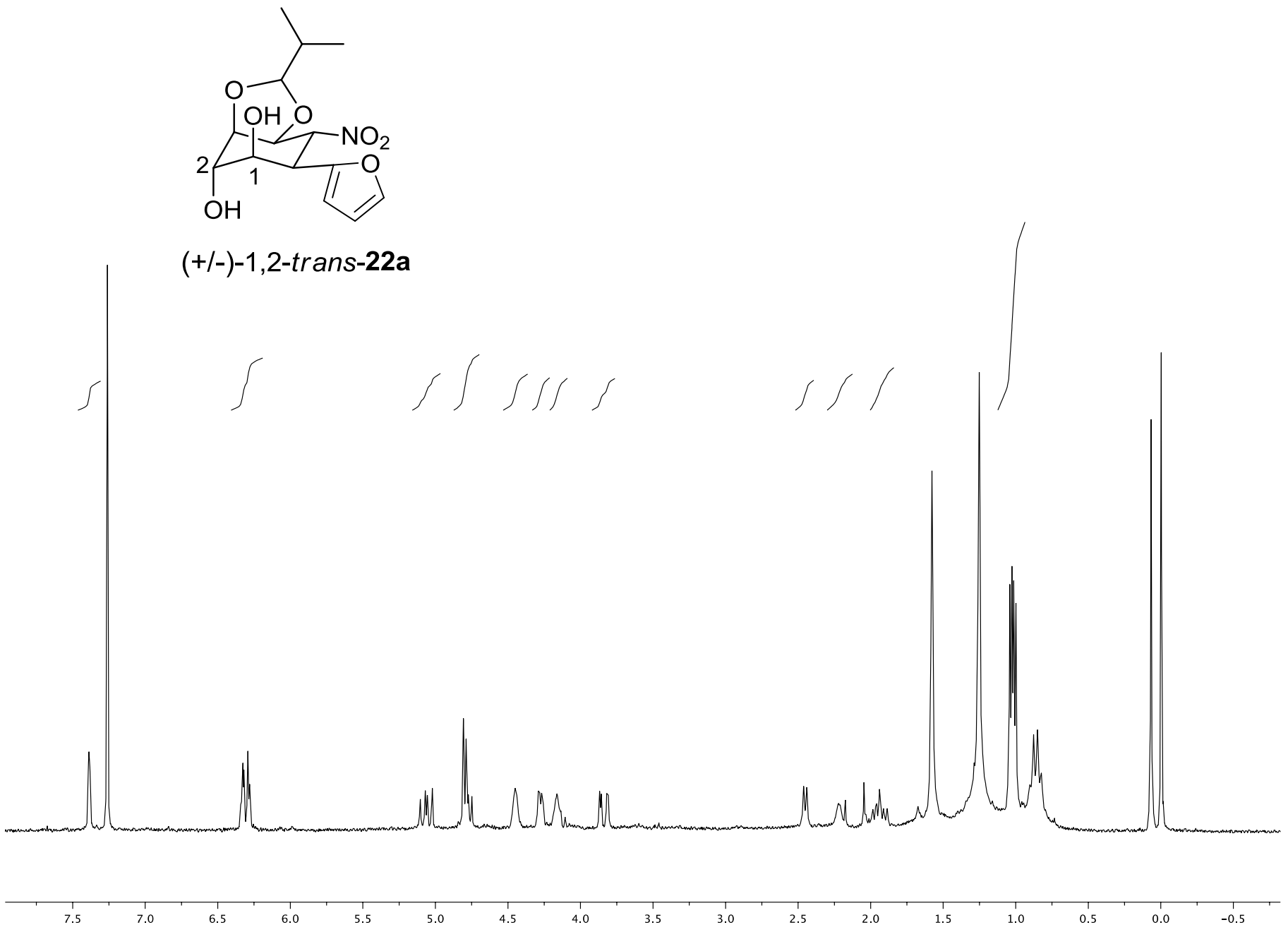

77.8
76.8
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



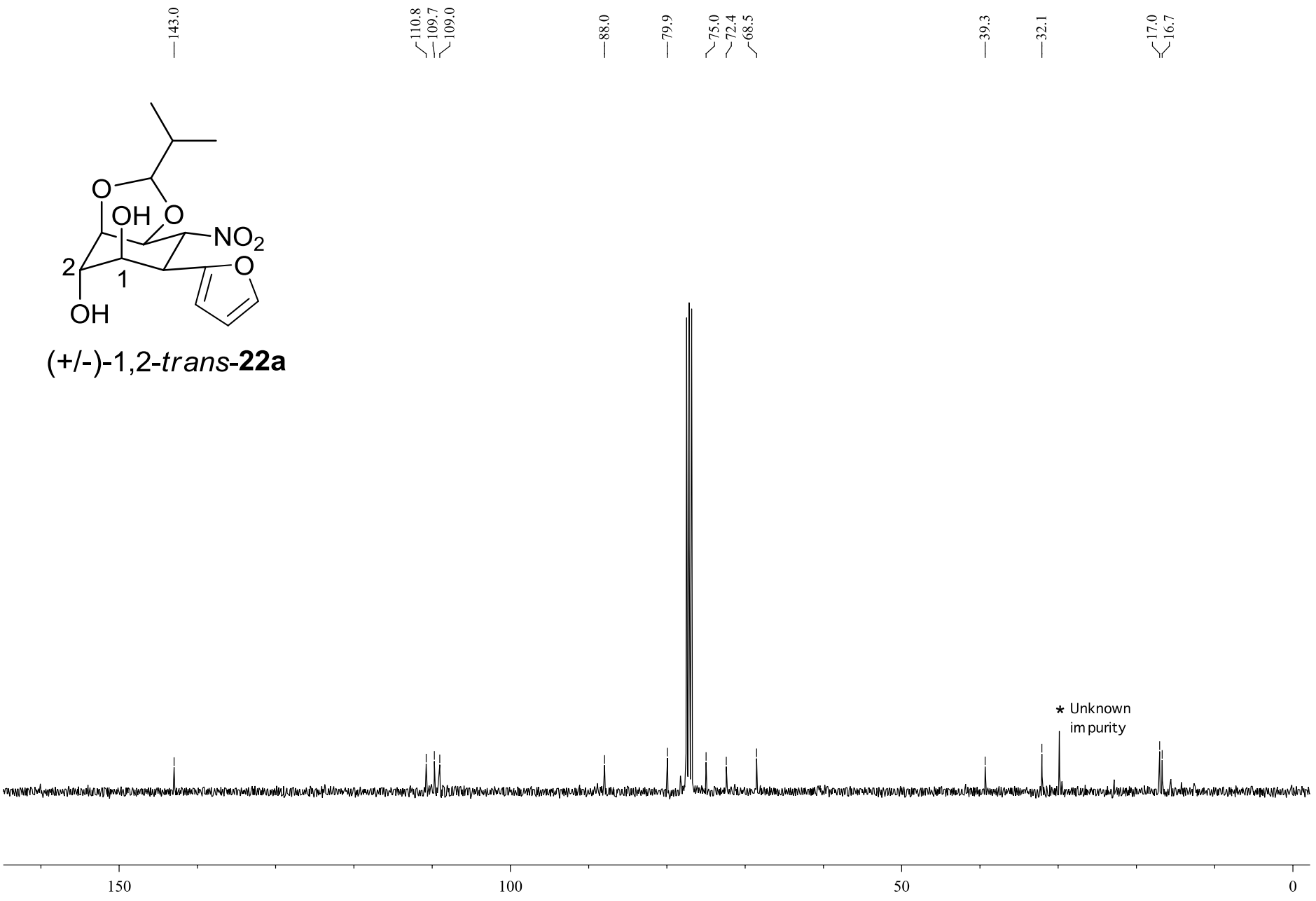
(+/-)-**20b**

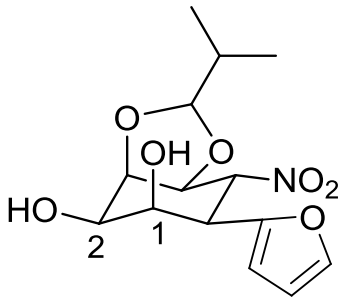



147.8
147.8
127.0
122.9
110.2
109.5
108.4
107.3
101.9
101.3
86.2
82.2
78.2
77.0
46.2
31.7
31.6
17.5
17.3
17.3
17.0
O
O
O
O
NO2
OH
O
O
(+/-)-20b
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

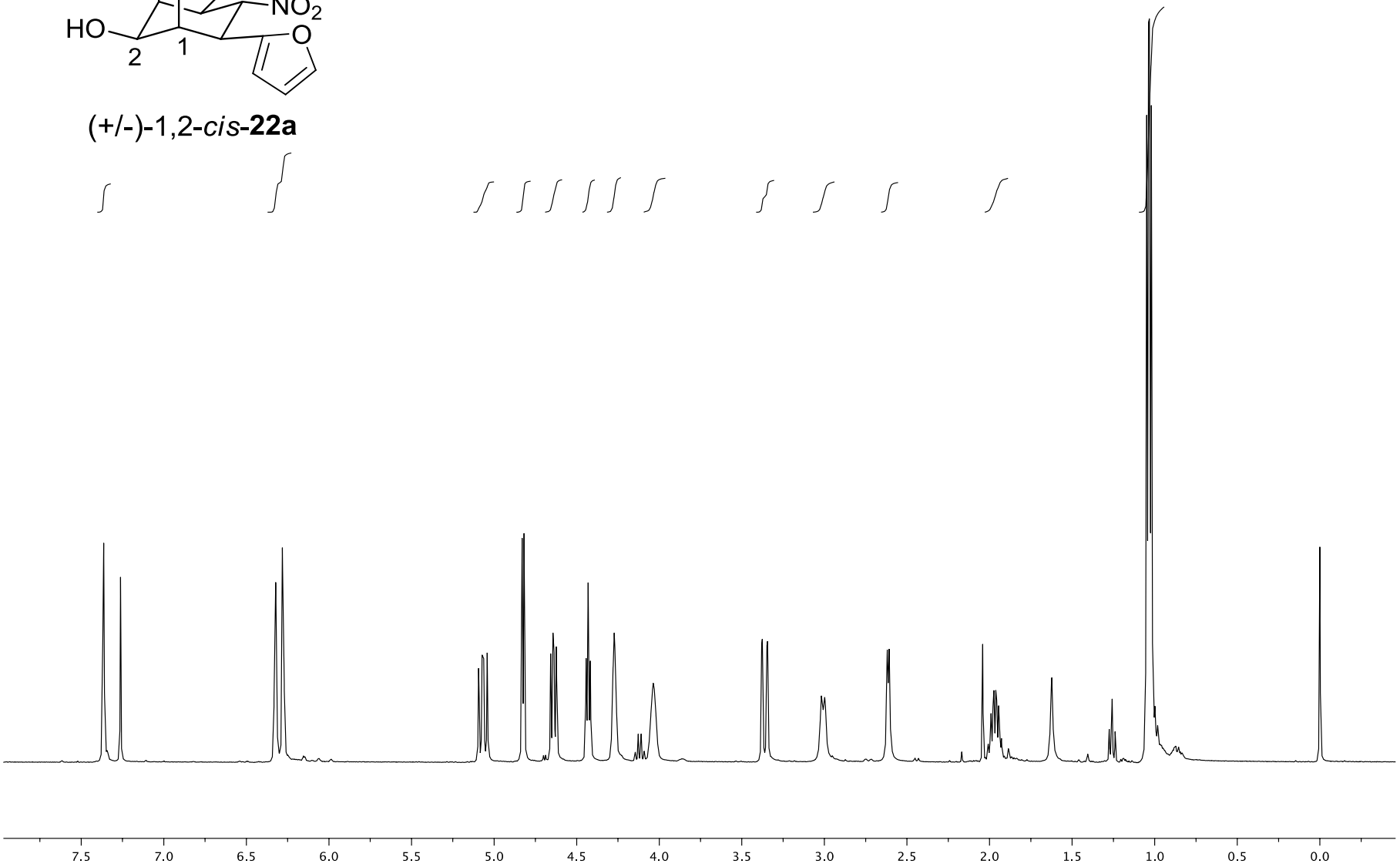


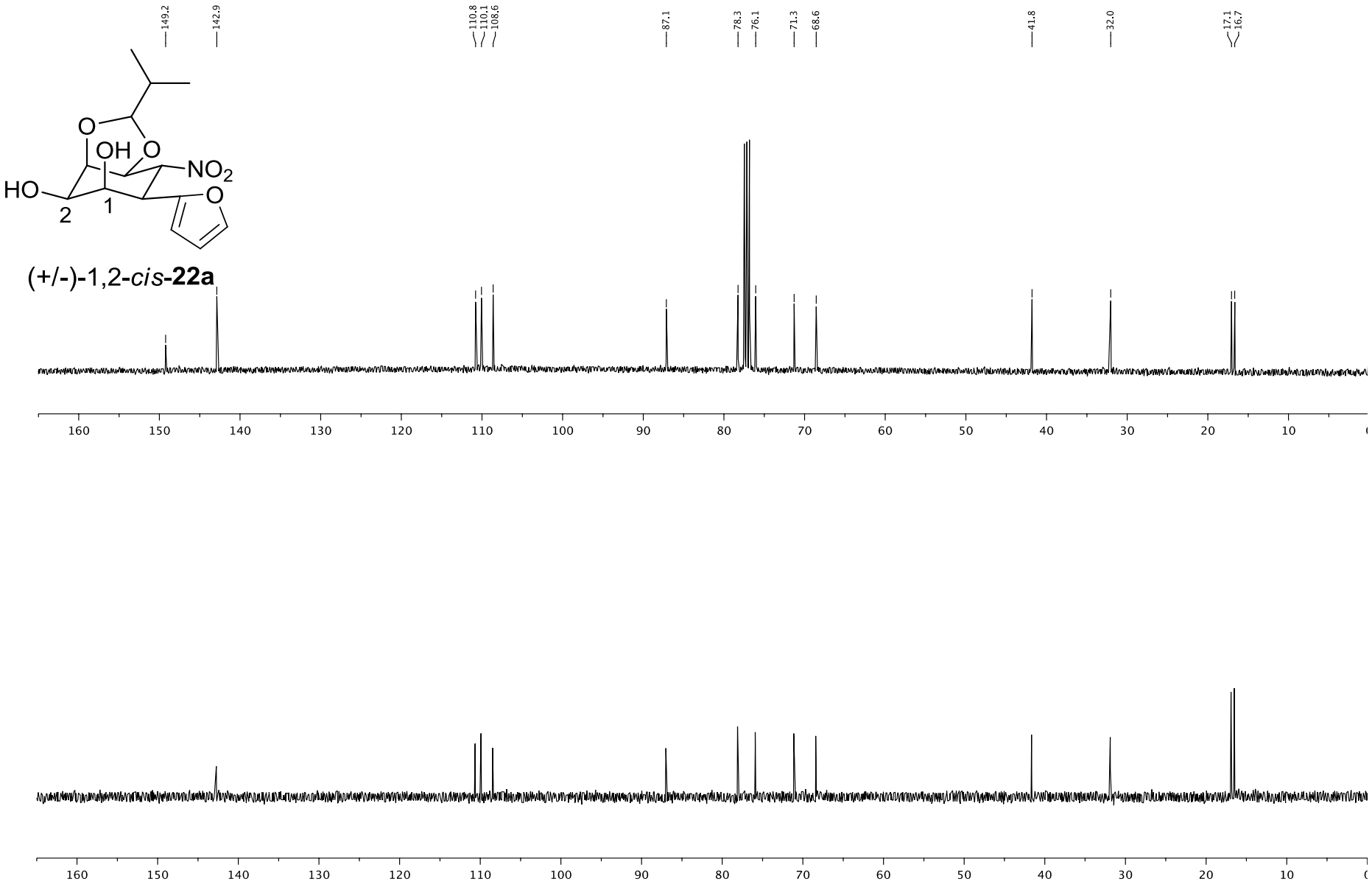
(+/-)-1,2-*trans*-**22a**

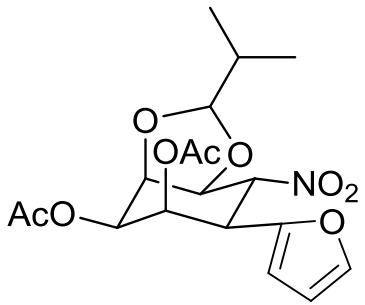

143.0
110.8
109.7
109.0
88.0
79.9
75.0
72.4
68.5
39.3
32.1
17.0
16.7
O
OH
O
NO2
2
1
O
OH
(+/-)-1,2-trans-22a
* Unknown
impurity
150
100
50
0



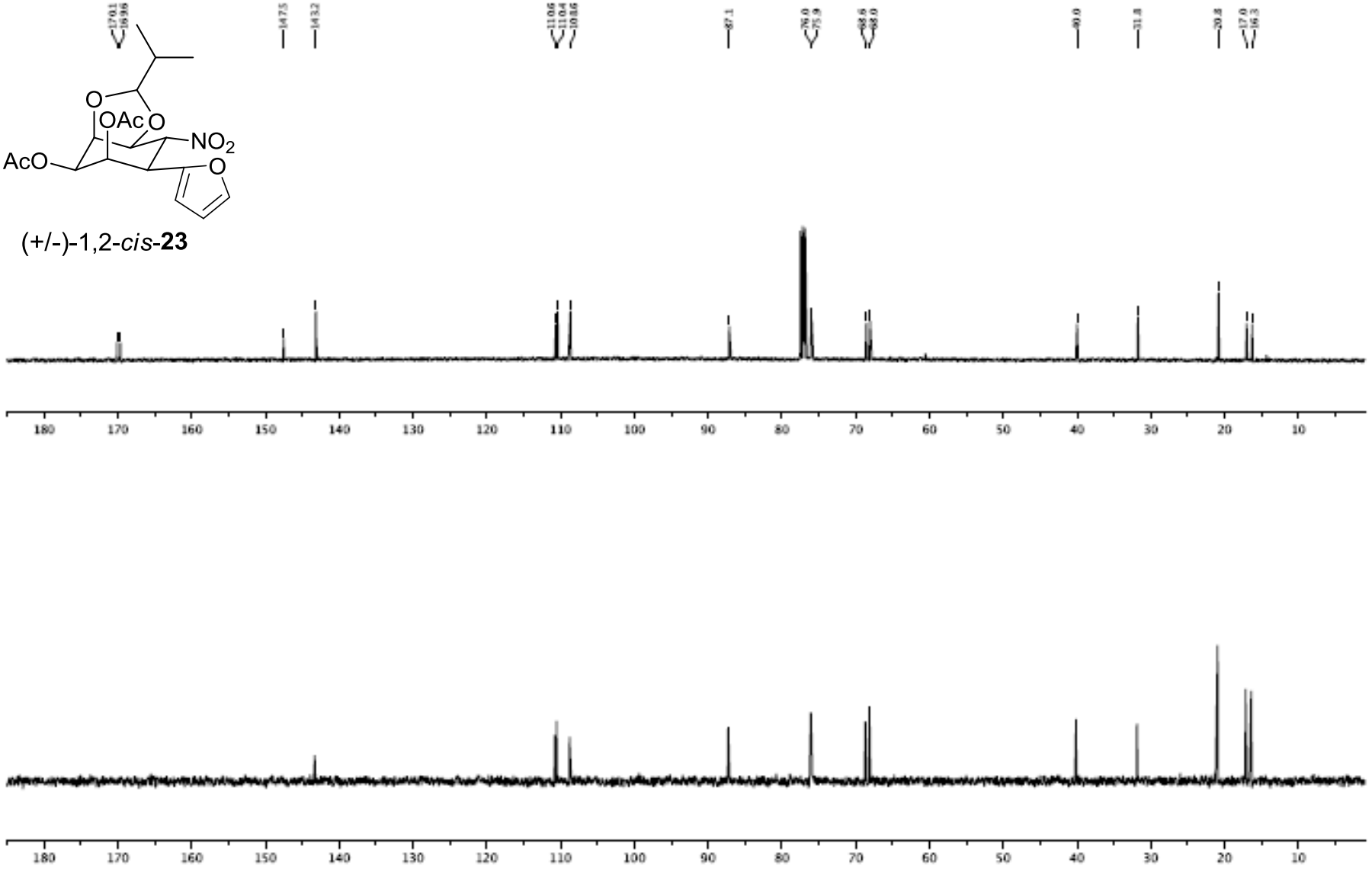
(+/-)-1,2-*cis*-**22a**



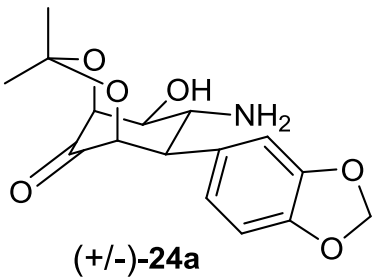

149.2
142.9
110.8
110.1
108.6
87.1
78.3
76.1
71.3
68.6
41.8
32.0
17.1
16.7
O
OH
O
NO2
HO
O
2
1
(+/-)-1,2-cis-22a
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10



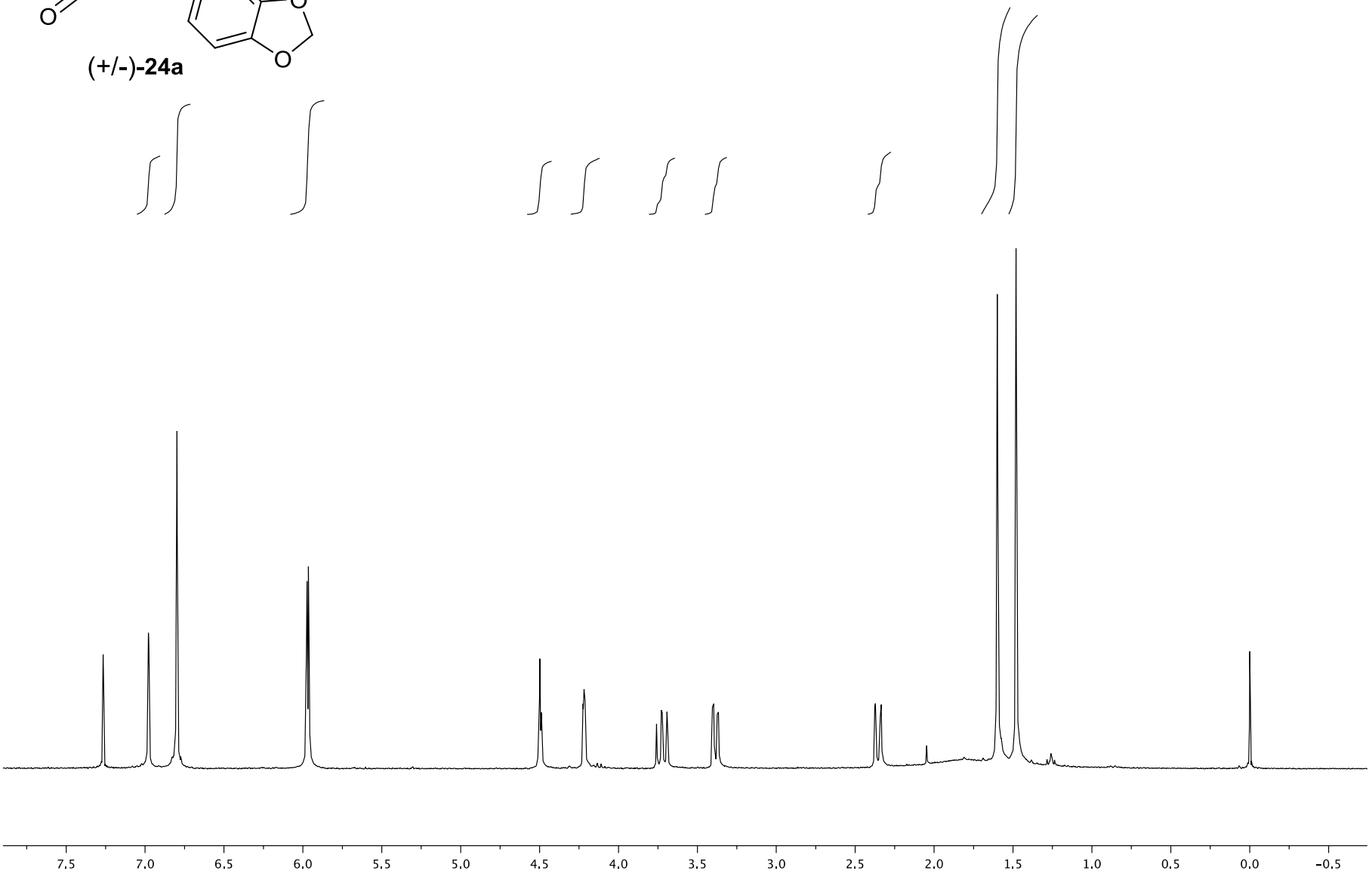
(+/-)-1,2-*cis*-**23**

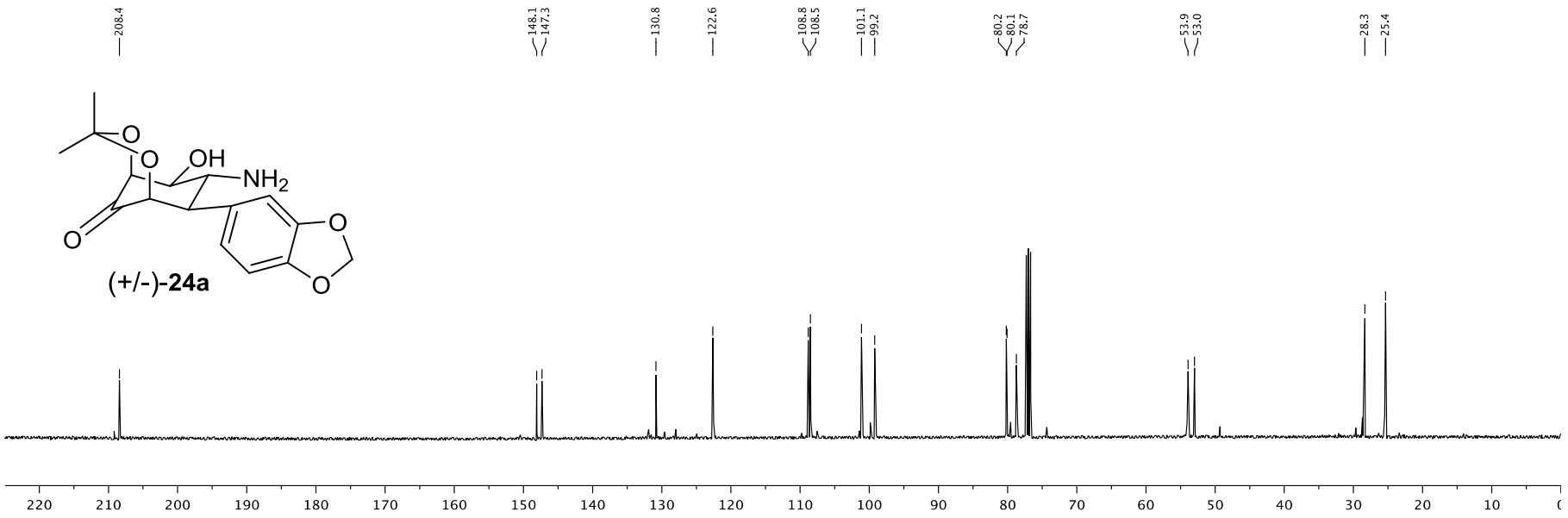

170.1
169.6
147.5
143.2
110.6
110.4
108.6
87.1
76.0
75.9
68.6
68.0
39.9
31.8
20.8
17.0
16.3
O
OAc
O
NO2
AcO
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

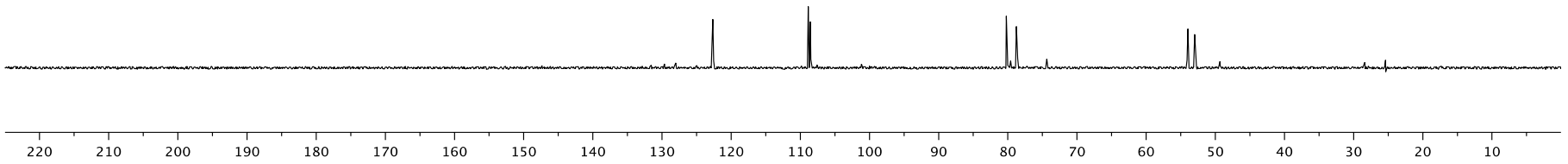
(+/-)-1,2-*cis*-**23**

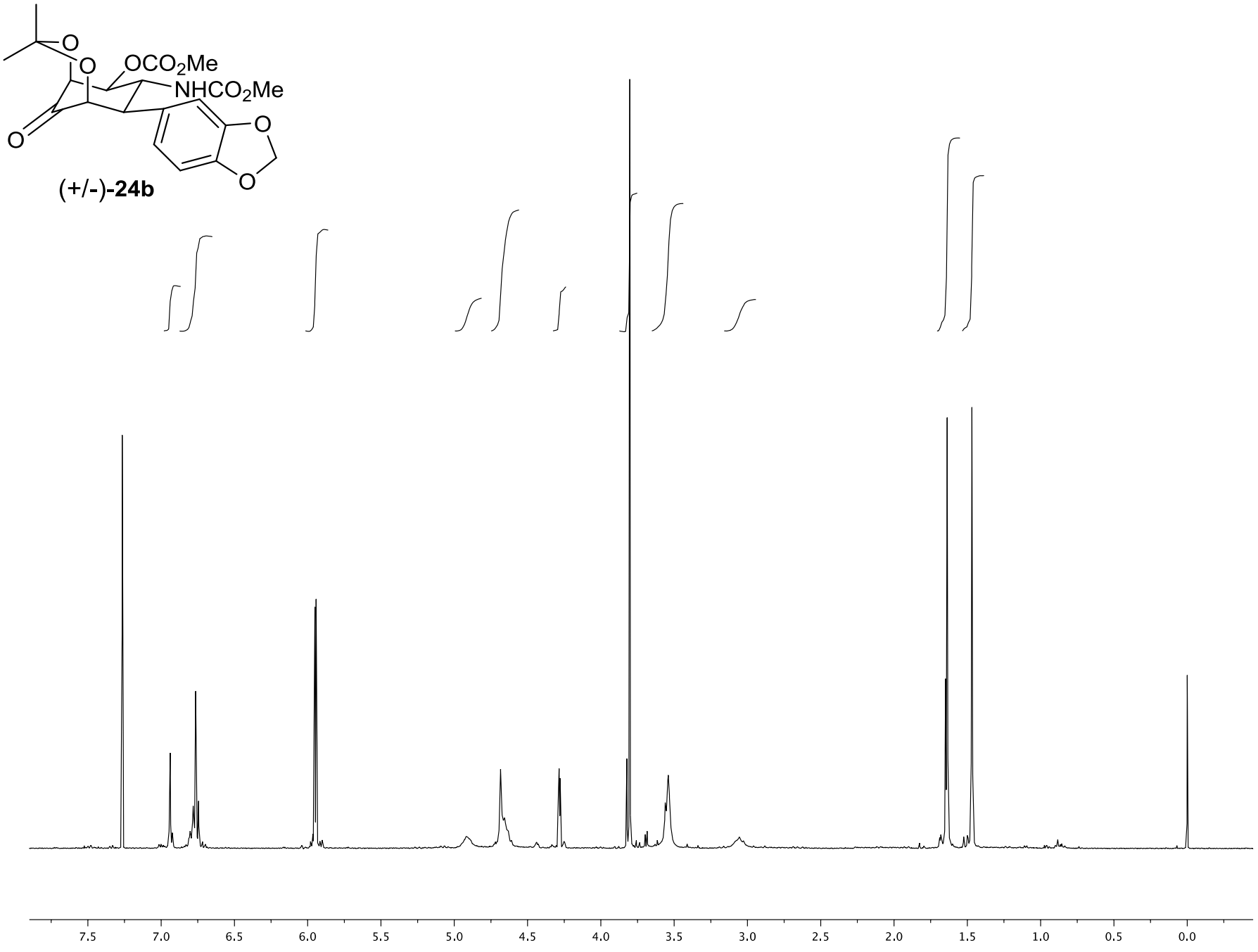


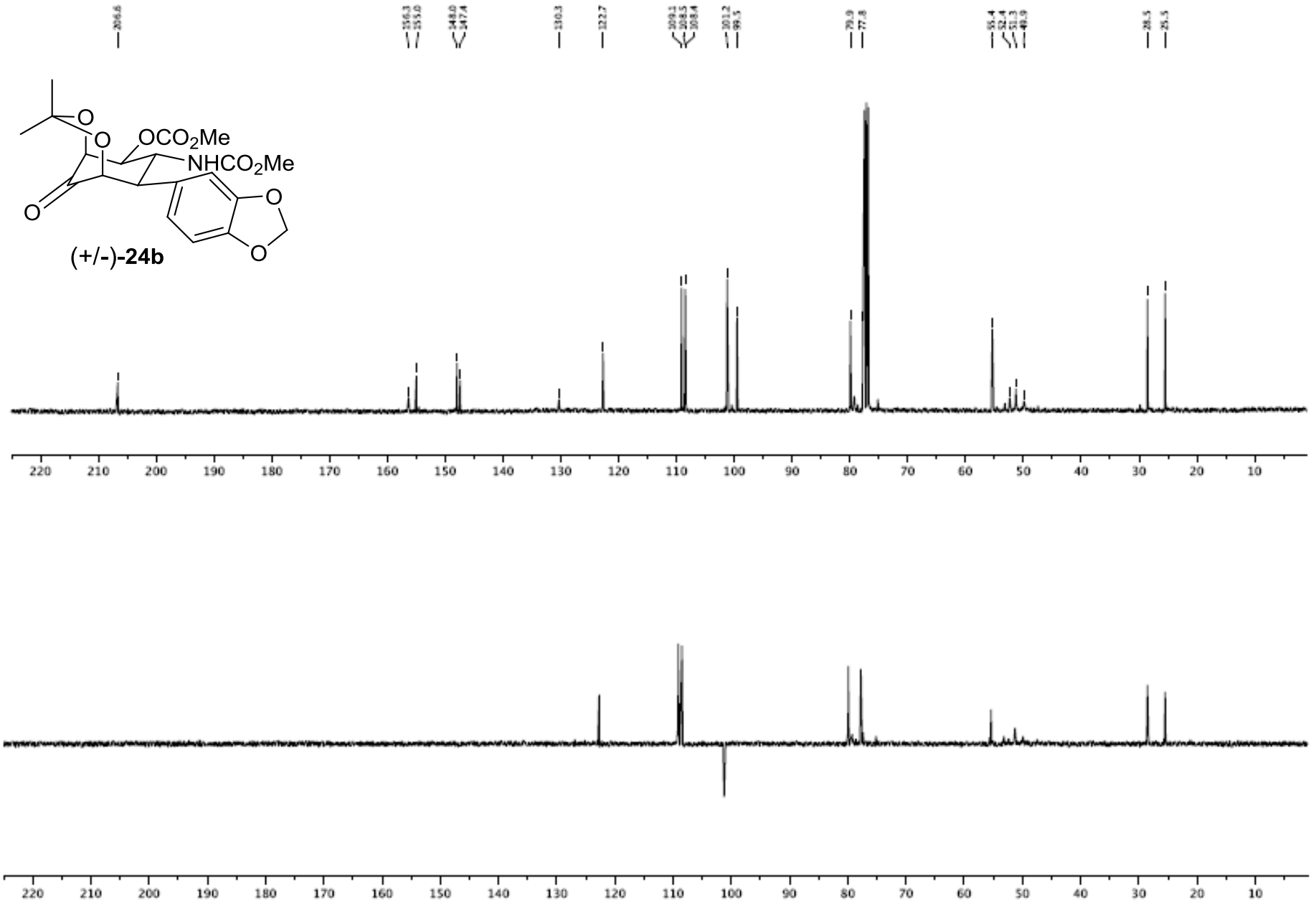
(+/-)-24a

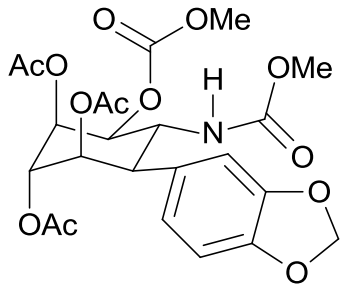



208.4
148.1
147.3
130.8
122.6
108.8
108.5
101.1
99.2
80.2
80.1
78.7
53.9
53.0
28.3
25.4
O
O
OH
NH2
O
O
O
(+/-)-24a
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

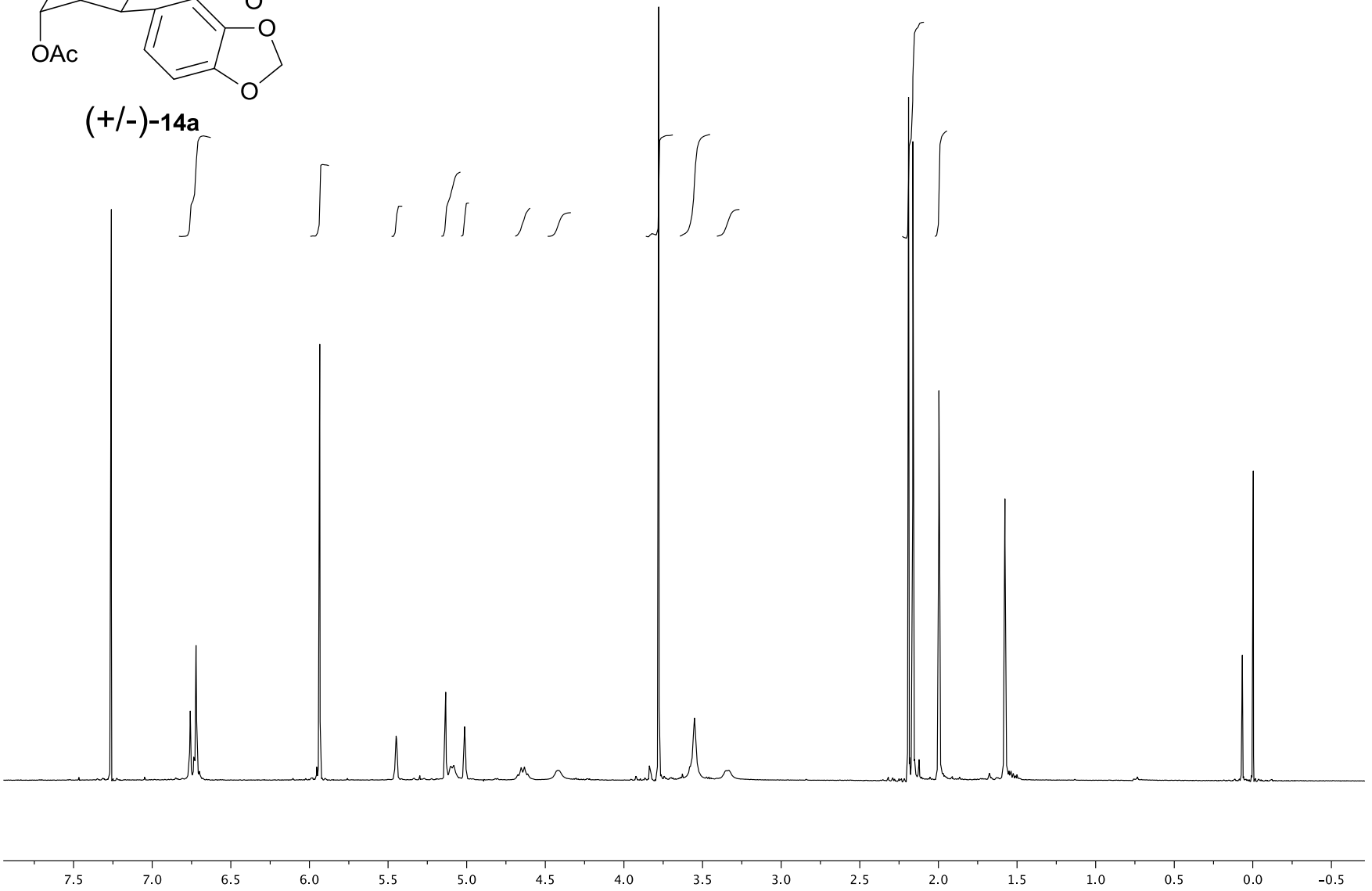

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

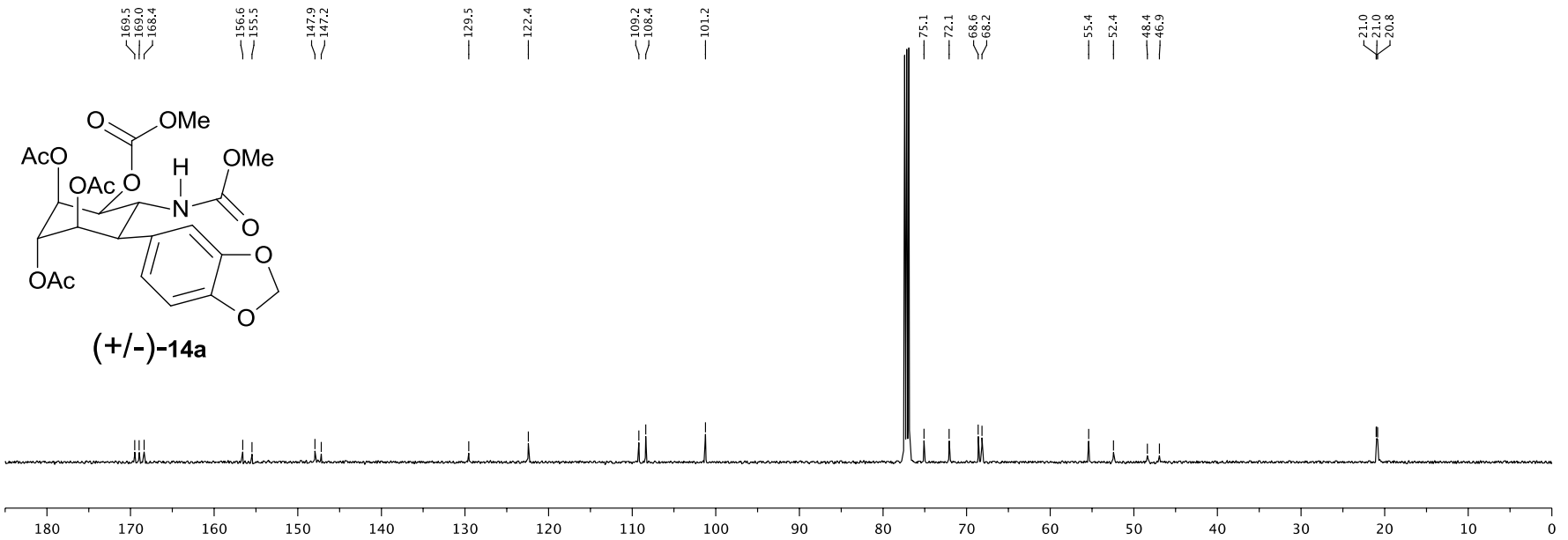

OCO2Me
NHCO2Me
(+/-)-24b
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

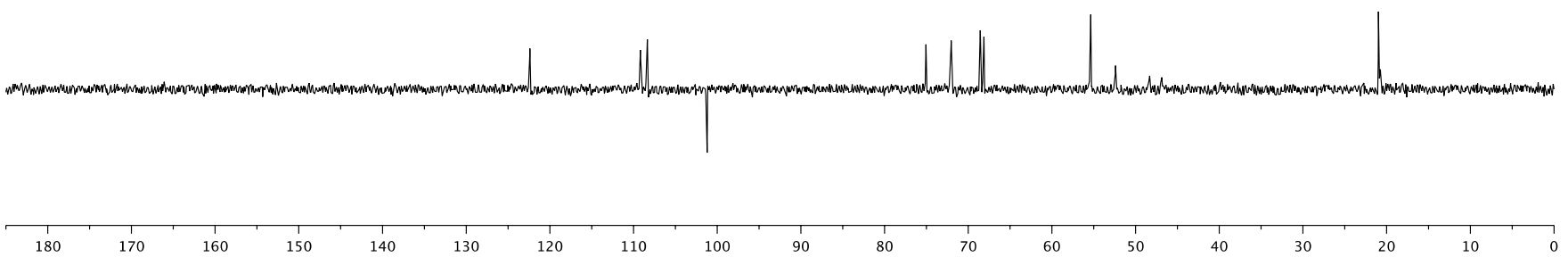

206.6
156.3
155.0
148.0
147.4
130.3
122.7
109.1
108.5
108.4
101.2
99.5
79.9
77.8
55.4
52.4
51.3
49.9
28.5
25.5
OCO2Me
NHCO2Me
O
(+/-)-24b
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

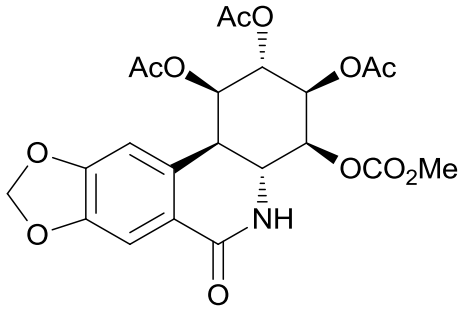

O
OMe
AcO
H
OMe
OAc
O
N
O
O
OAc
O

(+/-)-14a

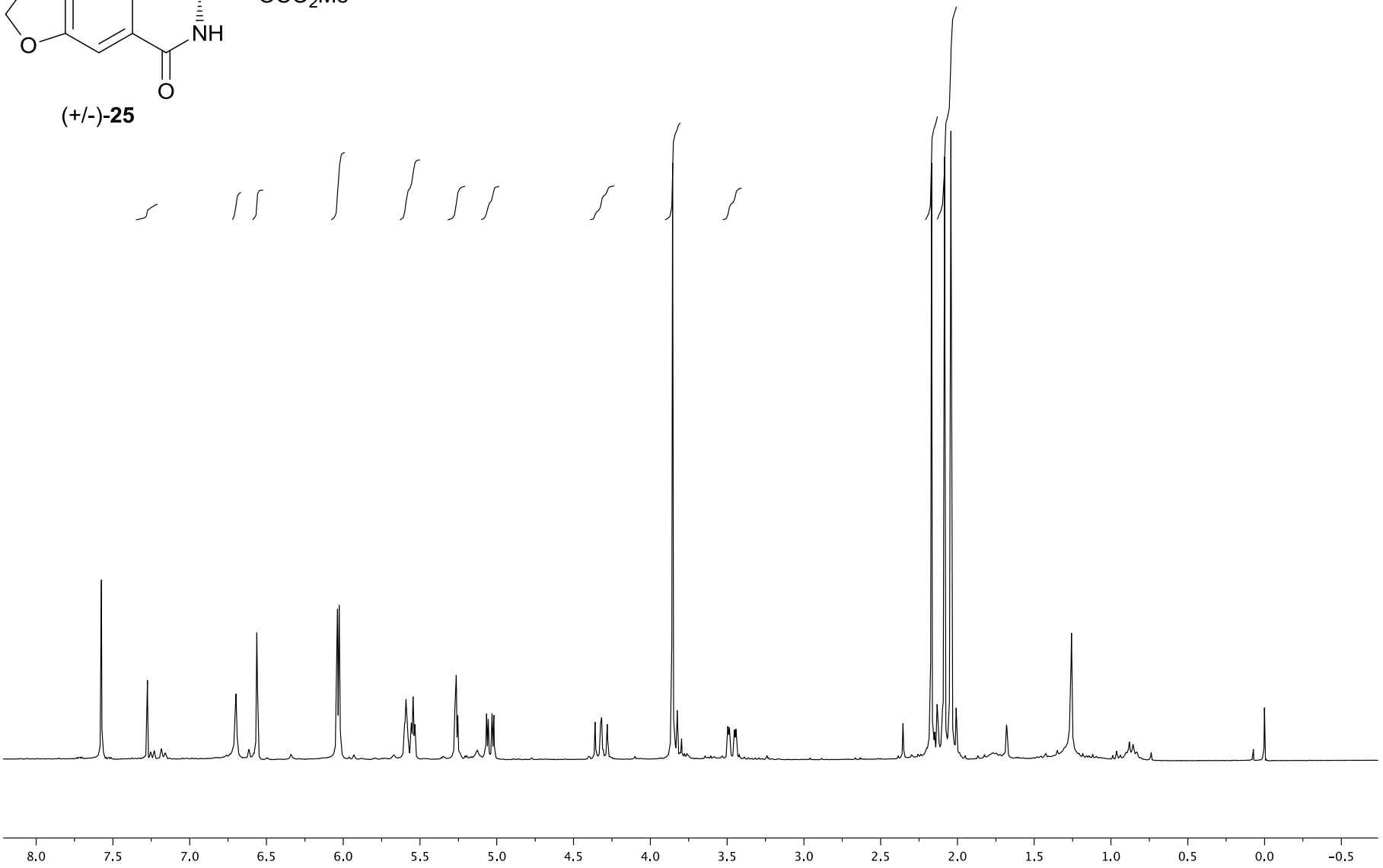

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

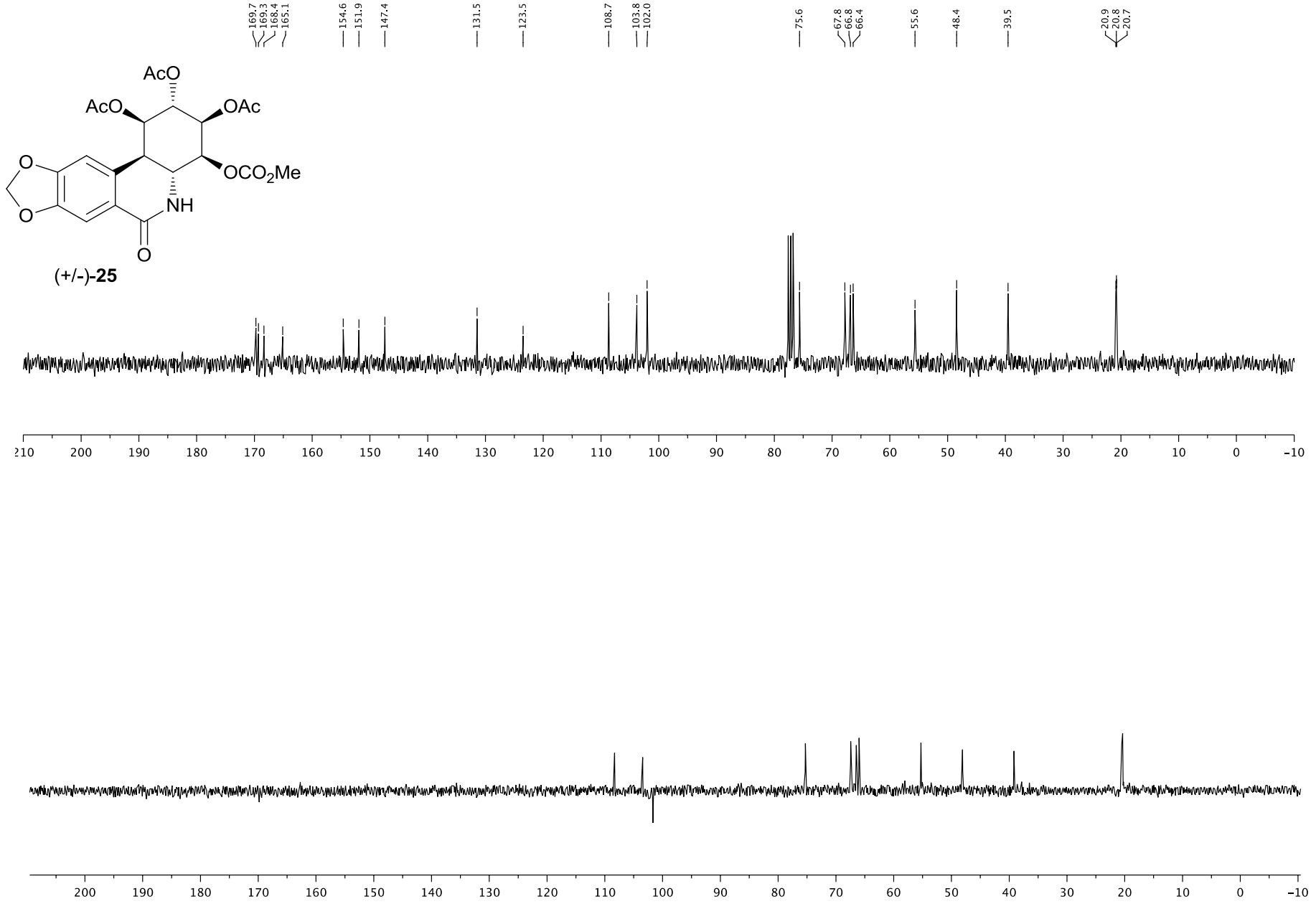

169.5
169.0
168.4
156.6
155.5
147.9
147.2
129.5
122.4
109.2
108.4
101.2
75.1
72.1
68.6
68.2
55.4
52.4
48.4
46.9
21.0
21.0
20.8
O
OMe
AcO
OAc
O
H
N
OMe
O
O
OAc
O
(+/-)-14a
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

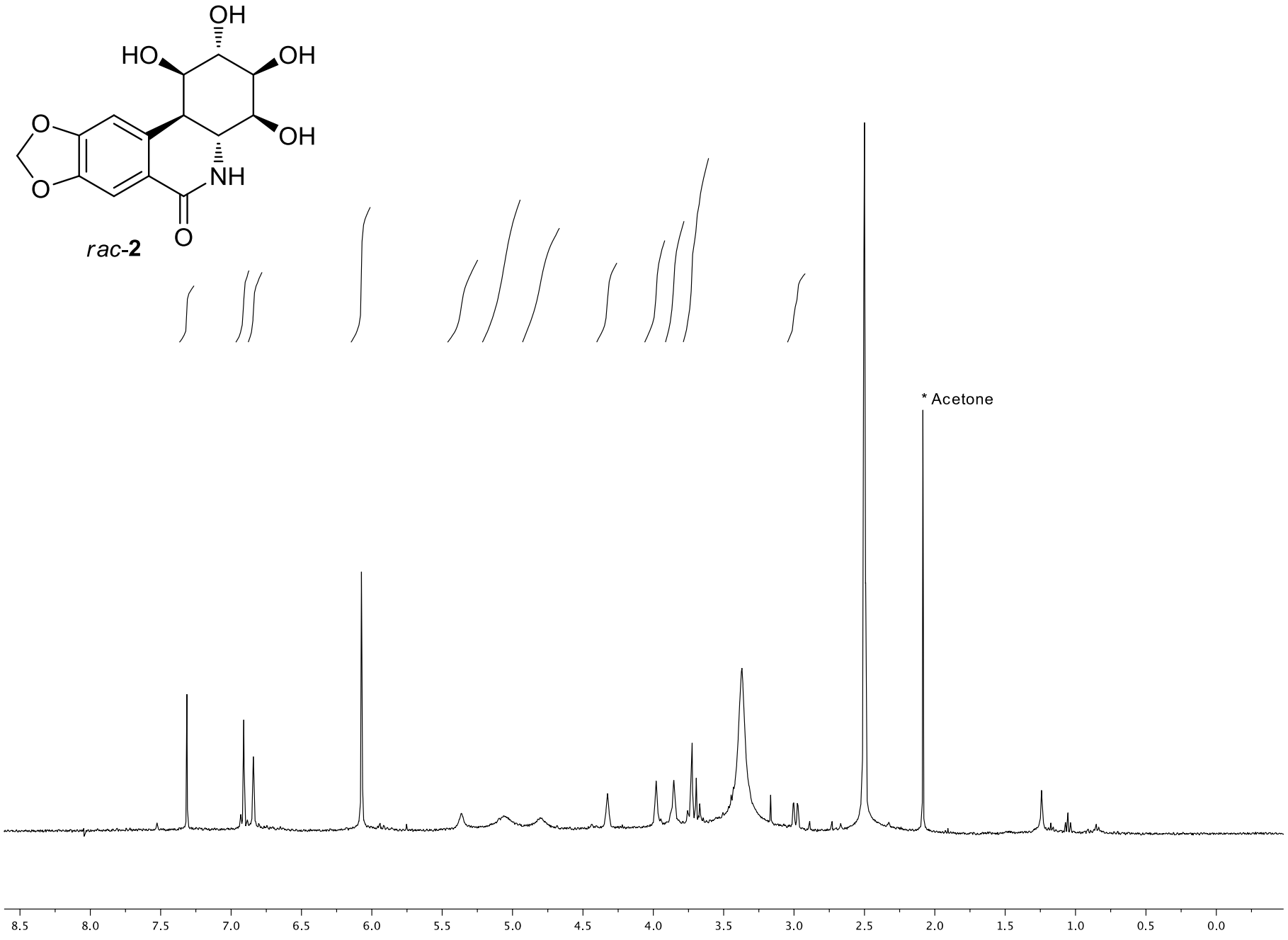

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

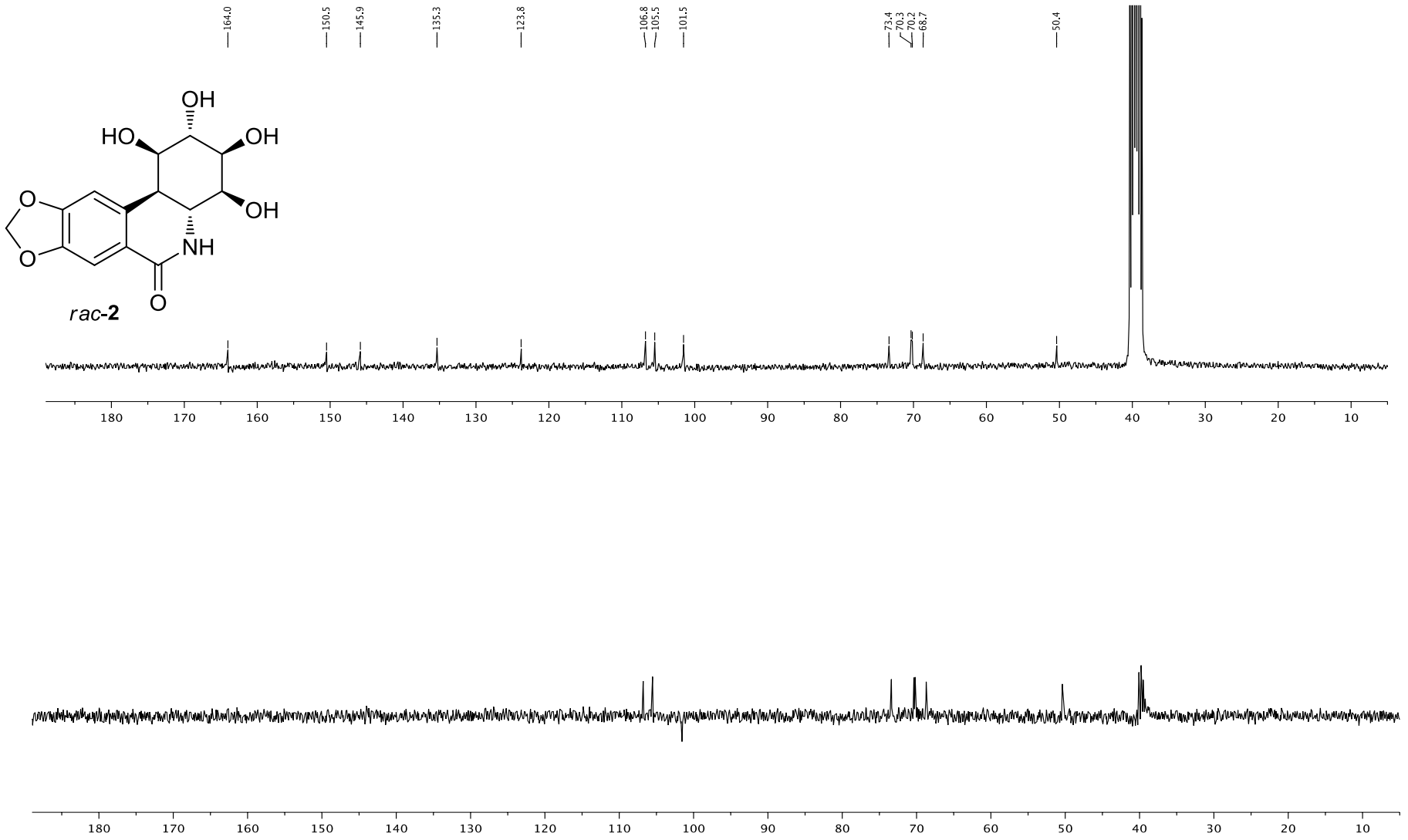

AcO
AcO
OAc
O
O
OCO2Me
NH
O

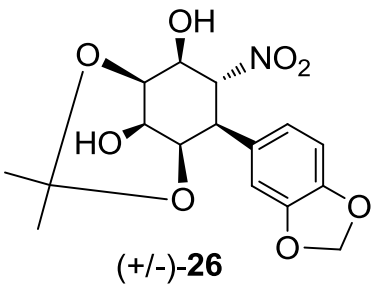
(+/-)-**25**


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

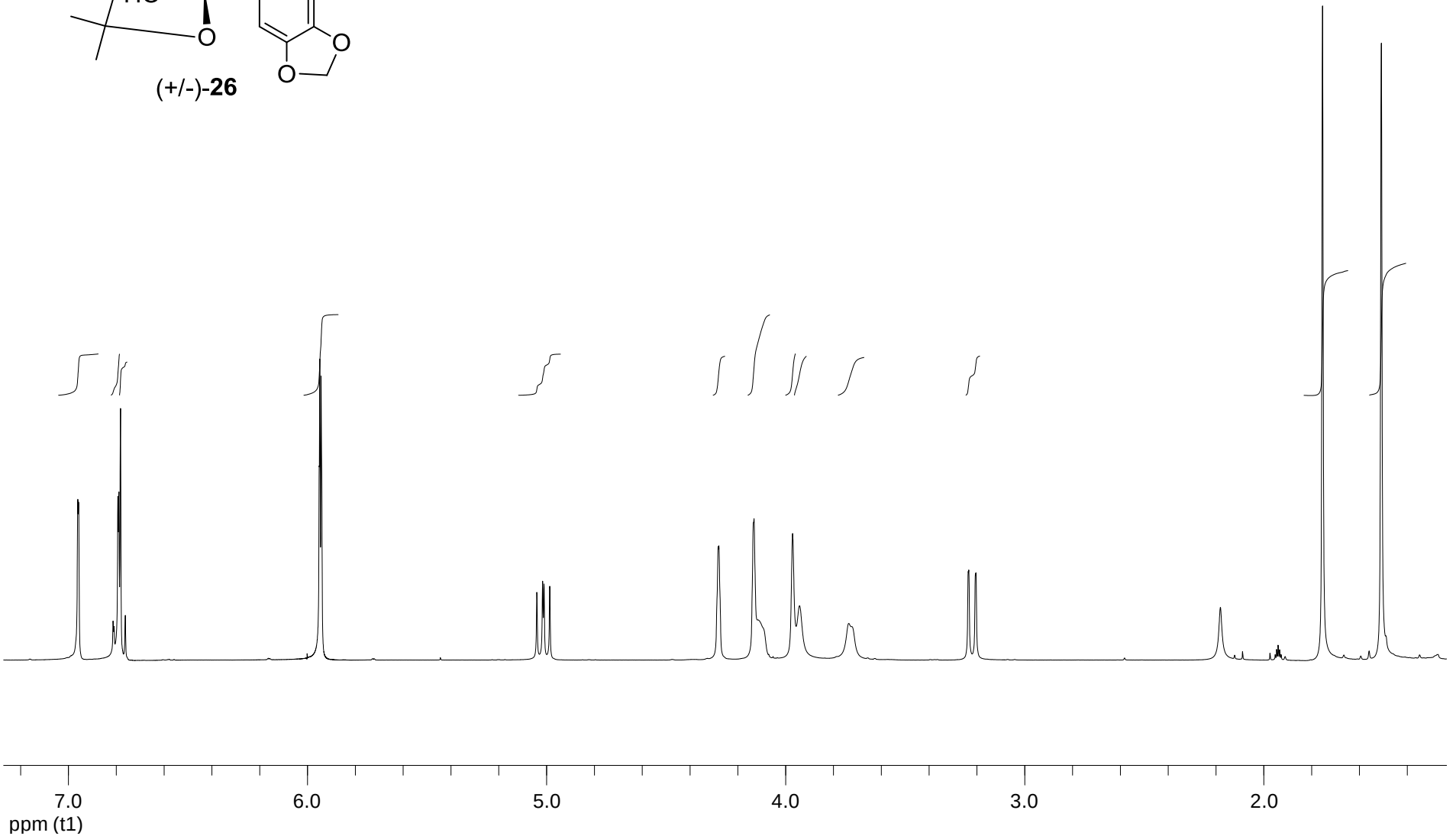

169.7
169.3
168.4
165.1
154.6
151.9
147.4
131.5
123.5
108.7
103.8
102.0
75.6
67.8
66.8
66.4
55.6
48.4
39.5
20.9
20.8
20.7
AcO
AcO
OAc
OCO2Me
O
O
NH
O
(+/-)-25
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

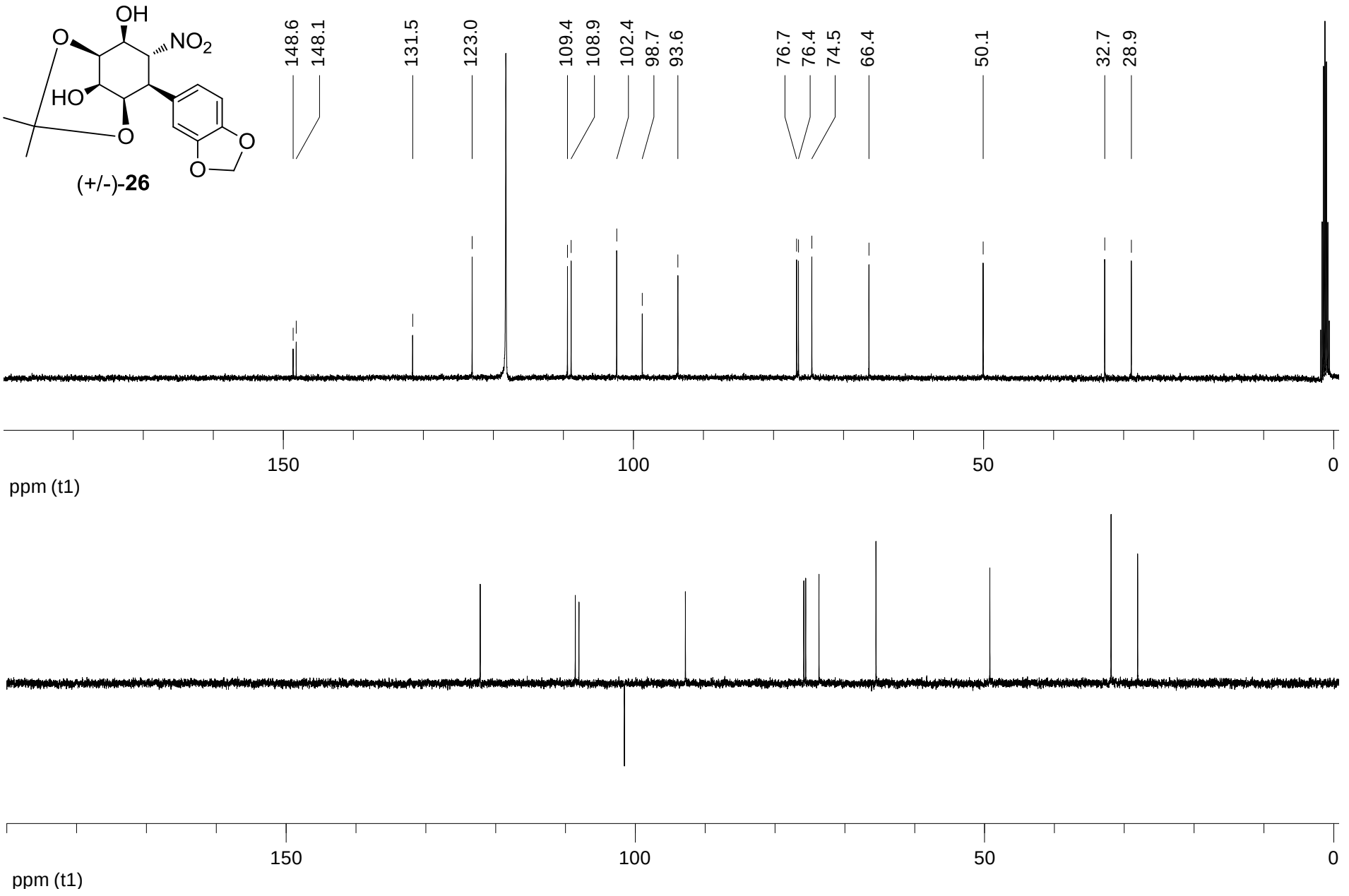

OH
HO
OH
OH
O
O
NH
O
rac-2
* Acetone
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

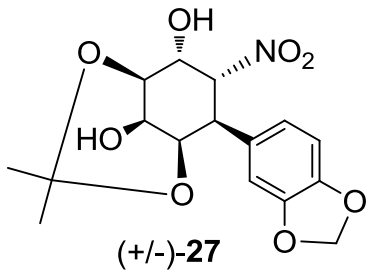

164.0
150.5
145.9
135.3
123.8
106.8
105.5
101.5
73.4
70.3
70.2
68.7
50.4
OH
HO
OH
OH
O
O
NH
O
rac-2
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10



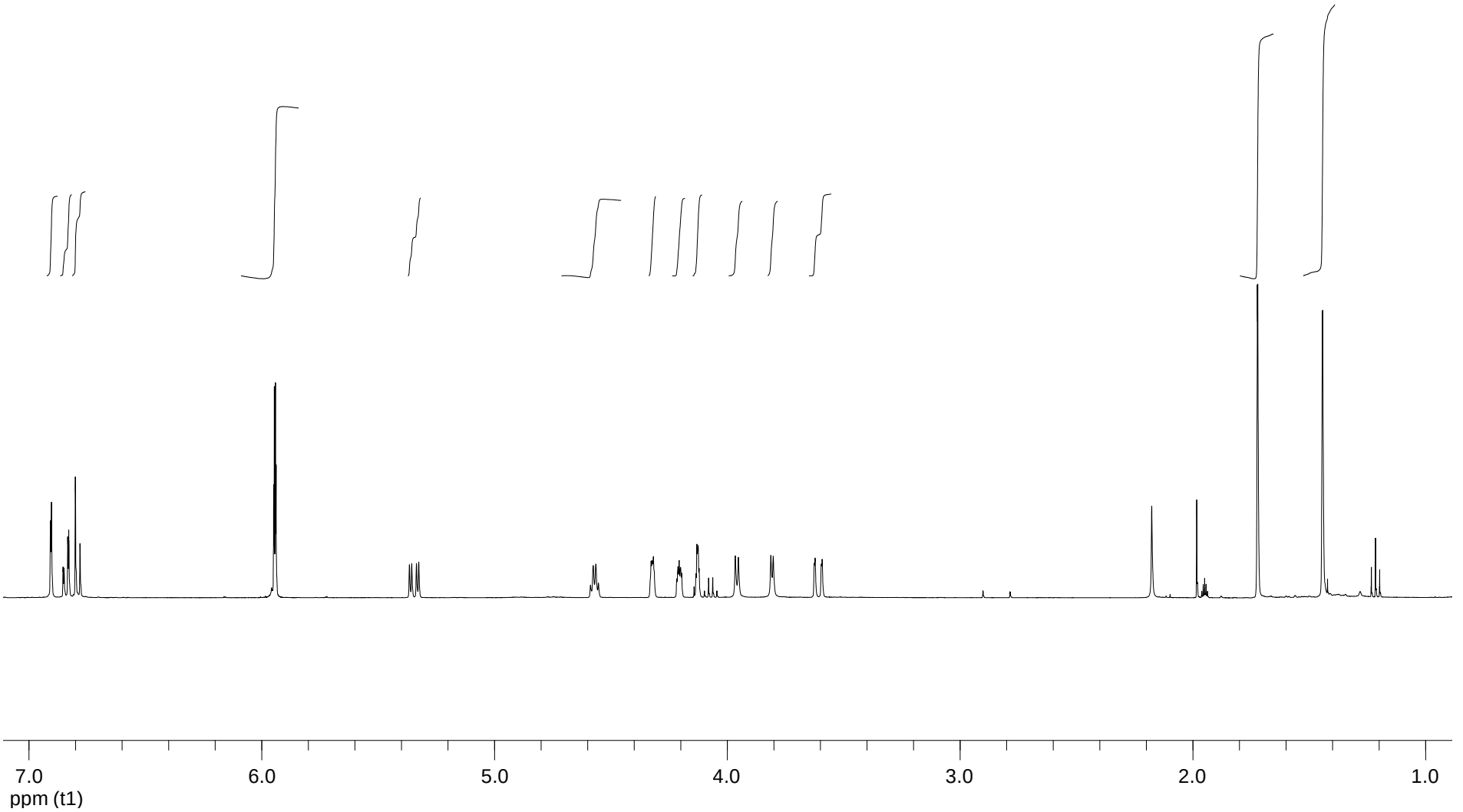
(+/-)-**26**

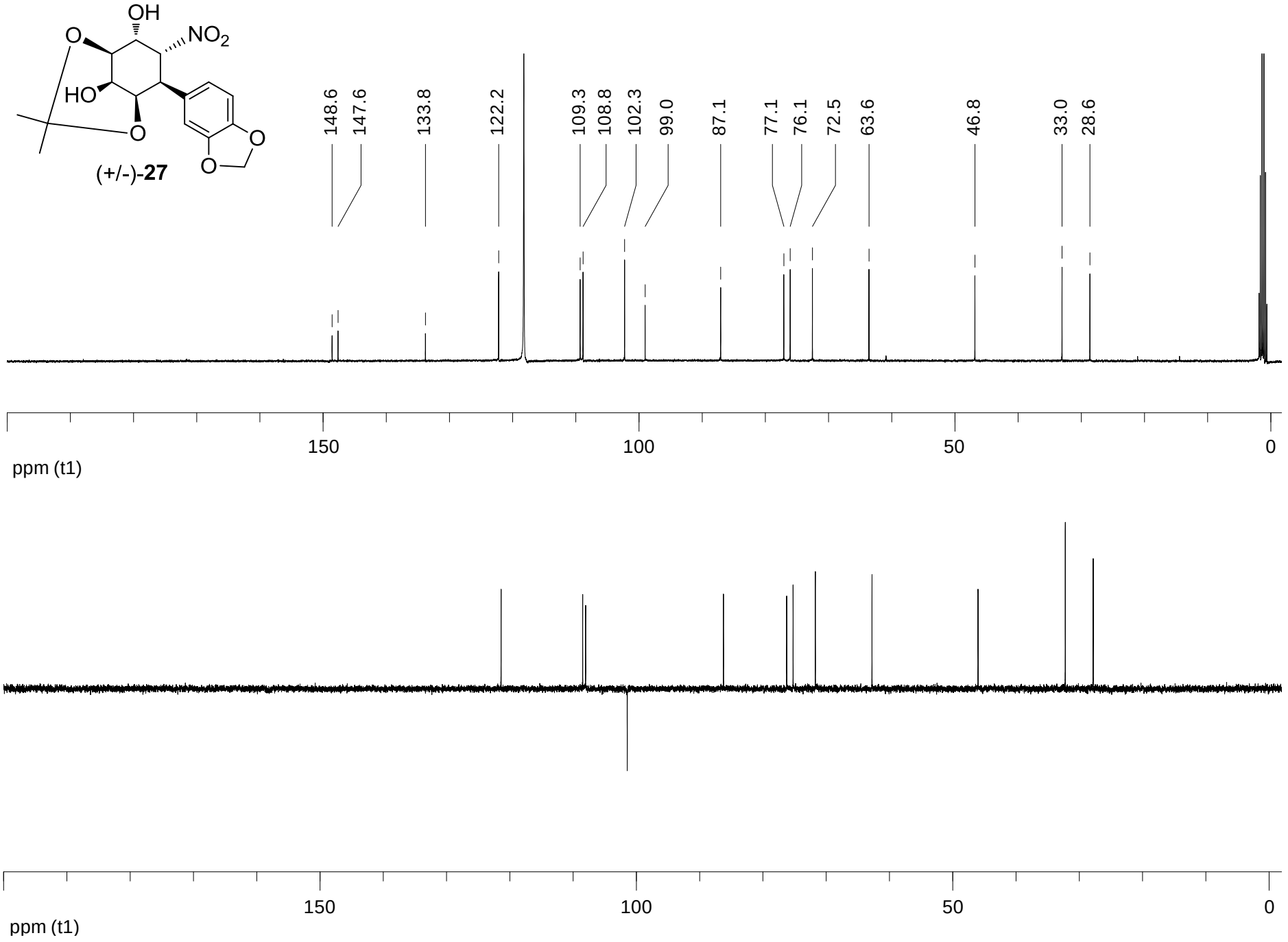


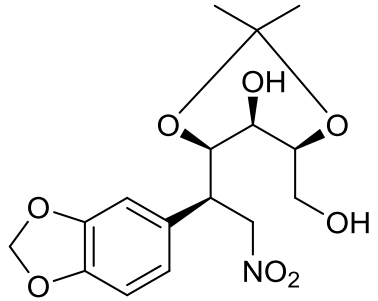

OH
O
NO2
HO
O
O
O
(+/-)-26
148.6
148.1
131.5
123.0
109.4
108.9
102.4
98.7
93.6
76.7
76.4
74.5
66.4
50.1
32.7
28.9
150
100
50
0
ppm (t1)
150
100
50
0
ppm (t1)



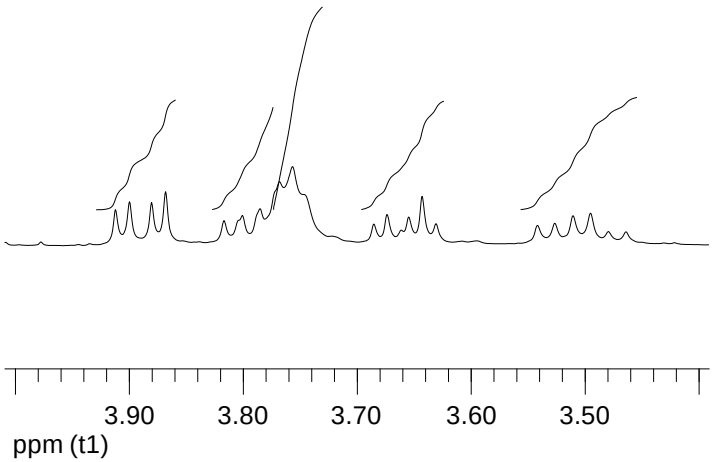
(+/-)-**27**



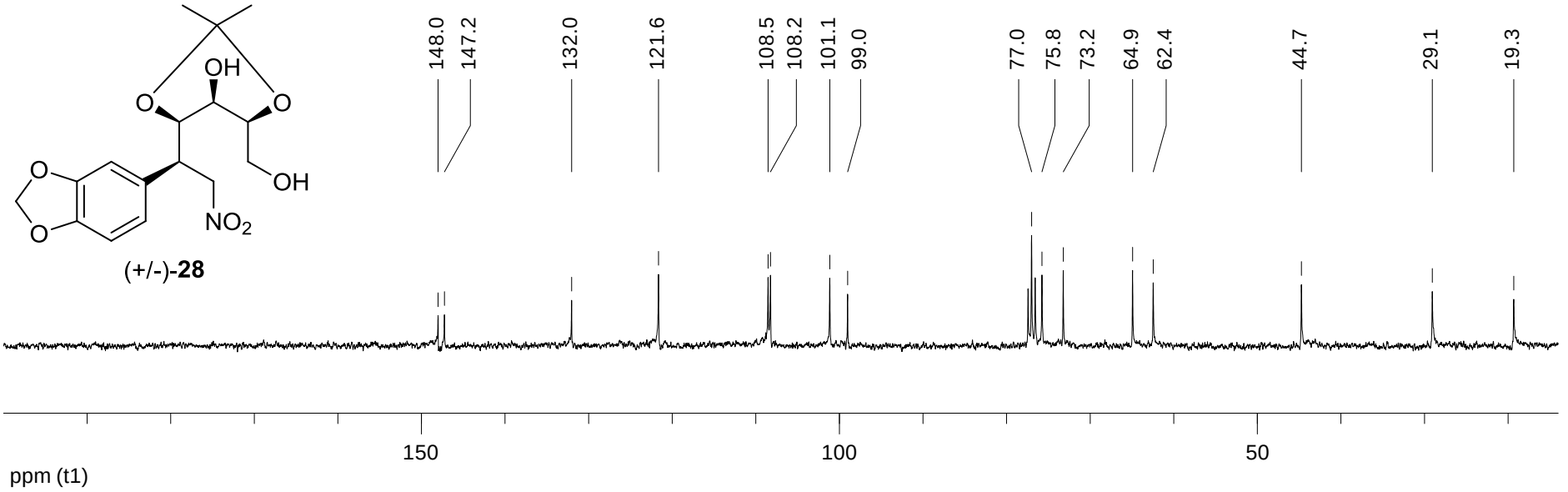

OH
O
NO2
HO
O
O
O
(+/-)-27
148.6
147.6
133.8
122.2
109.3
108.8
102.3
99.0
87.1
77.1
76.1
72.5
63.6
46.8
33.0
28.6
150
100
50
0
ppm (t1)
150
100
50
0
ppm (t1)

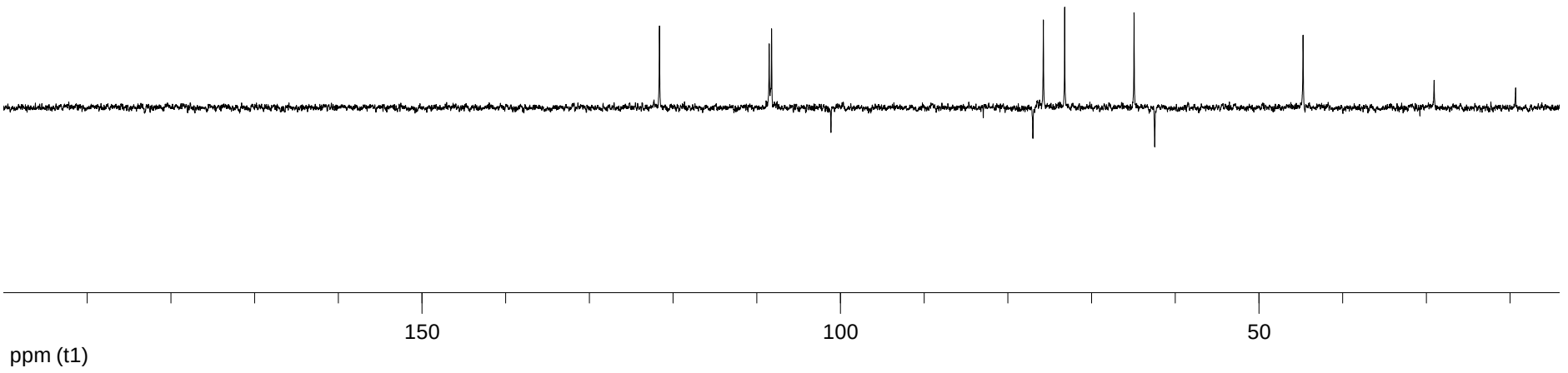

OH
O
O
O
O
OH
NO2

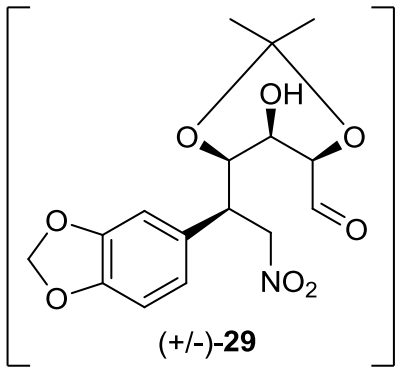
(+/-)-**28**


3.90
3.80
3.70
3.60
3.50
ppm (t1)

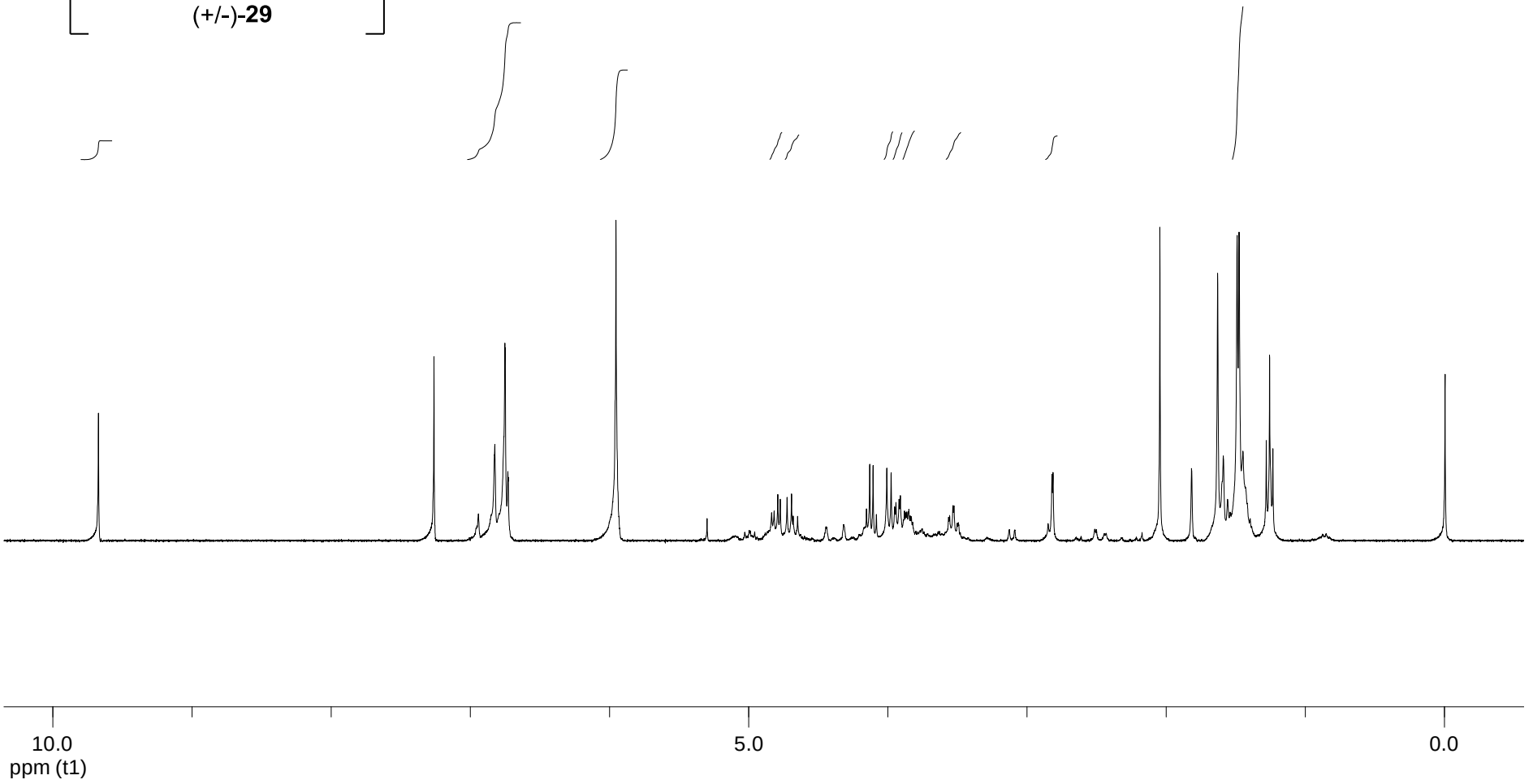
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

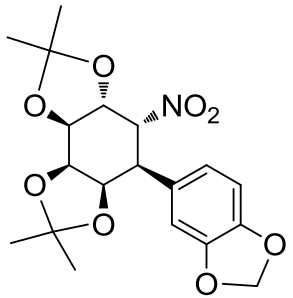

148.0
147.2
132.0
121.6
108.5
108.2
101.1
99.0
77.0
75.8
73.2
64.9
62.4
44.7
29.1
19.3
OH
O
O
O
O
OH
NO2
(+/-)-28
150
100
50
ppm (t1)


150
100
50
ppm (t1)

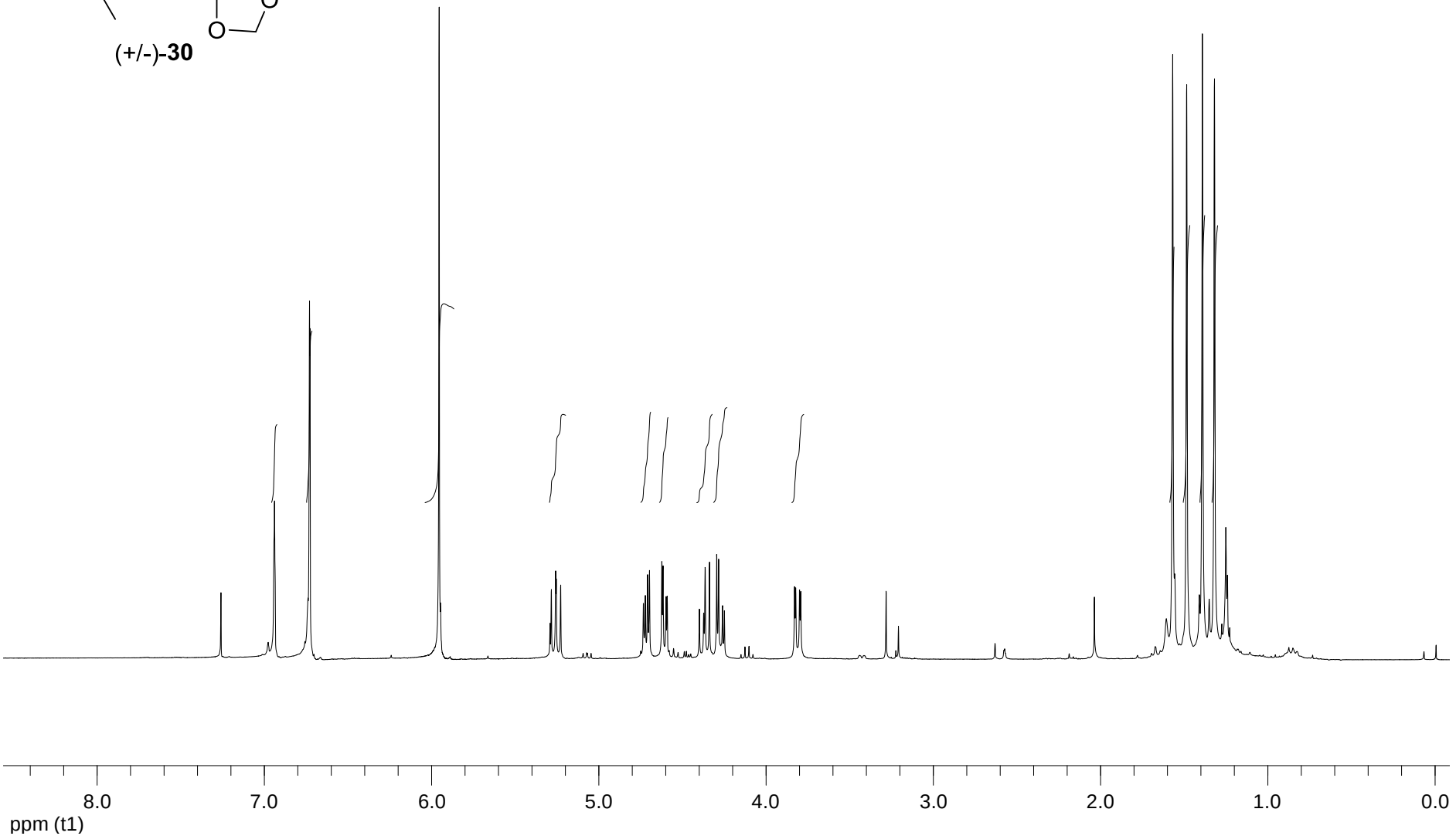


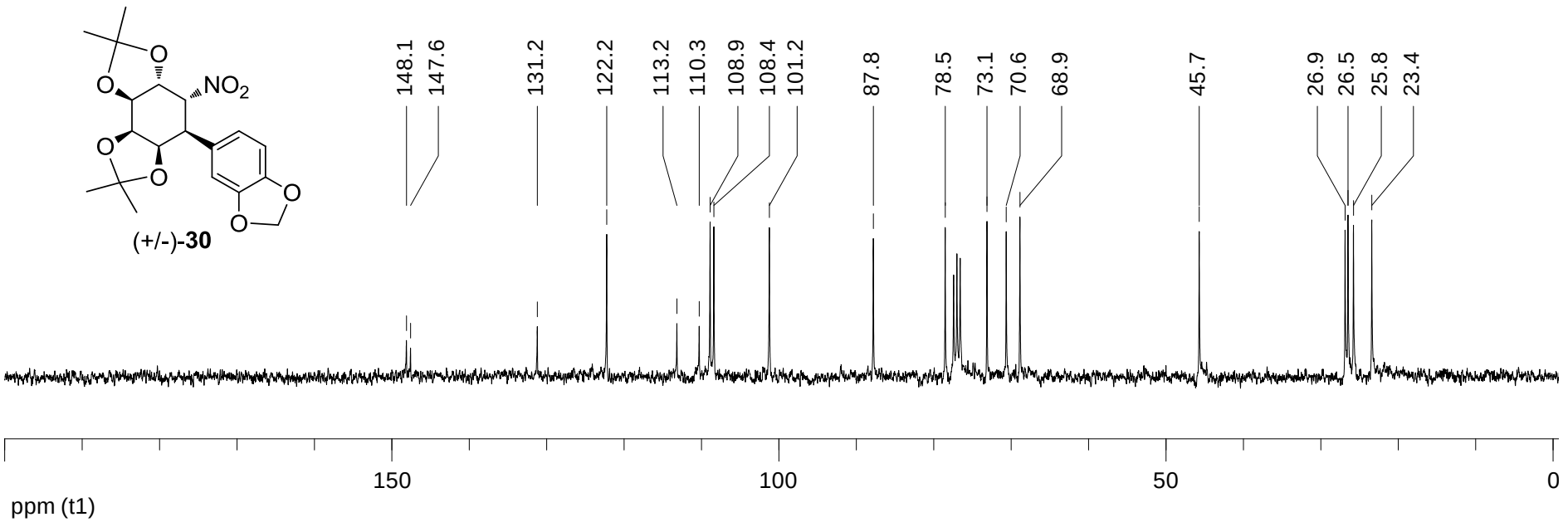
(+/-)-**29**



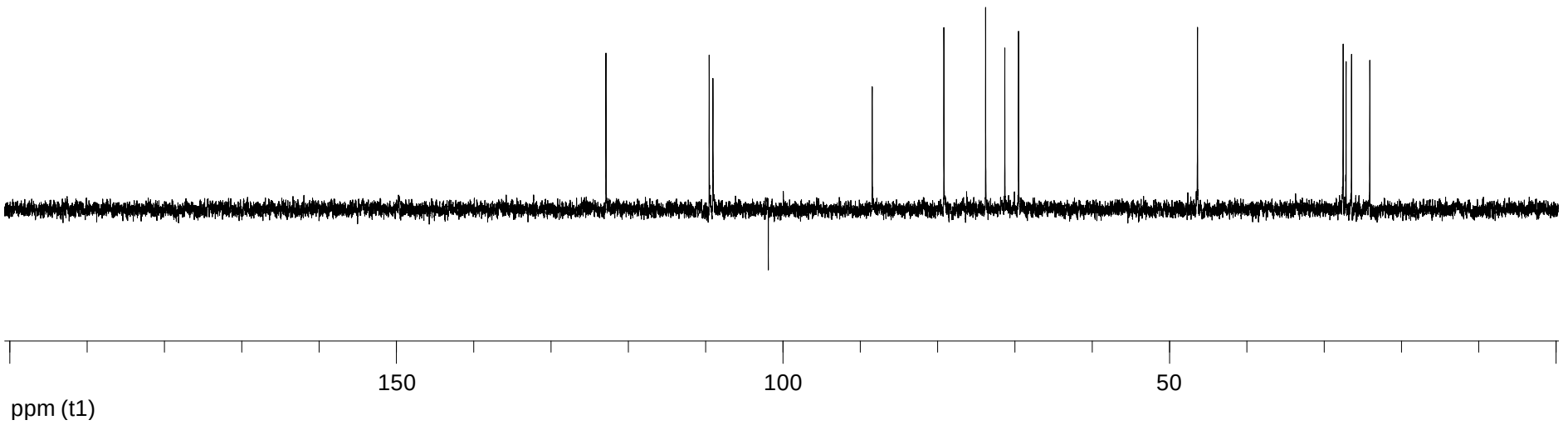


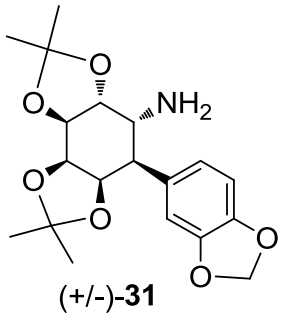
(+/-)-**30**



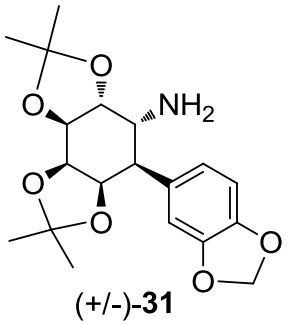

148.1
147.6
131.2
122.2
113.2
110.3
108.9
108.4
101.2
87.8
78.5
73.1
70.6
68.9
45.7
26.9
26.5
25.8
23.4
150
100
50
0
ppm (t1)

(+/-)-**30**


150
100
50
ppm (t1)

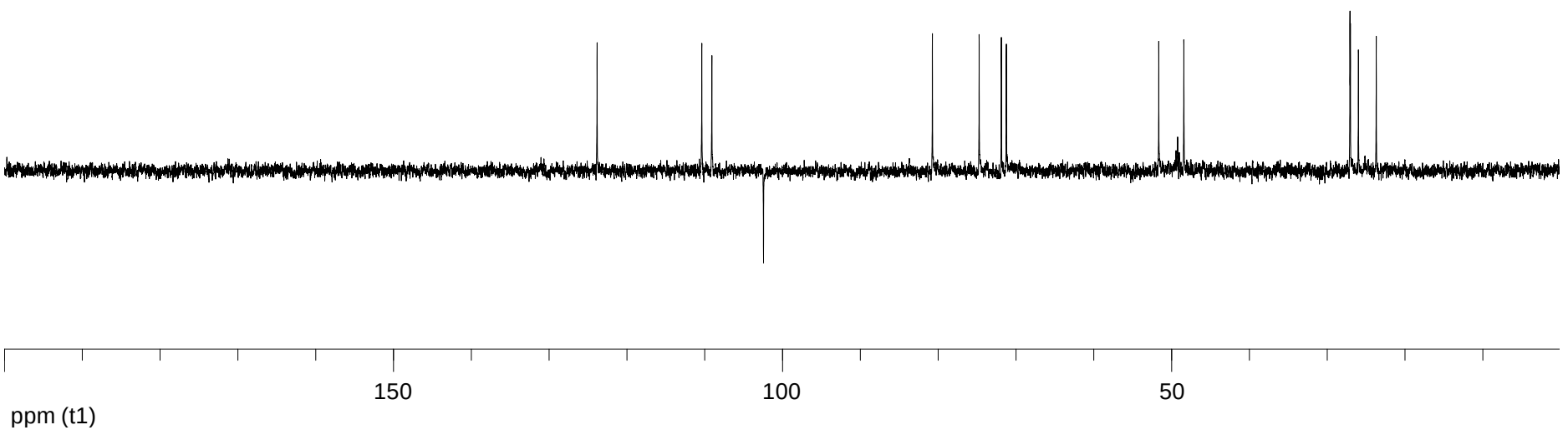


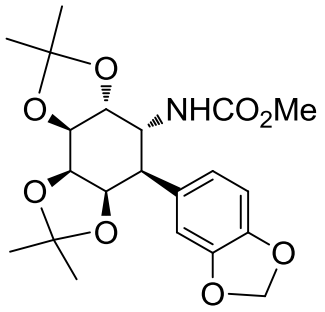
(+/-)-**31**


NH2
O
O
O
O
O
O

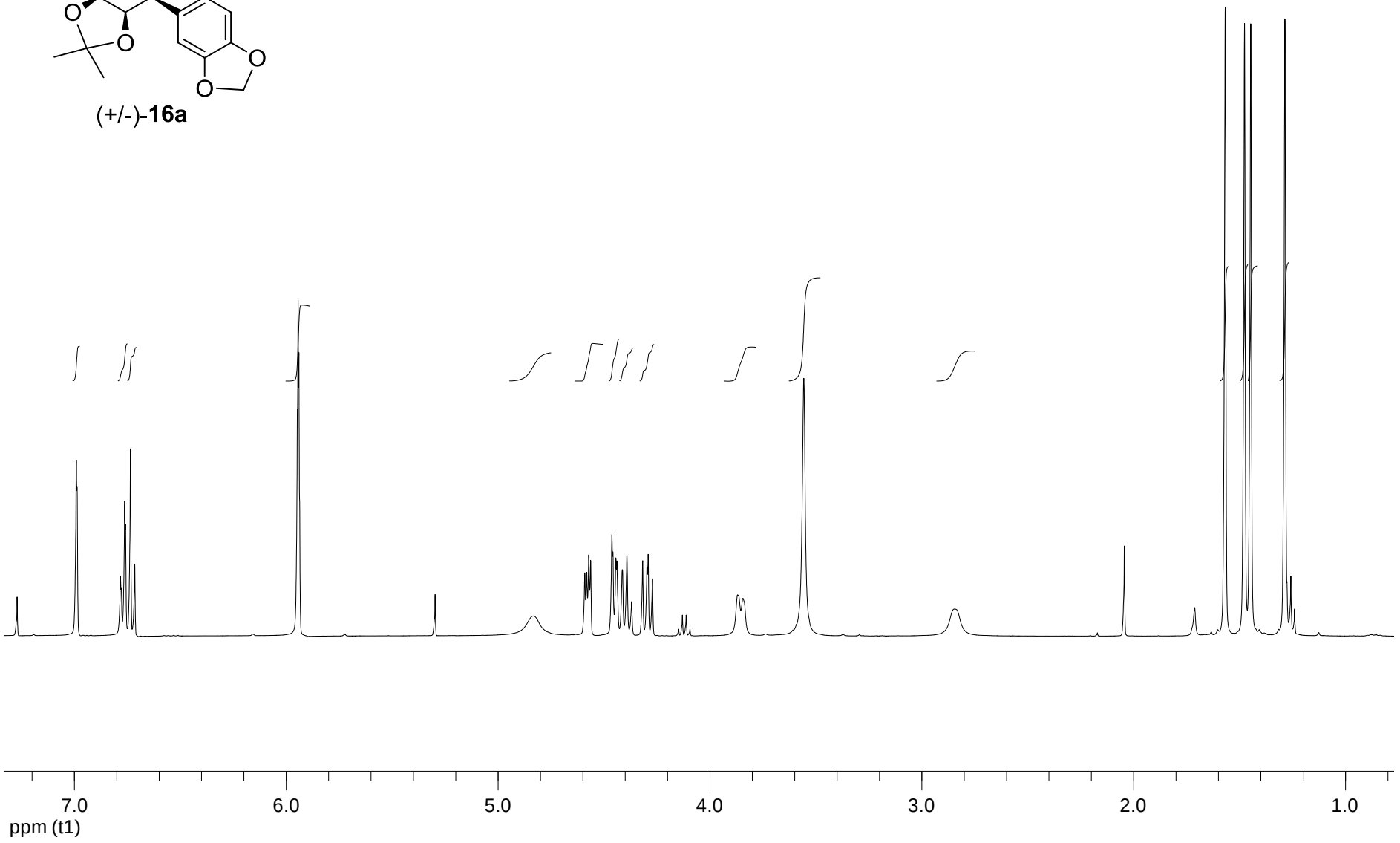
(+/-)-**31**

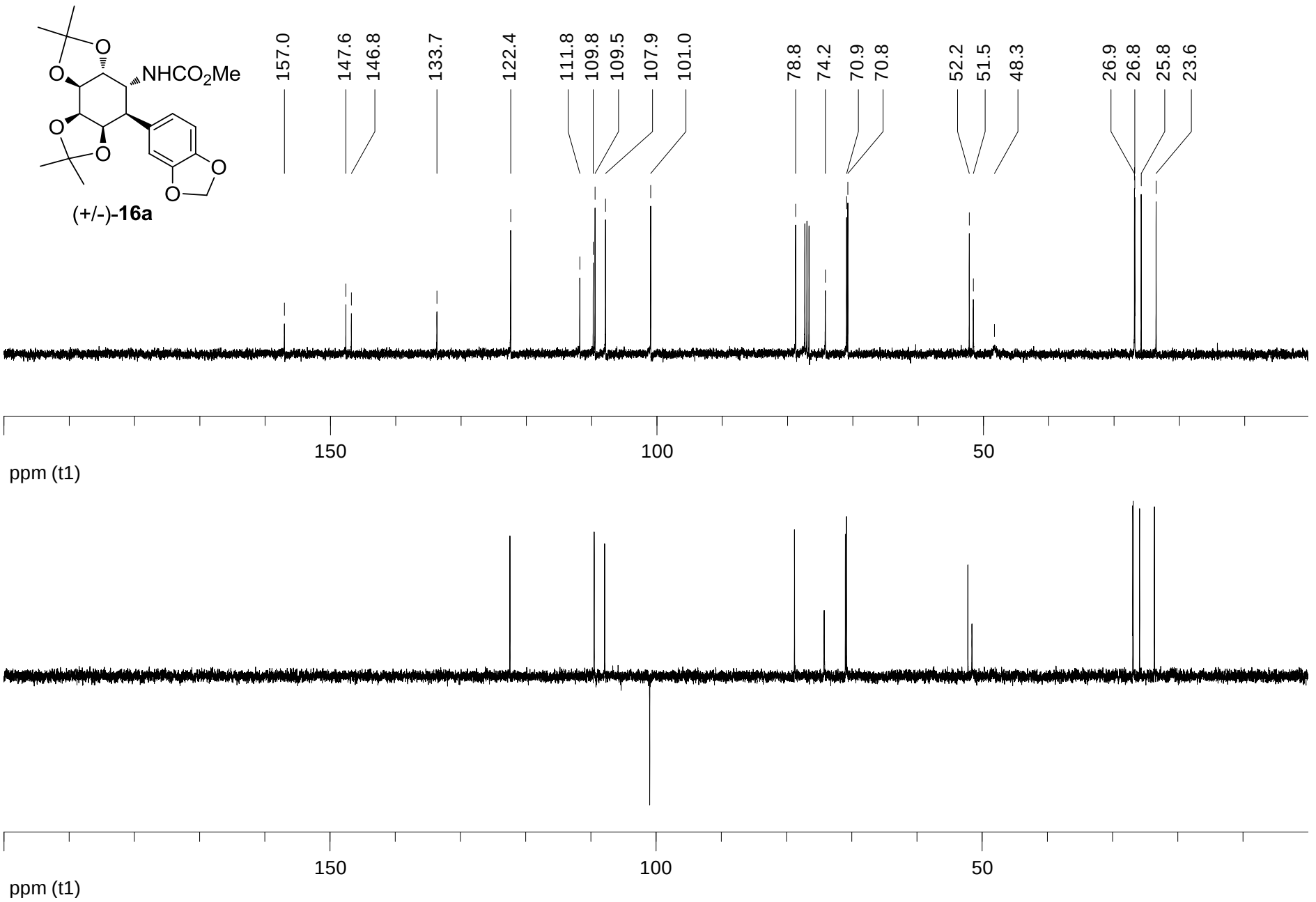
149.5
148.9
133.6
123.9
113.7
111.1
110.5
109.2
102.6
80.9
74.8
72.0
71.4
51.8
48.5
27.2
27.1
26.1
23.8
150
100
50
ppm (t1)

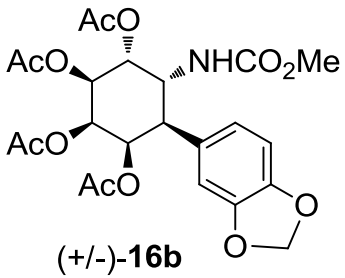

150
100
50
ppm (t1)



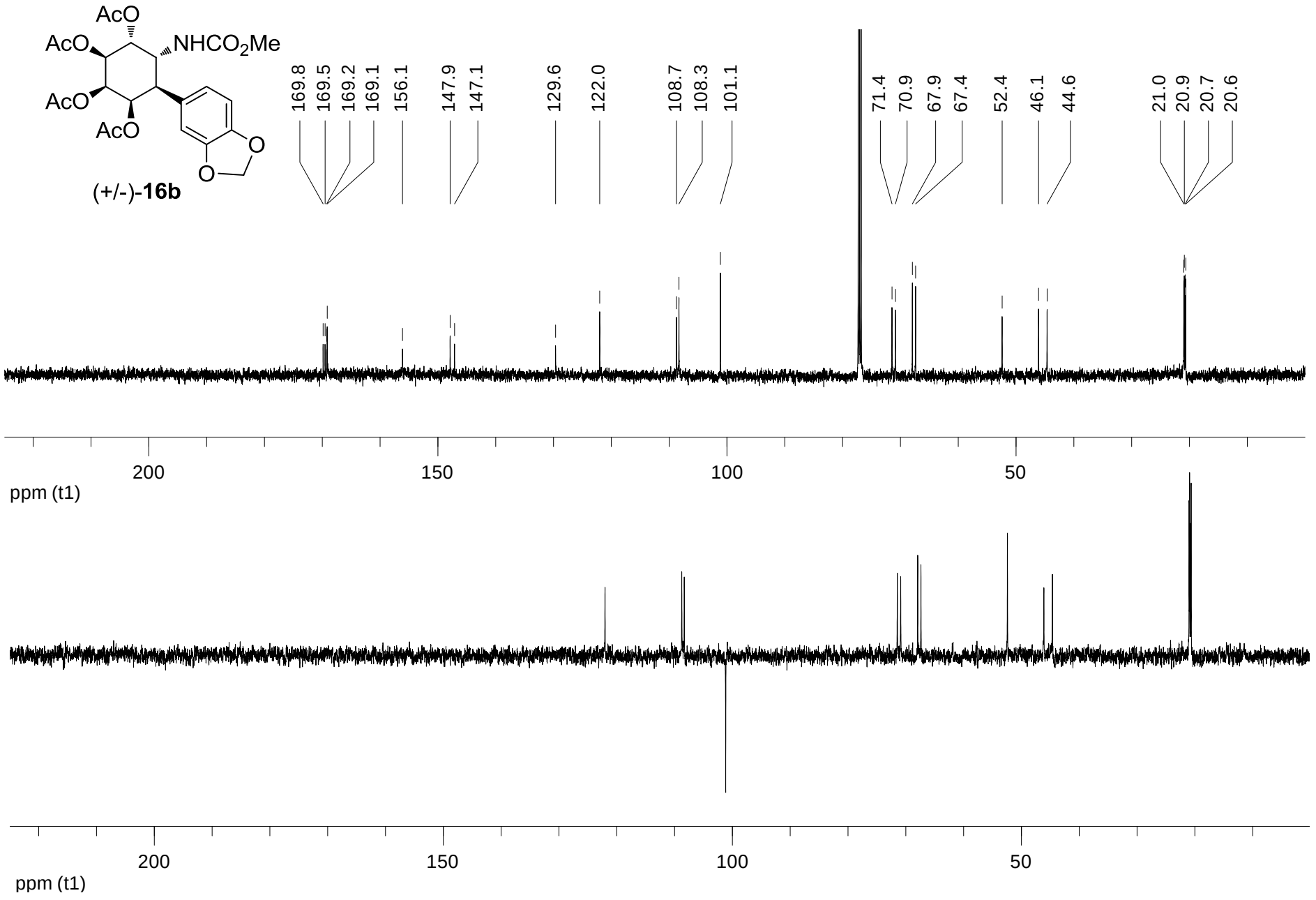
(+/-)-**16a**

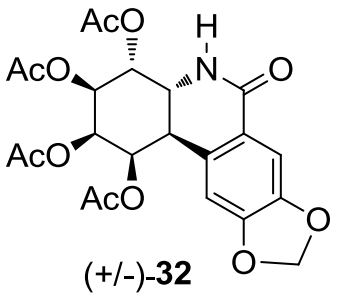



NHCO2Me
(+/-)-16a
157.0
147.6
146.8
133.7
122.4
111.8
109.8
109.5
107.9
101.0
78.8
74.2
70.9
70.8
52.2
51.5
48.3
26.9
26.8
25.8
23.6
150
100
50
ppm (t1)
150
100
50
ppm (t1)

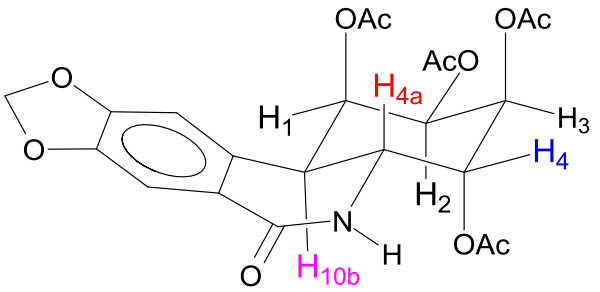


(+/-)-**16b**


AcO
AcO
NHCO2Me
AcO
AcO
O
O
(+/-)-16b
169.8
169.5
169.2
169.1
156.1
147.9
147.1
129.6
122.0
108.7
108.3
101.1
71.4
70.9
67.9
67.4
52.4
46.1
44.6
21.0
20.9
20.7
20.6
200
150
100
50
ppm (t1)
200
150
100
50
ppm (t1)



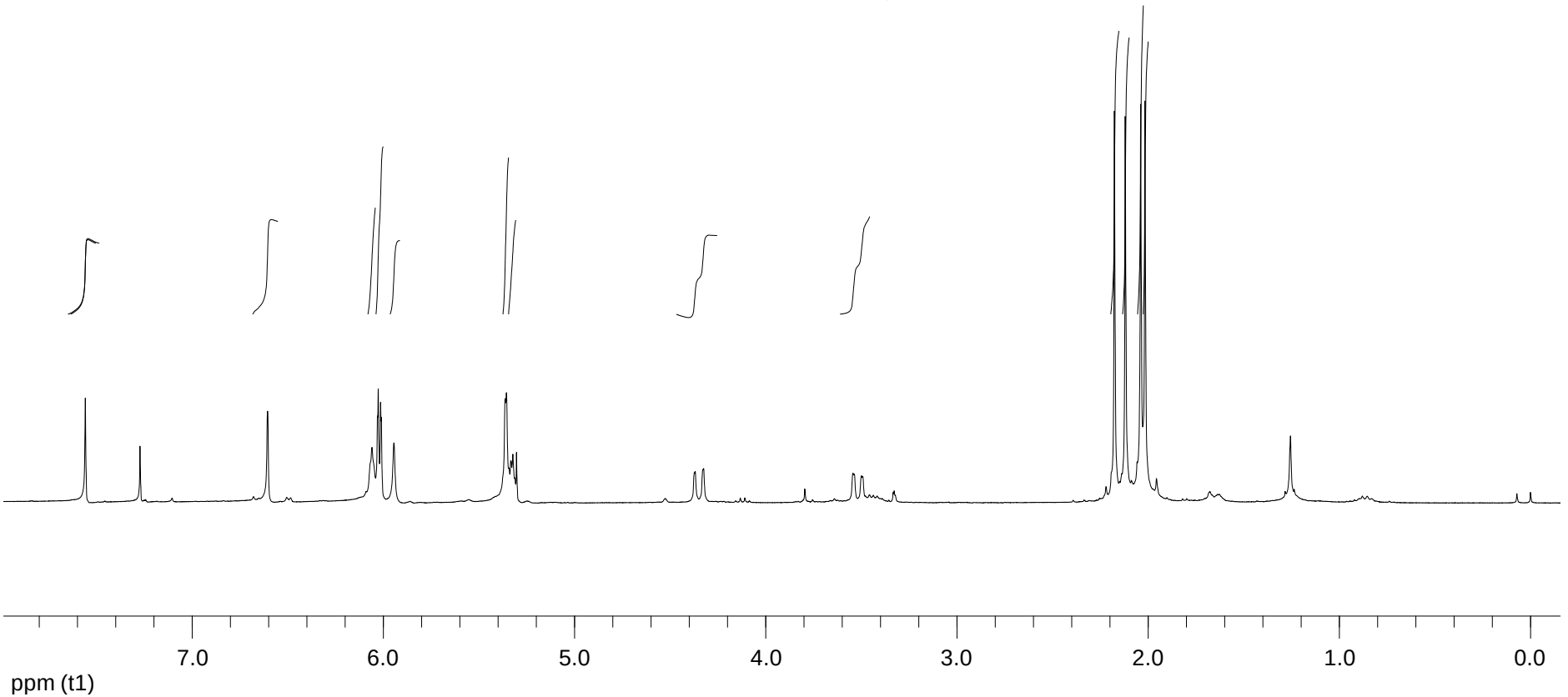
(+/-)-**32**

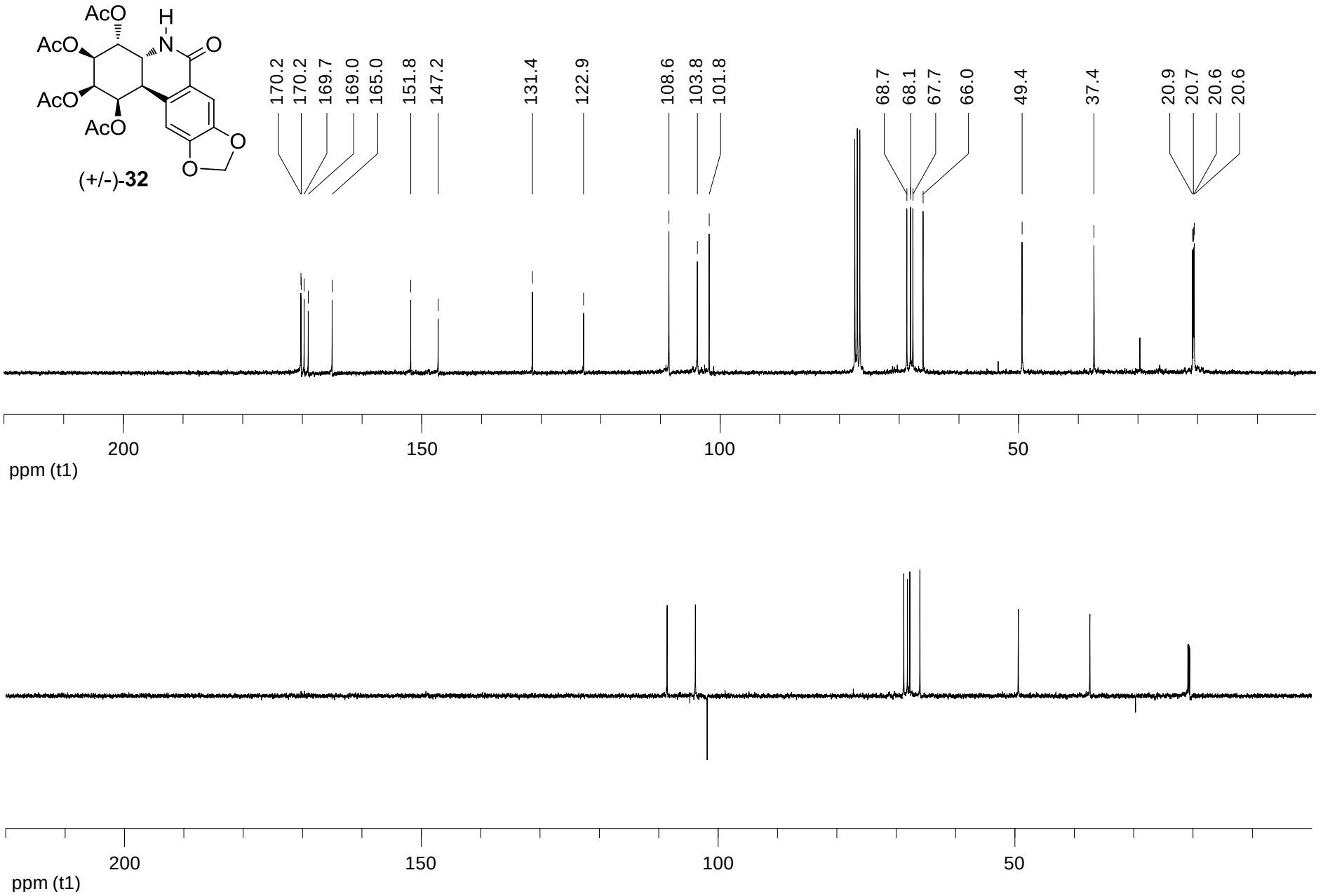


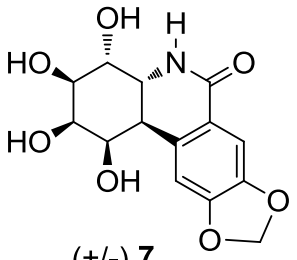
$J_{1,\ 10b}$ = 2.1 Hz

$J_{10b,\ 4a}$ = 13.3 Hz

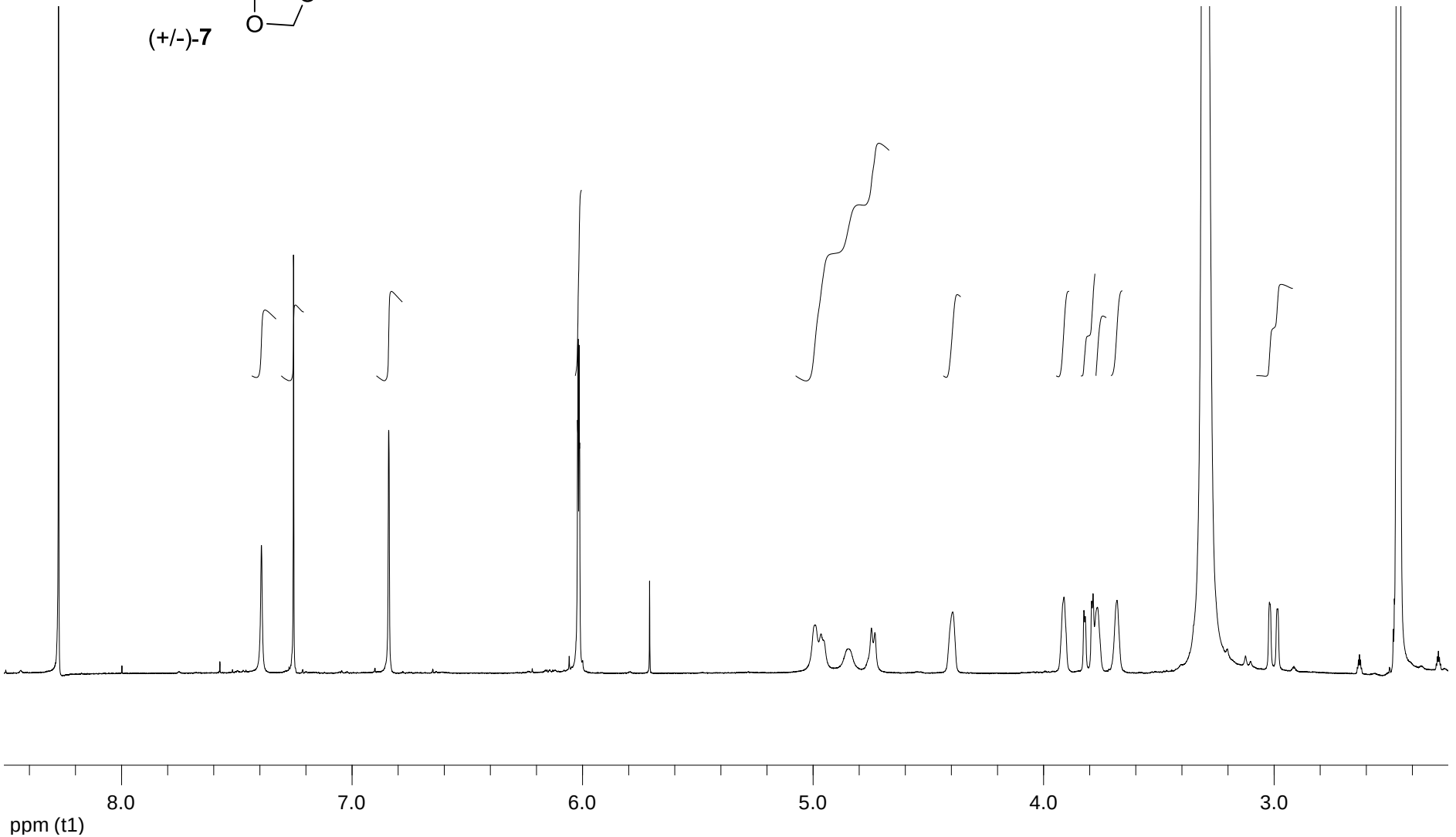
$J_{4a,4}$ = 1.3 Hz

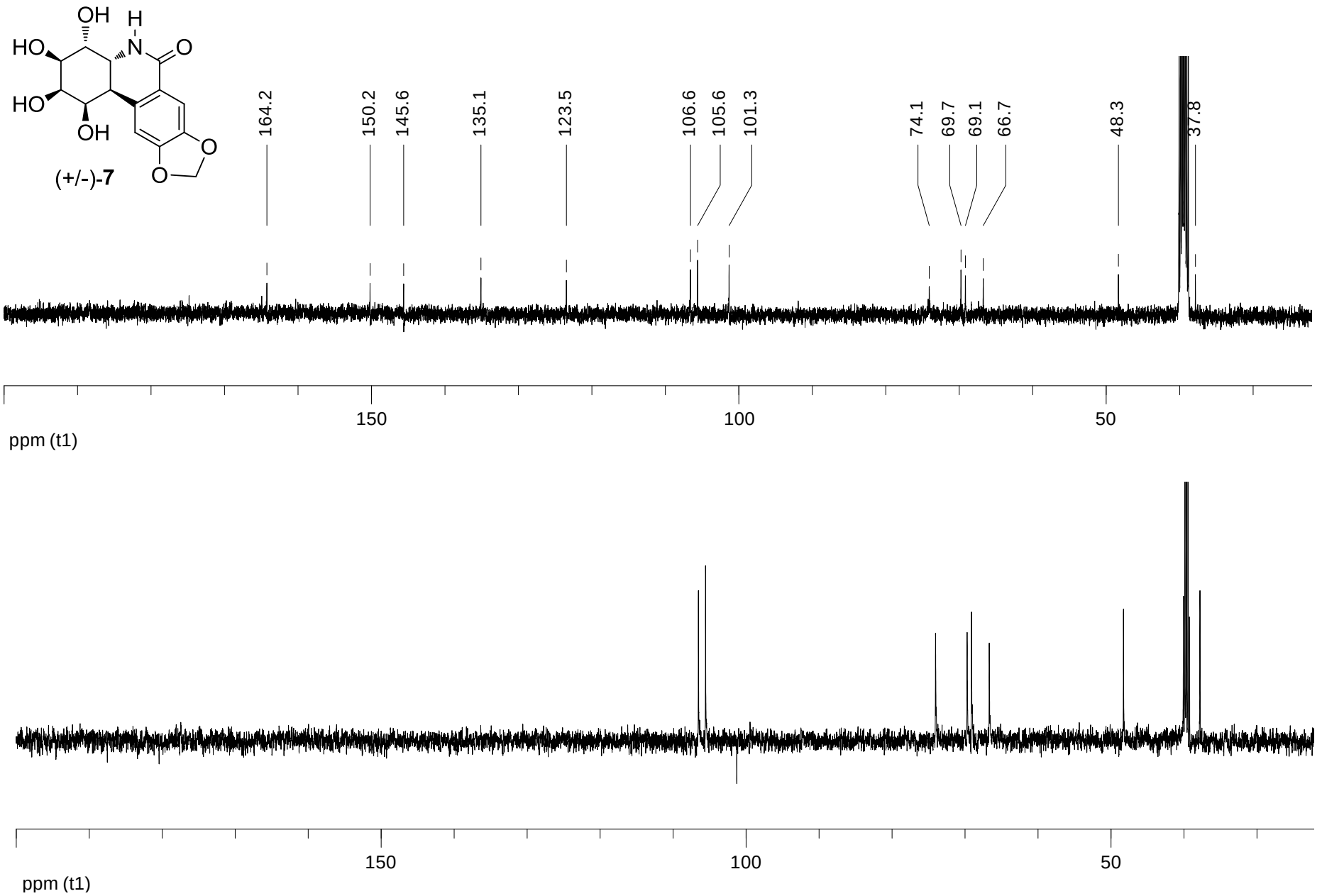


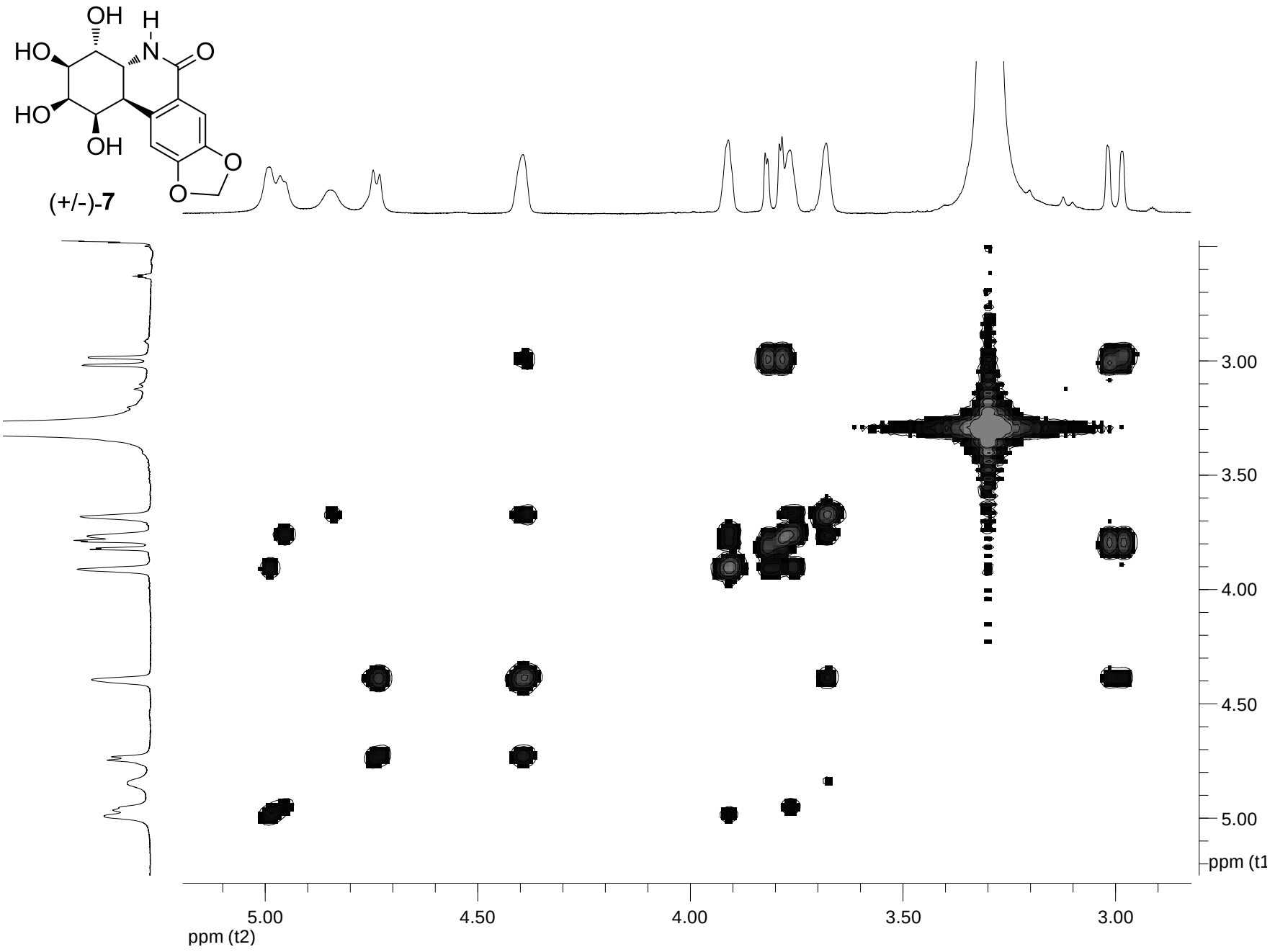

AcO
AcO
AcO
AcO
H
N
O
O
O
O
(+/-)-32
170.2
170.2
169.7
169.0
165.0
151.8
147.2
131.4
122.9
108.6
103.8
101.8
68.7
68.1
67.7
66.0
49.4
37.4
20.9
20.7
20.6
20.6
200
150
100
50
ppm (t1)
200
150
100
50
ppm (t1)

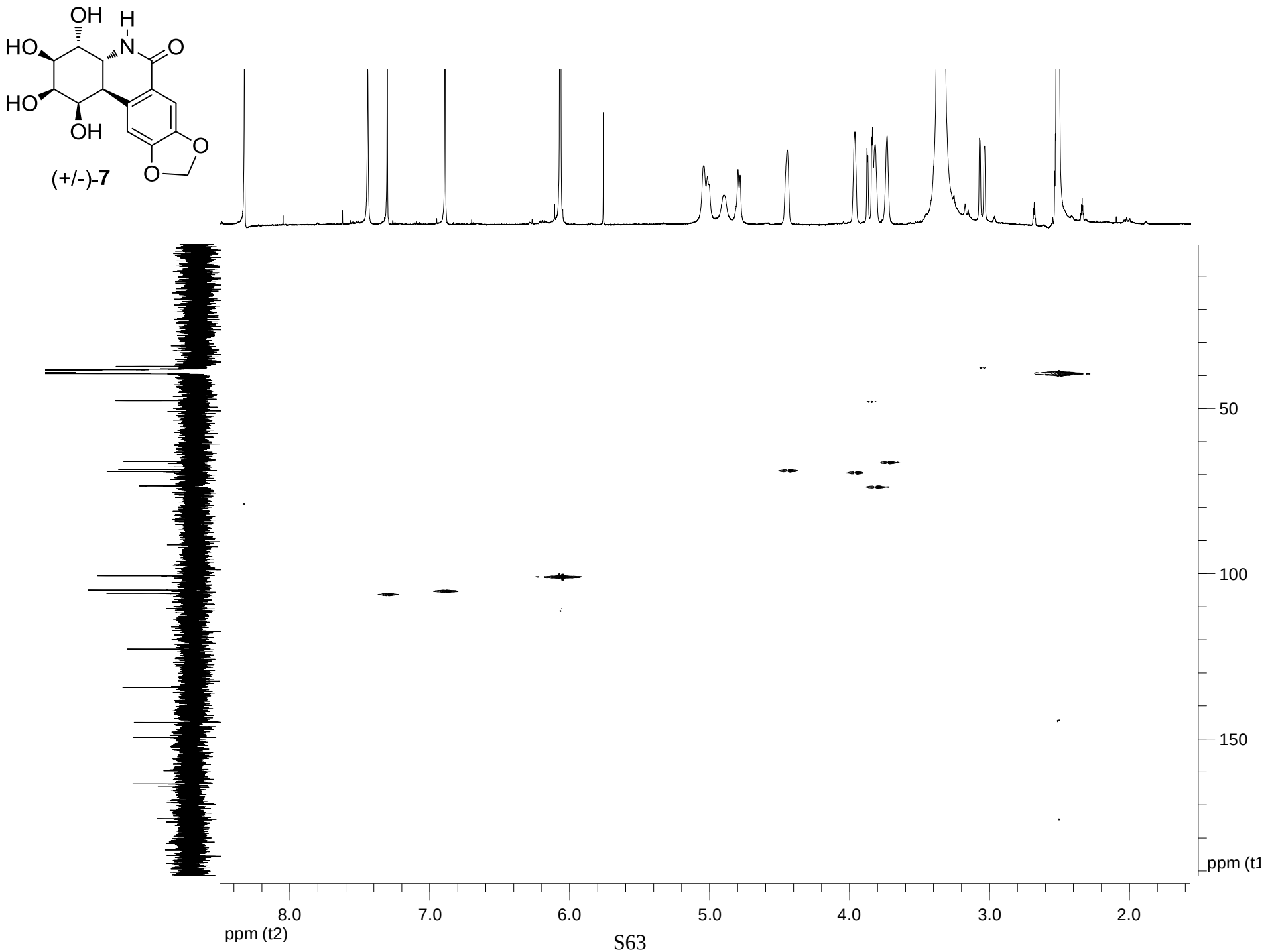


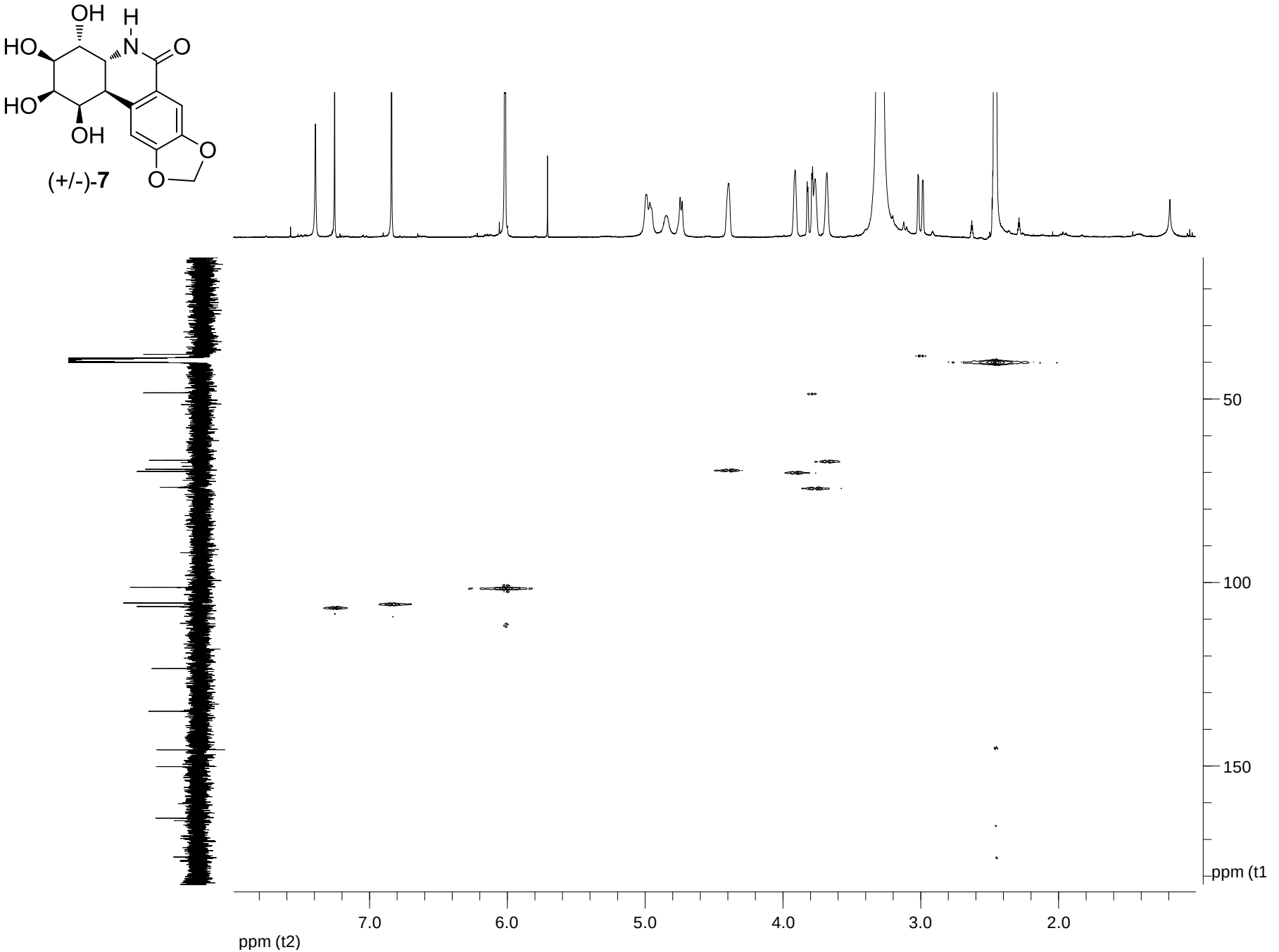
(+/-)-**7**

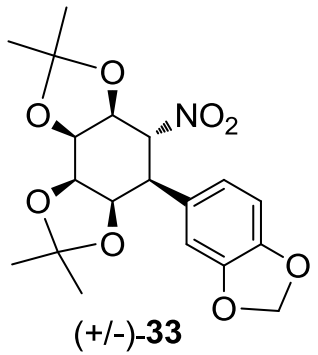



OH
H
HO
N
O
HO
OH
O
O
(+/-)-7
164.2
150.2
145.6
135.1
123.5
106.6
105.6
101.3
74.1
69.7
69.1
66.7
48.3
37.8
150
100
50
ppm (t1)
150
100
50
ppm (t1)

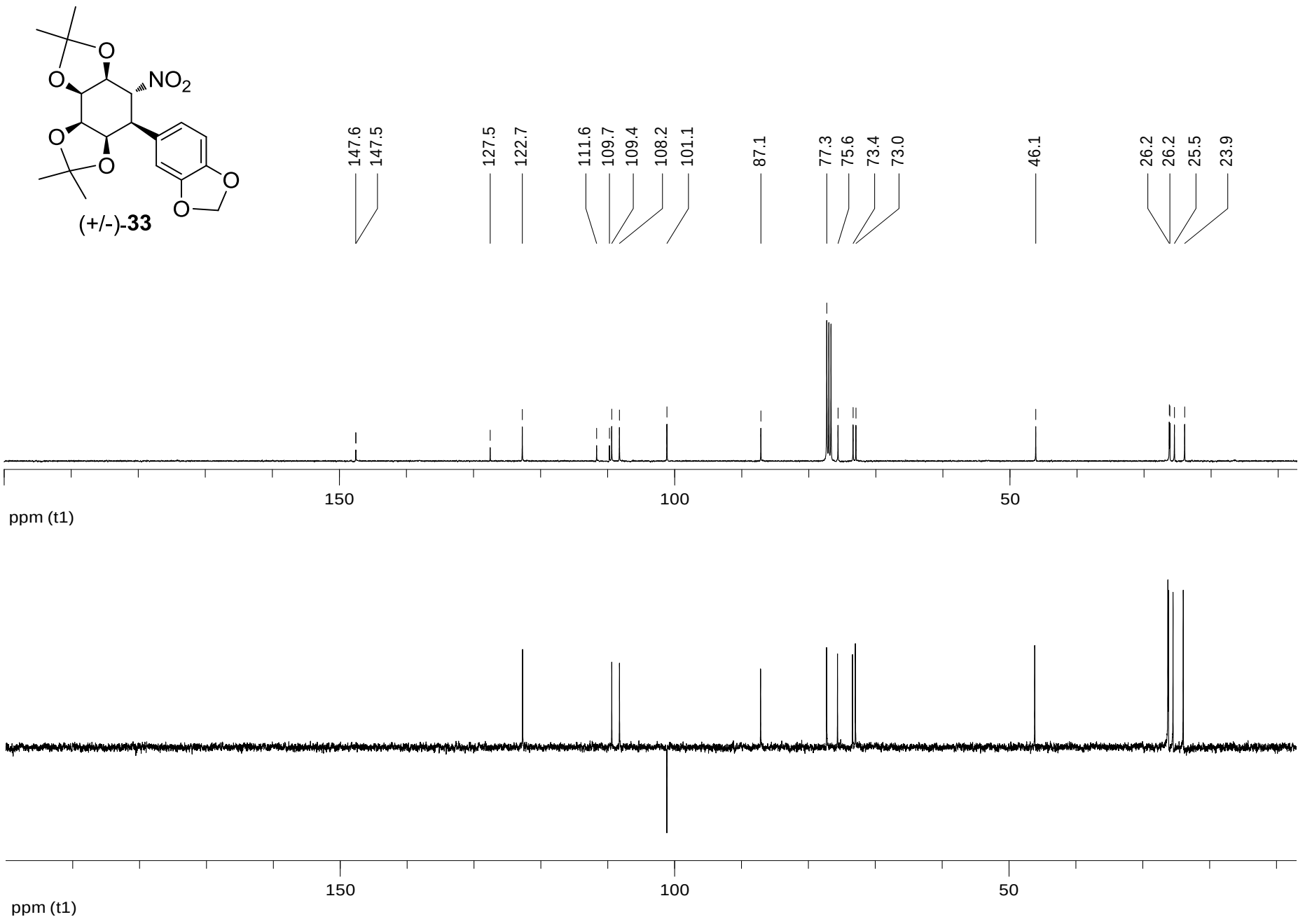

OH
H
HO
N
O
HO
OH
O
O
(+/-)-7
3.00
3.50
4.00
4.50
5.00
ppm (t1
5.00
4.50
4.00
3.50
3.00
ppm (t2)


OH
H
HO
N
O
HO
OH
O
O
(+/-)-7
50
100
150
ppm (t1
8.0
7.0
6.0
5.0
4.0
3.0
2.0
ppm (t2)


OH
H
HO
N
O
HO
OH
O
O
(+/-)-7
50
100
150
ppm (t1
7.0
6.0
5.0
4.0
3.0
2.0
ppm (t2)



(+/-)-**33**


(+/-)-33
147.6
147.5
127.5
122.7
111.6
109.7
109.4
108.2
101.1
87.1
77.3
75.6
73.4
73.0
46.1
26.2
26.2
25.5
23.9
150
100
50
ppm (t1)
150
100
50
ppm (t1)

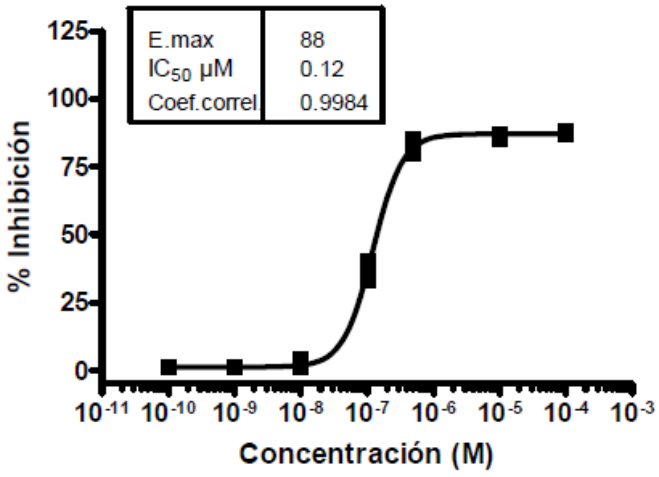
Cytotoxicity data

Cell line: NCI-H460

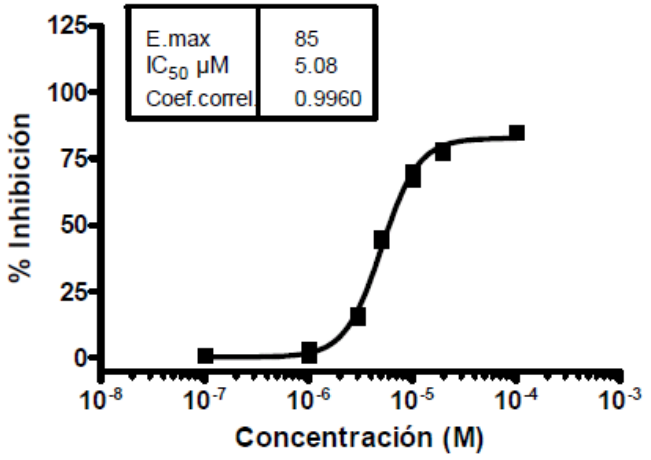
Culture conditions: RPMI 1640 supplemented with 10% FBS (Fetal Bovine Serum) in air/CO_2 (95:5) at 37ºC.

Method: cellular growth inhibition was determined using a system based on the use of Sulforhodamine B at the USEF Drug Screening Platform at the University of Santiago de Compostela.

Compound	**MW**	**IC_{50}** (µM and µg/mL)	**Standard error** (µM)	**% Growth inhibition** at 100 µM
Narciclasine (**3**)	307.26	0.12 µM = 0.037 µg/mL	0.002	
(+/-)-7-Deoxy-PST (*rac*-**2**)	309.27	5.08 µM = 1.57 µg/mL	0.09	85 +/- 1
(+/-)-7-Deoxy-2-*epi*-PST (**5**)	309.27	> 100 µM ≈ 31 µg/mL		16 +/- 5
(+/-)-7-Deoxy-2,4-di-*epi*-PST (**7**)	309.27			1 +/- 1



Narciclasine (**3**)



(+/-)-7-Deoxy-PST (*rac*-**2**)