Supplementary information

Diastereoselective formal total synthesis of (+/-)-triptolide *via* a novel cationic cyclisation of 2-alkenyl-1,3-dithiolane

Sylvie Goncalves,[a] Paul Hellier,[b] Marc Nicolas,[b] Alain Wagner,[a] Rachid Baati[a,]*

[a] University of Strasbourg, Faculty of Pharmacy, CNRS/UMR 7199 – Laboratory of Functional ChemoSystems, 74, route du Rhin BP60024, 67400 Illkirch, France

[b] Les Laboratoires Pierre Fabre CCDC, 16 rue Jean de Rostand, 83000 Gaillac, France

*e-mail: baati@bioorga.u-strasbg.fr

Content:

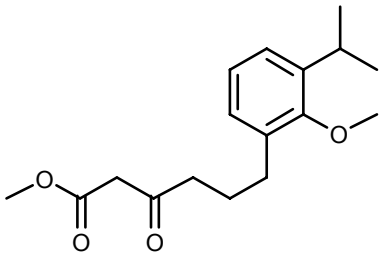
1. General Methods

All reactions were carried out in a flame dried glassware under an argon atmosphere with dry solvents, under anhydrous conditions unless otherwise indicated. Solvents for reactions were dried using a dry solvent station GT S100. All reactions were controlled by analytical thin-layer chromatography using Merck pre-coated silica gel plates with F254 indicator. Visualization was accomplished by UV light (254 nm), cerium sulfate or vanillin stains. Yields refer to chromatographically and spectroscopically pure compounds, unless ortherwise indicated. Purifications by column chromatography were carried out using Merck silicagel Si 60 (0.040-0.063). Yields determined by liquid chromatography were done using a SPD-20A Shimadzu apparatus equipped with a Zorbax 300SB-C18 column, using a mixture of acetonitrile and water as eluent. ^{1}H NMR and ^{13}C NMR were recorded on a Brucker Advance 400 (400 MHz ^{1}HNMR, 100MHz ^{13}C NMR). Chemical shift values (δ) are reported in ppm (residual chloroform δ = 7.26 ppm for ^{1}H; residual chloroform δ = 77.16 ppm for ^{13}C). The proton spectra are reported as follows δ (multiplicity, coupling constant *J*, number of protons). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint. (quintuplet), hept (heptuplet), m (multiplet). Infra-red spectra were recorded with a Nicolet 380 FT-IR apparatus. High resolution mass spectra were recorded with an Agilent Q-Tof 6520 apparatus equipped with a positive ESI source. Melting points were recorded with a Stuart Scientific SMP3 apparatus.

All reagents were purchased from Sigma-Aldrich, ABCR, Alfa-Aesar, and Acros and known compounds were prepared by cited standard literature procedure.

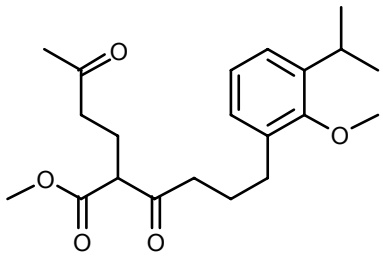
2. General Procedures and Analytical Datas

Methyl 6-(3-isopropyl-2-methoxyphenyl)-3-oxohexanoate 7



Methylacetoacetate (1.08 mL, 9.86 mmol, 1.0 eq.) was added, dropwise at 0°C, to a solution of lithium diisopropylamide 1.8 M (20.01 mmol, 2.0 eq.) in tetrahydrofurane (50 mL). After being stirred for 20 minutes, a solution of 1-(2-iodoethyl)-3-isopropyl-2-methoxybenzene **6**[1] (3.00 g, 9.86 mmol, 1.0 eq.) in tetrahydrofurane (2.5 mL) was added at 0°C and then, the reaction mixture stirred overnight at room temperature. After addition of water (50 mL), the aqueous phase was extracted by diethyl ether (3*50 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and evaporated. The residue was purified by flash chromatography on a silica gel column (eluent: 80/20 cyclohexane/ethyl acetate) to give **7** a pale yellow oil (2.19 g, 76 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (dd, J = 2.0 Hz, J = 7.2 Hz, 1H), 7.01 (m, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 3.45 (s, 2H), 3.27 (hept., J = 6.4 Hz, 1H), 2.63 (t, J = 7.2 Hz, 2H), 2.54 (t, J = 7.2 Hz, 2H), 1.90 (quint., J = 7.2 Hz, 2H), 1.22 (d, J = 7.2 Hz, 6H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.61, 167.81, 155.76, 142.06, 134.35, 127.66, 124.87, 124.55, 61.75, 52.39, 49.19, 42.33, 29.05, 26.52, 24.44, 24.11 ; IR (neat): ν 2960, 1747, 1716, 1461, 1436, 1314, 1250, 1202, 1167, 1050, 1009, 797, 765 ; HRMS (ESI, *m/z*): calcd. for $C_{17}H_{24}O_4$ $[M+H]^+$, 293.1753; found, 293.1757.

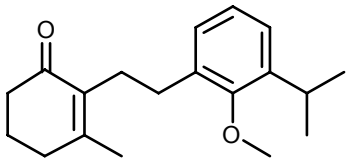
Methyl 6-(3-isopropyl-2-methoxyphenyl)-3-oxo-2-(3-oxobutyl)hexanoate 8



Potassium carbonate (554 mg, 4.00 mmol, 1.0 eq.) followed by a solution of methylvinylketone (340 µL, 4.00 mmol, 1.0 eq.) in dichloromethane (2 mL) were added to a solution of **7** (1.17 g, 4.00 mmol, 1.0 eq.) in dichloromethane (11 mL). The reaction mixture was stirred 16 hours. After addition of water (25 mL), the aqueous phase was extracted by diethyl ether (3*20 mL). The combined organic extracts were washed with brine, dried over

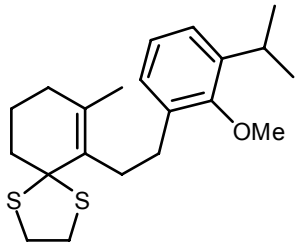
sodium sulfate and evaporated. The residue was purified by flash chromatography on a silica gel column (eluent: chloroform) to give **8** as a pale yellow oil (1.42 g, 96 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (dd, J = 2.0 Hz, J = 7.2 Hz, 1H), 6.98 (m, 2H), 3.71 (s, 3H), 3.70 (s, 3 H), 3.51 (t, J = 6.8 Hz, 1H), 3.26 (hept., J = 6.8 Hz, 1H), 2.53 (m, 4H), 2.46 (t, J = 7.2 Hz, 1H), 2.12 (s, 3H), 2.07 (m, 2H), 1.87 (m, 2H), 1.21 (d, J = 6.8 Hz, 6H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.55, 204.87, 170.16, 155.75, 142.04, 134.40, 127.57, 124.82, 124.50, 61.78, 57.41, 52.49, 41.56, 40.66, 30.03, 29.10, 26.52, 24.43, 24.13, 24.08, 21.95 ; IR (neat): ν 2960, 1743, 1712, 1461, 1430, 1362, 1250, 1202, 1163, 1009, 797, 766 ; HRMS (ESI, *m/z*): calcd. for $C_{21}H_{30}O_5$ $[M+K]^+$, 401.1730; found, 401.1725.

2-[2-(3-isopropyl-2-methoxyphenyl)ethyl]-3-methylcyclohex-2-en-1-one 5



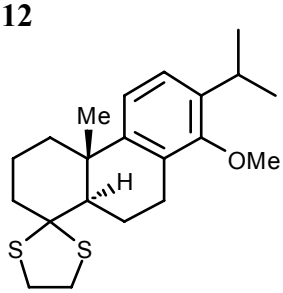
1,5-Diazabicyclo[5.4.0]undec-5-ene (660 µL, 4.39 mmol, 1,1 eq.) was added to a solution of **8** (1.42 g, 3.92 mmol, 1.0 eq.) in acetonitrile (60 mL) and the reaction mixture stirred for 3.5 hours at 80°C. Then, after cooling and addition of water (40 mL), the aqueous phase was extracted by diethyl ether (3*30 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and evaporated. The residue was purified by flash chromatography on a silica gel column (eluent: 80/20 cyclohexane/ethyl acetate) to give **5** as a yellow oil (1.02 g, 90 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (t, J = 4.8 Hz, 1H), 7.01 (d, J = 4.8 Hz, 1H), 3.74 (s, 3H), 3.27 (sept., J = 7.2 Hz, 1H), 2.56 (m, 4H), 2.38 (t, J = 7.2 Hz, 2H), 2.25 (t, J = 6.0 Hz, 2H), 1.89 (quint., J = 6.8 Hz, 2H), 1.69 (s, 3H), 1.21 (d, J = 7.2 Hz, 6H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.87, 155.92, 155.86, 141.83, 135.08, 134.88, 128.26, 124.60, 124.30, 61.80, 38.08, 33.02, 29.62, 26.87, 26.49, 24.13, 22.40, 20.94 ; IR (neat): ν 2961, 2934, 2868, 1664, 1629, 1462, 1428, 1380, 1252, 1202, 1169, 1050, 1012, 797, 767 ; HRMS (ESI, *m/z*): calcd. for $C_{19}H_{26}O_2$ $[M+K]^+$, 325.1569; found, 325.1564.

2-isopropyl-6-[2-(7-methyl-1,4-dithiaspiro[4.5]dec-6-en-6-yl)ethyl]phenylmethyl ether 10



1,2-ethanedithiol (490 µL, 5.73 mmol, 1.1 eq.) and indium (III) trifluoromethanesulfonate (295 mg, 0.524 mmol, 0.1 eq.) were added successively to a solution of **5** (1.50 g, 5.25 mmol, 1.0 eq.) in dichloromethane (25 mL) and the reaction mixture was stirred for 24 hours. Then, additional 1,2-ethanedithiol (490 µL, 5.73 mmol, 1.1 eq.) and $In(OTf)_3$ (295 mg, 0.524 mmol, 0.1 eq.) were added. After 6 hours of stirring, dilution with dichloromethane (20 mL) and water (40 mL), the aqueous phase was extracted by dichloromethane (2*20 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and evaporated. The residue was purified by flash chromatography on a silica gel column (eluent: 95/5 cyclohexane/ethyl acetate) to give **10** as a colorless solid (1.86 g, 98%). Mp: 55-56°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (m, 2H), 7.03 (m, 1H), 3.78 (s, 3H), 3.31 (m, 5H), 2.91 (m, 2H), 2.53 (m, 2H), 2.00 (m, 2H), 1.80 (m, 5H), 1.23 (d, J = 8.0 Hz, 6H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.71, 141.94, 136.11, 134.51, 131.22, 127.50, 124.47, 124.46, 61.94, 44.55, 40.38, 32.65, 31.91, 31.52, 26.45, 24.23, 22.68, 20.80 ; IR (neat): ν 2961, 2930, 2864, 1487, 1450, 1413, 1327, 1277, 1238, 1163, 1032, 913, 824, 746, 669 ; HRMS (ESI, *m/z*): calcd. for $C_{21}H_{30}OS_2$ $[M+Na]^+$, 385.1636, found, 385.1638.

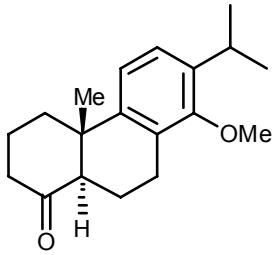
(+/-)-7'-isopropyl-4a'-methyl-3',4',4a',9',10',10a'-hexahydro-2'H-spiro[1,3-dithiolane-2,1'-phenanthren]-8'-yl methyl ether 12



Fresh trimethylsilyl trifluoromethanesulfonate (50 µL, 0.243 mmol, 1.1 eq.) was added to a solution of 1,3-dithiolane (80 mg, 0.221 mmol, 1.0 eq.) in 1,2-dichloroethane (7 mL) and the reaction mixture was stirred 16 hours at room temperature. Then, after addition of water (20 mL), the aqueous phase was extracted by dichloromethane (3*10 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and evaporated. The residue was

purified by flash chromatography on a silica gel column (eluent: 95/5 cyclohexane/ethyl acetate) to give **12** as a colorless solid (72 mg, 90%). Mp: 129-131°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00 (q, J = 8.4 Hz, 2H), 3.72 (s, 3H), 3.22 (m, 4H), 3.03 (m, 2H), 2.73 (m, 1H), 2.37 (m, 1H), 2.24 (m, 2H), 2.05 (d, J = 11.6 Hz, 1H), 1.83 (m, 3H), 1.71 (m, 1H), 1.43 (m, 1H), 1.25 (s, 3H), 1.20 (d, J = 7.2 Hz, 6H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.11, 147.51, 136.38, 128.90, 123.95, 120.67, 73.01, 60.61, 51.30, 46.82, 40.77, 39.67, 38.50, 38.19, 26.25, 24.97, 24.92, 24.08, 24.04, 22.06, 21.13 ; IR (neat): ν 2959, 2930, 2866, 1484, 1451, 1410, 1327, 1277, 1032, 913, 817, 734, 669 ; HRMS (ESI, *m/z*): calcd. for $C_{21}H_{30}OS_2$ $[M+Na]^+$, 385.1636, found, 385.1638.

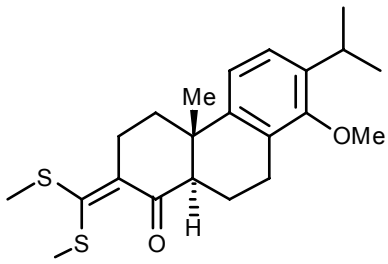
(+/-)-7-isopropyl-8-methoxy-4a-methyl-3,4,4a,9,10,10a-hexahydrophenanthren-1(2*H*)-one 4



Trifluoroacetic acid (70 µL, 0.790 mmol, 10.0 eq) and bis-trifluoroacetoxyiodobenzene (39 mg, 0.079 mmol, 1.0 eq.) was added to a solution of **12** (29 mg, 0.079 mmol, 1.0 eq.) in a mixture of acetonitrile (400 µL) and water (400 µL). After being stirred 30 minutes, additional bis-trifluoroacetoxyiodobenzene (79 mg, 0.158 mmol, 2.0 eq.) was added and the mixture stirred 2.5 hours. Then, after addition of water (10 mL), the aqueous phase was extracted by diethyl ether (3*10 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and evaporated. The residue was purified by flash chromatography on a silica gel column (eluent: 80/20 cyclohexane/ethyl acetate) to give **(+/-)-4** as a colorless solid (19 mg, 85 %). Mp: 130-132°C ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (dd, J = 4.0 Hz, J = 8.4 Hz, 2H), 3.25 (sept., J = 6.8 Hz, 1H), 3.03 (qd, J = 1.2 Hz, J = 17.6 Hz, 1H), 2.56 (m, 2H), 2.38 (m, 3H), 1.97 (m, 3H), 1.84 (td, J = 4.4 Hz, J = 12.8 Hz, 1H), 1.69 (m, 1H), 1.20 (dd, J = 3.6 Hz, J = 7.2 Hz, 6H), 1.05 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.57, 155.28, 144.79, 139.03, 128.65, 124.16, 121.15, 60.66, 55.24, 42.55, 41.01, 37.35, 26.29, 24.05, 24.00, 23.79, 23.24, 22.72, 17.20 ; IR (neat): ν 2959, 1712, 1484, 1455, 1410, 1377, 1327, 1261, 1139, 1071, 1058, 1031, 948, 818 ; HRMS (ESI, *m/z*): calcd. for $C_{19}H_{26}O_2$ $[M+H]^+$, 287.2011, found, 287.2013.

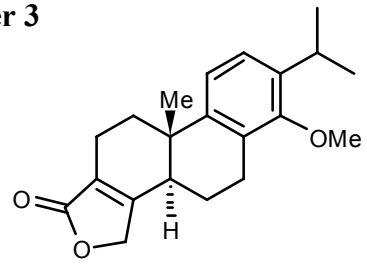
Crystallographic Data could be obtained *via* the Cambridge Crystallographic Data Center, e-mail: www.cdc.cam.ac.uk/data_request/cif., n° of deposite: CCDC 753095.

(+/-)-2-[bis(methylthio)methylene]-7-isopropyl-8-methoxy-4a-methyl-3,4,4a,9,10,10a-hexahydrophenanthren-1(2*H*)-one 17



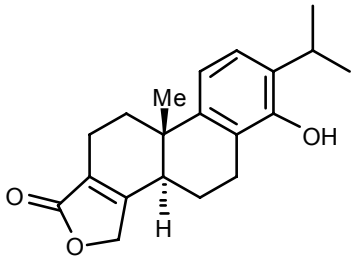
Lithium diisopropylamide 1.8 M (100 µL, 0.179 mmol, 1.0 eq.) was slowly added at -78°C to a solution of **(+/-)-4** (50 mg, 0.175 mmol, 1.0 eq.) in tetrahydrofurane (250 µL) and the reaction mixture stirred 30 minutes. Then, carbon disulfide (20 µL, 0.193 mmol, 1.1 eq.) was added rapidly and the reaction mixture stirred again 2 hours at -78°C before the addition of methyl iodide (30 µL, 0.385 mmol, 2.2 eq.). The reaction mixture was stirred at room temperature and water (10 mL) was added. The aqueous phase was extracted by diethyl ether (3*10 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and evaporated. The residue was purified by flash chromatography on a silica gel column (eluent: 90/10 cyclohexane/ethyl acetate) to give **(+/-)-15** as a yellow solid (57 mg, 84 %). Mp: 104-106°C ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (m, 2H), 3.72 (s, 3H), 3.36 (m, 1H), 3.27 (quint., J = 6.8 Hz, 1H), 3.07 (m, 1H), 2.82-2.57 (m, 4H), 2.45 (m, 1H), 2.39 (s, 3H), 2.37 (s, 3H), 1.90 (dt, 1H), 1.69 (dq, 1H), 1.21 (dd, J = 6.8 Hz, J = 3.2 Hz, 6H), 1.11 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.19, 155.18, 144.55, 144.05, 139.56, 139.02, 128.86, 124.21, 121.33, 60.69, 56.09, 40.22, 37.25, 29.83, 26.29, 24.04, 24.02, 23.89, 23.60, 18.31, 17.98, 17.62 ; IR (neat): ν 2959, 2867, 1684, 1485, 1456, 1410, 1327, 1263, 1200, 1107, 1059, 1032, 972, 819 ; HRMS (ESI, *m/z*): calcd. for $C_{22}H_{30}O_2S_2$ $[M+H]^+$, 391.1765, found, 391.1766.

(+/-)-Triptophenolide Methyl Ether 3



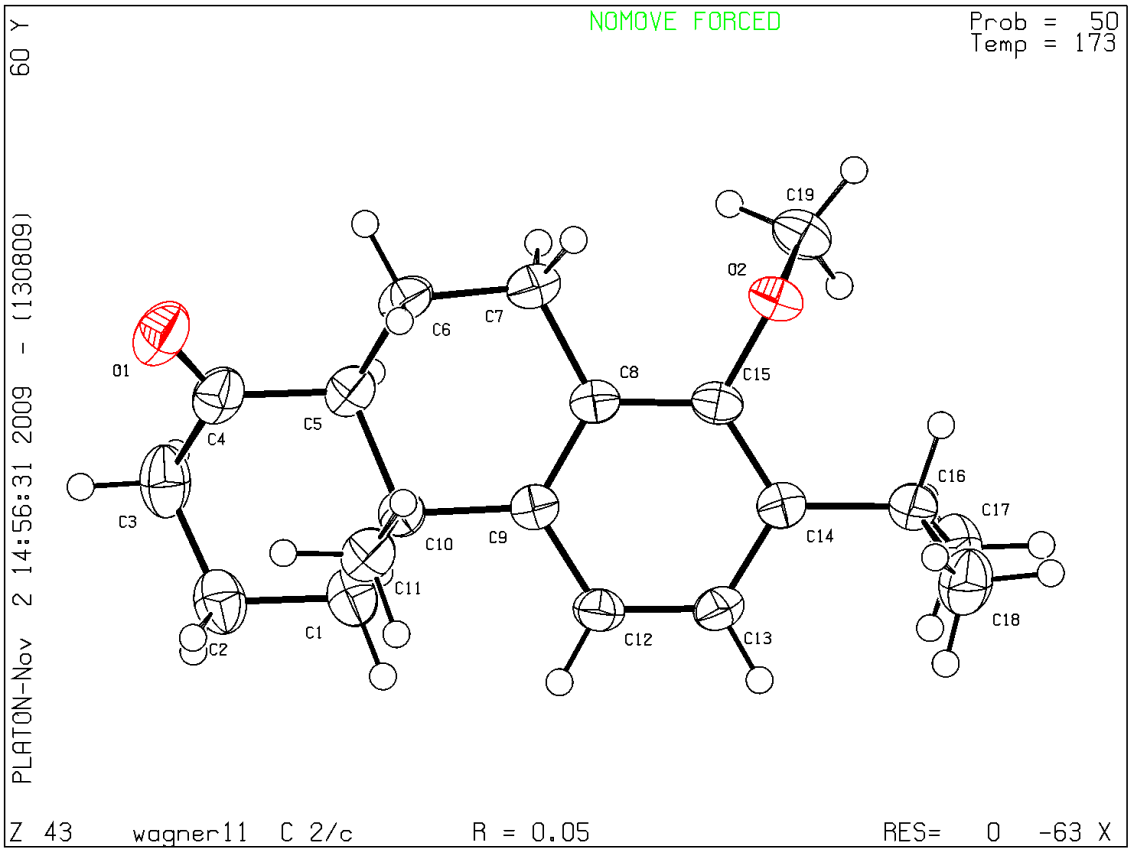
Butyllithium 1.6 M (530 µL, 0.791 mmol, 1.1 eq.) was slowly added at 0°C, over a period of several minutes, to a solution of trimethylsulfonium iodide (178 mg, 0.863 mmol, 1.2 eq.) in tetrahydrofurane (2.3 mL) and the reaction mixture stirred 5 minutes at 0°C. Then, a solution of **(+/-)-24** (281 mg, 0.719 mmol, 1.0 eq) in tetrahydrofuran (150 µL) was added and the reaction mixture stirred 30 minutes at 0°C followed by 2 hours at room temperature. The reaction mixture was concentrated, taken up into methanol (9 mL) and HCl 6N (1.5 mL) and stirred overnight. After addition of water (300mL) was added, the aqueous phase was extracted by diethyl ether (3*20 mL). The combined organic extracts were washed with brine, dried over sodium sulfate and evaporated. The residue was purified by flash chromatography on a silica gel column (eluent: 80/20 cyclohexane/ethyl acetate) to give **(+/-)-3** as a colorless solid (124 mg, 53 %). Analytical datas were identical to the ones reported in the literature.[2]

(+/-)-Triptophenolide 2

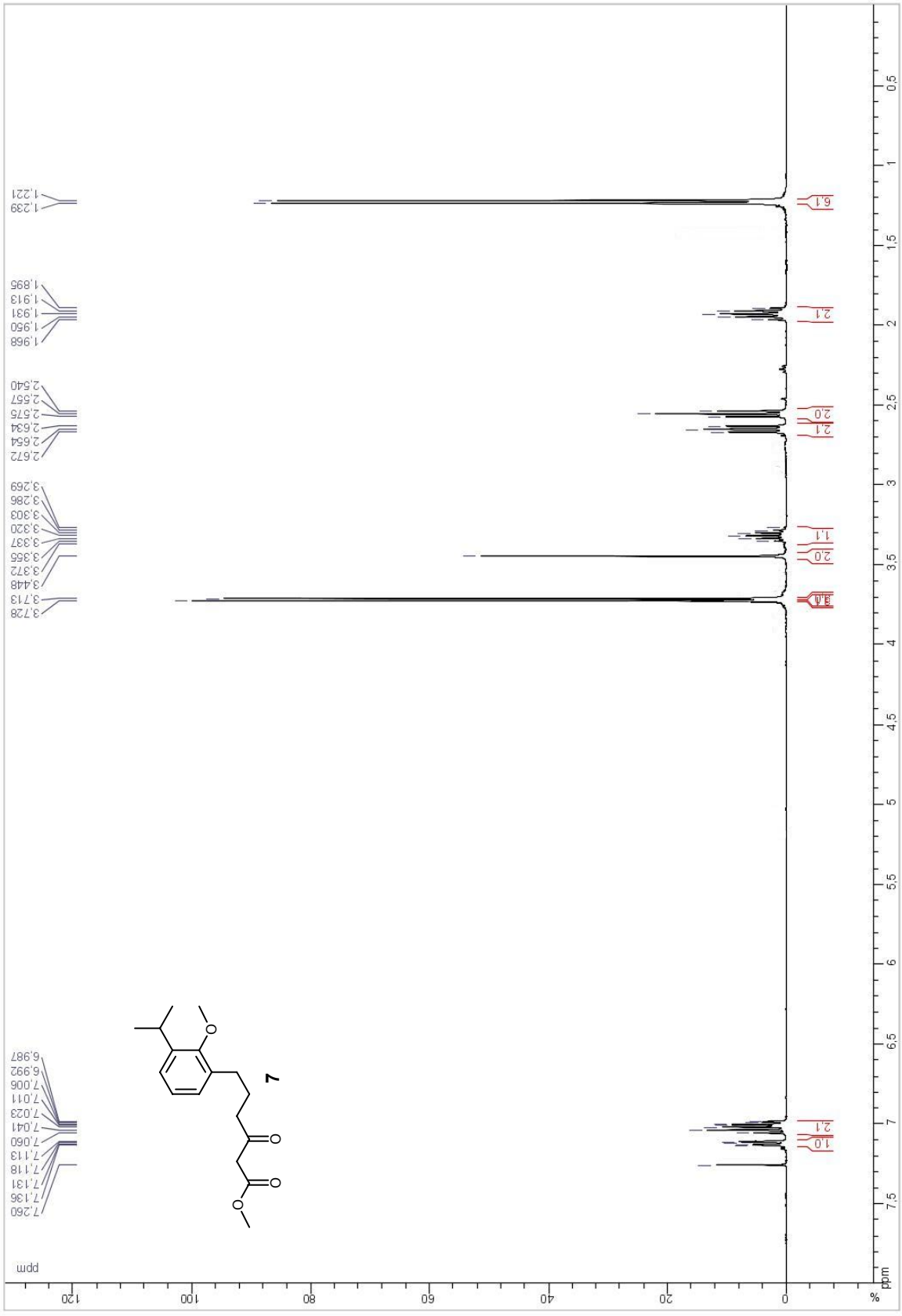


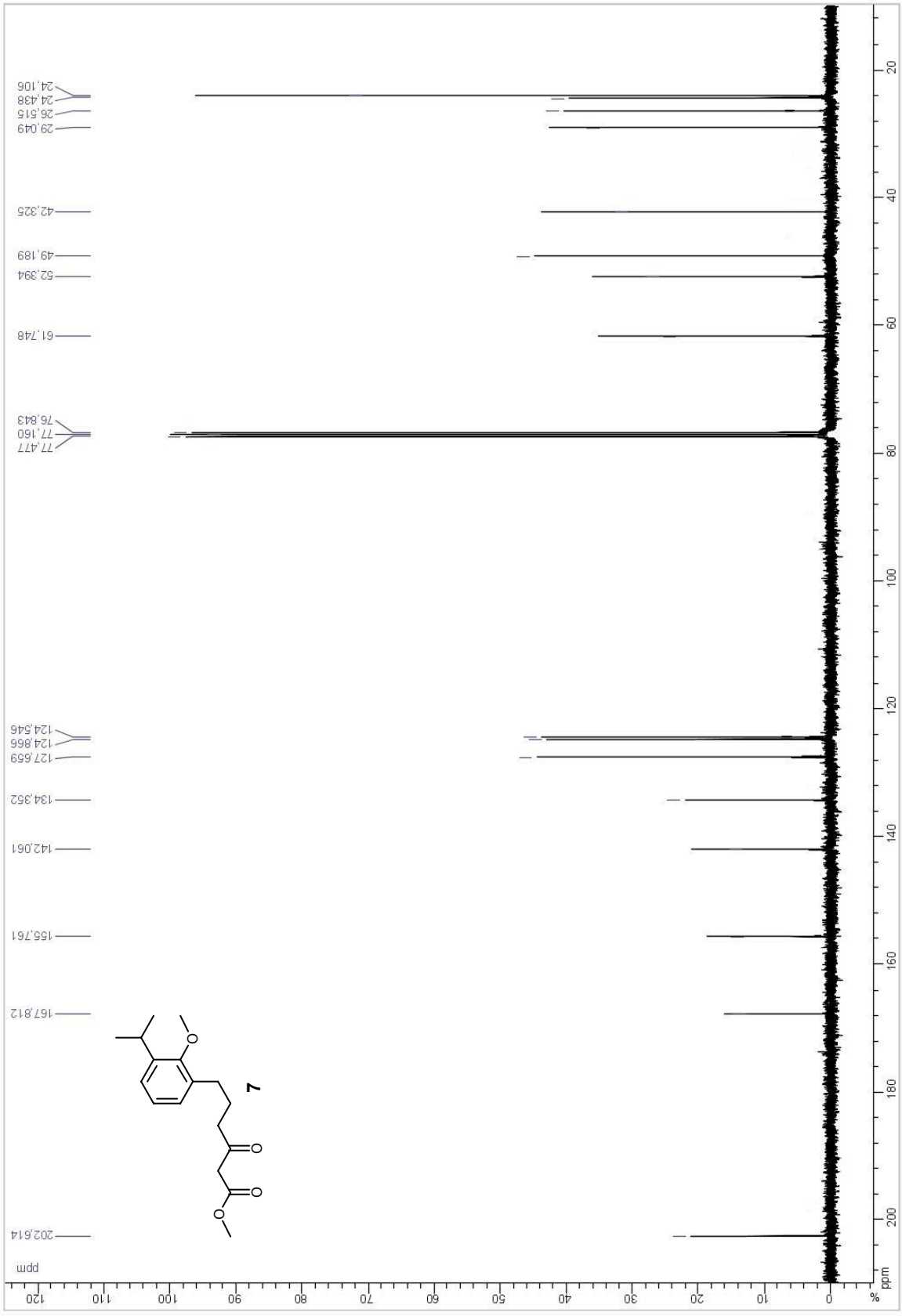
(+/-)-2 was obtained from **(+/-)-3** *via* a described procedure in 92% of yield. Analytical datas were identical to the ones reported in the literature. [2]

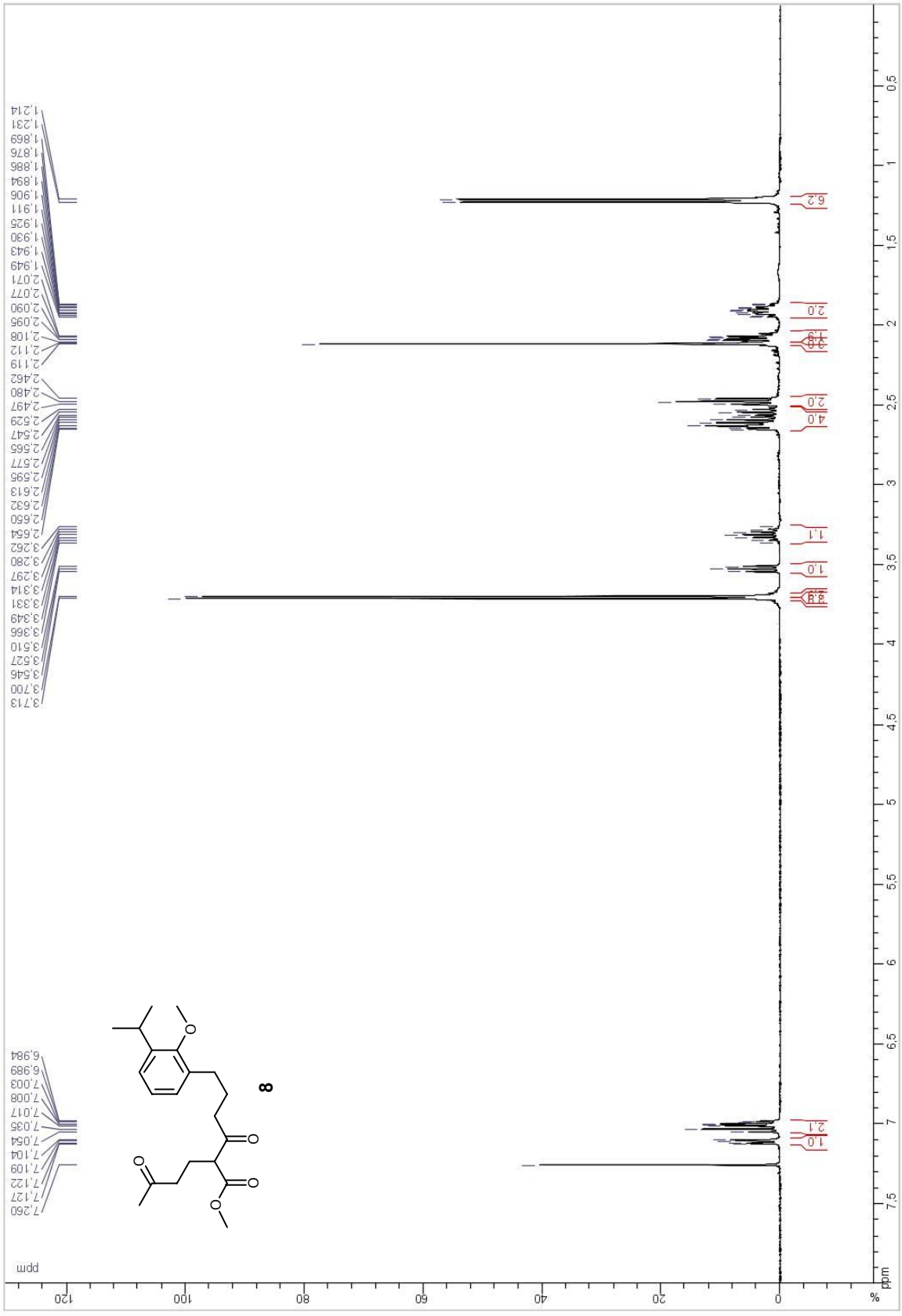
3. Cristallographic structure of the *trans*-decaline (+/-)-4

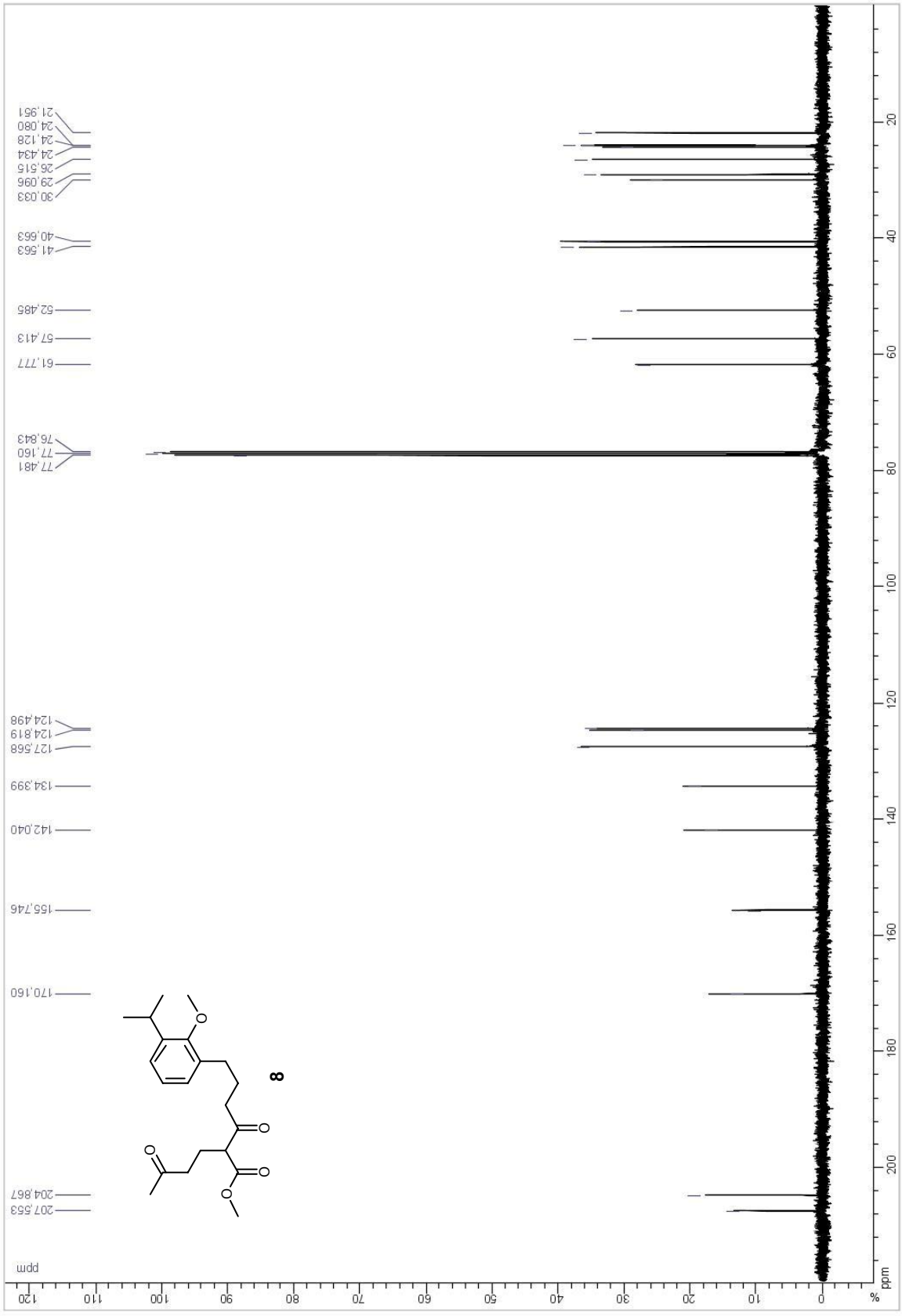


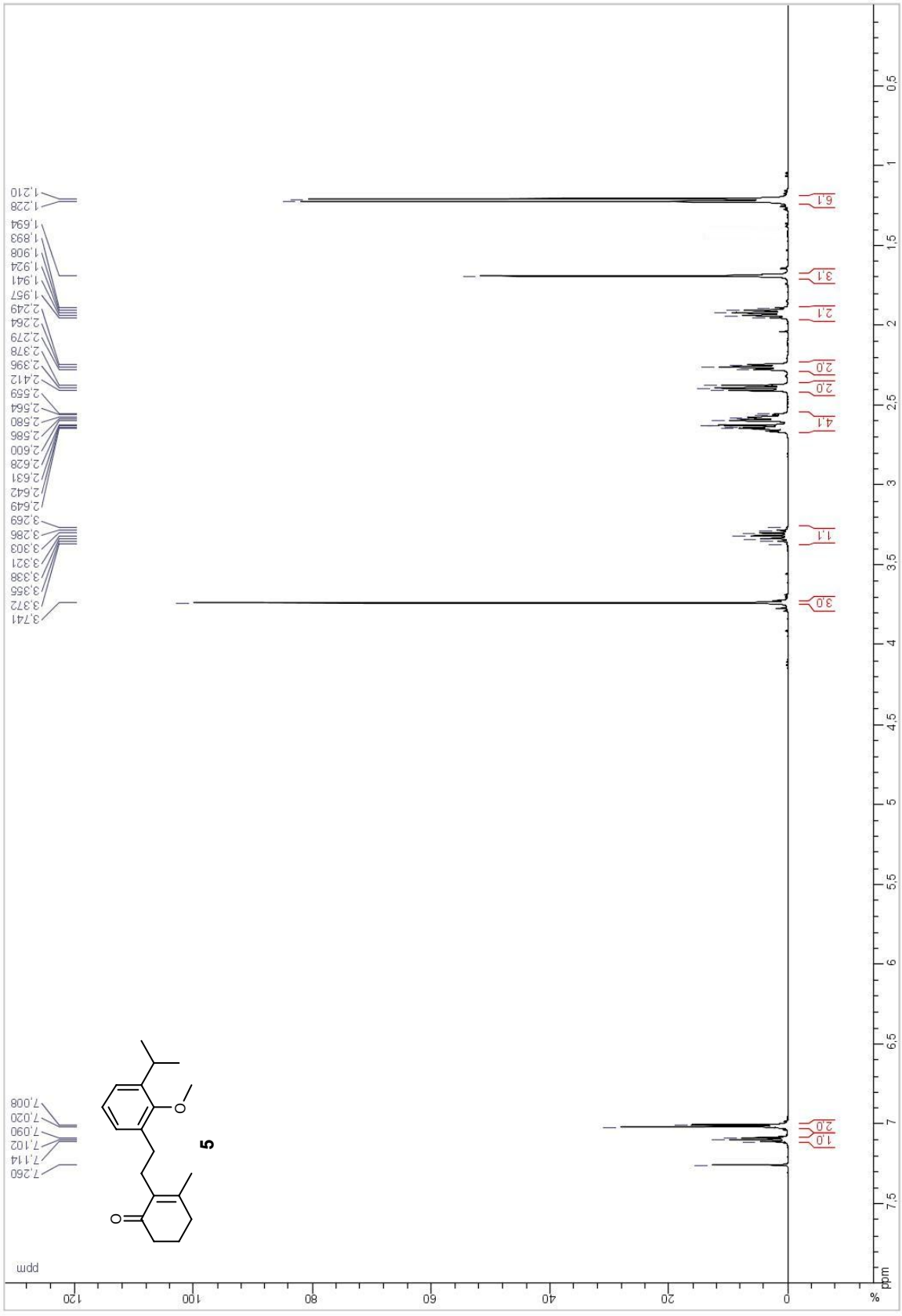
4. ^{1}H NMR and ^{13}C NMR spectra of new compounds

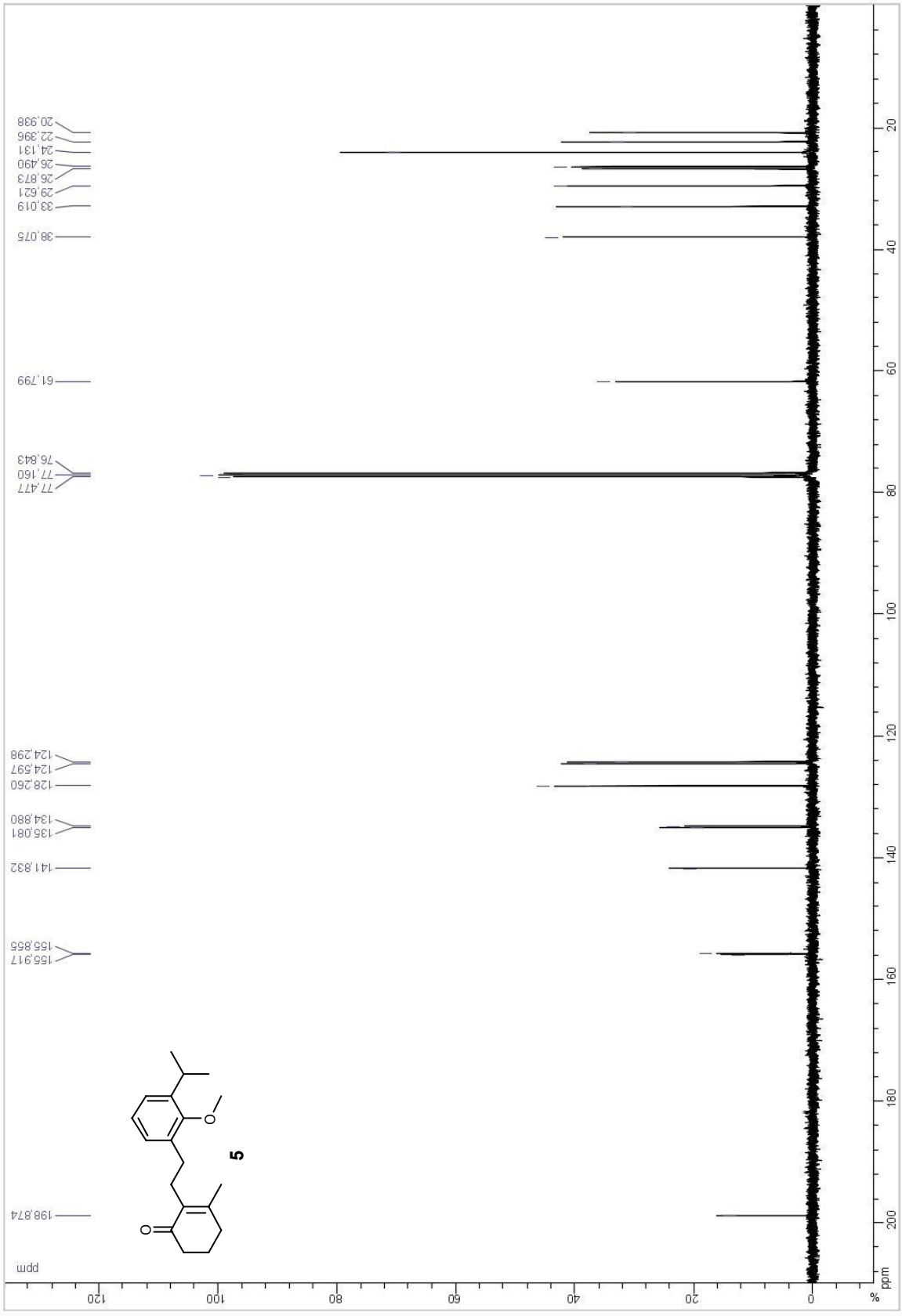

1.221
1.239
1.868
1.895
1.913
1.931
1.950
1.968
2.540
2.557
2.575
2.634
2.654
2.672
3.269
3.286
3.303
3.320
3.337
3.355
3.372
3.448
3.713
3.728
6.987
6.992
7.006
7.011
7.023
7.041
7.060
7.113
7.118
7.131
7.136
7.260
6.1
2.1
2.0
2.1
1.1
2.0
3.0
2.1
1.0
7
O
O
O
O
ppm
%

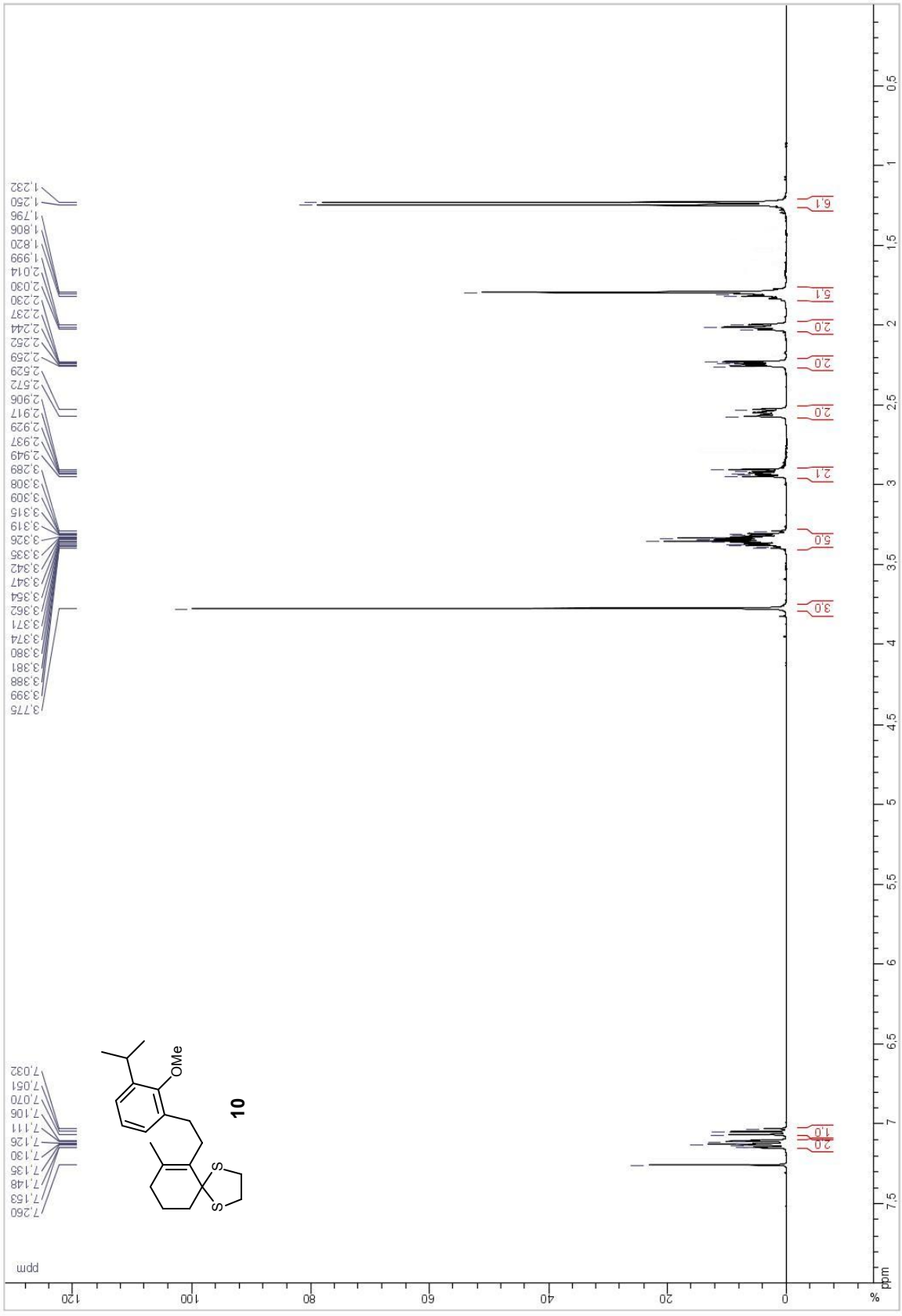

24.106
24.438
26.515
29.049
42.325
49.189
52.394
61.748
76.843
77.160
77.477
124.546
124.866
127.659
134.352
142.061
155.761
167.812
202.614
ppm
7

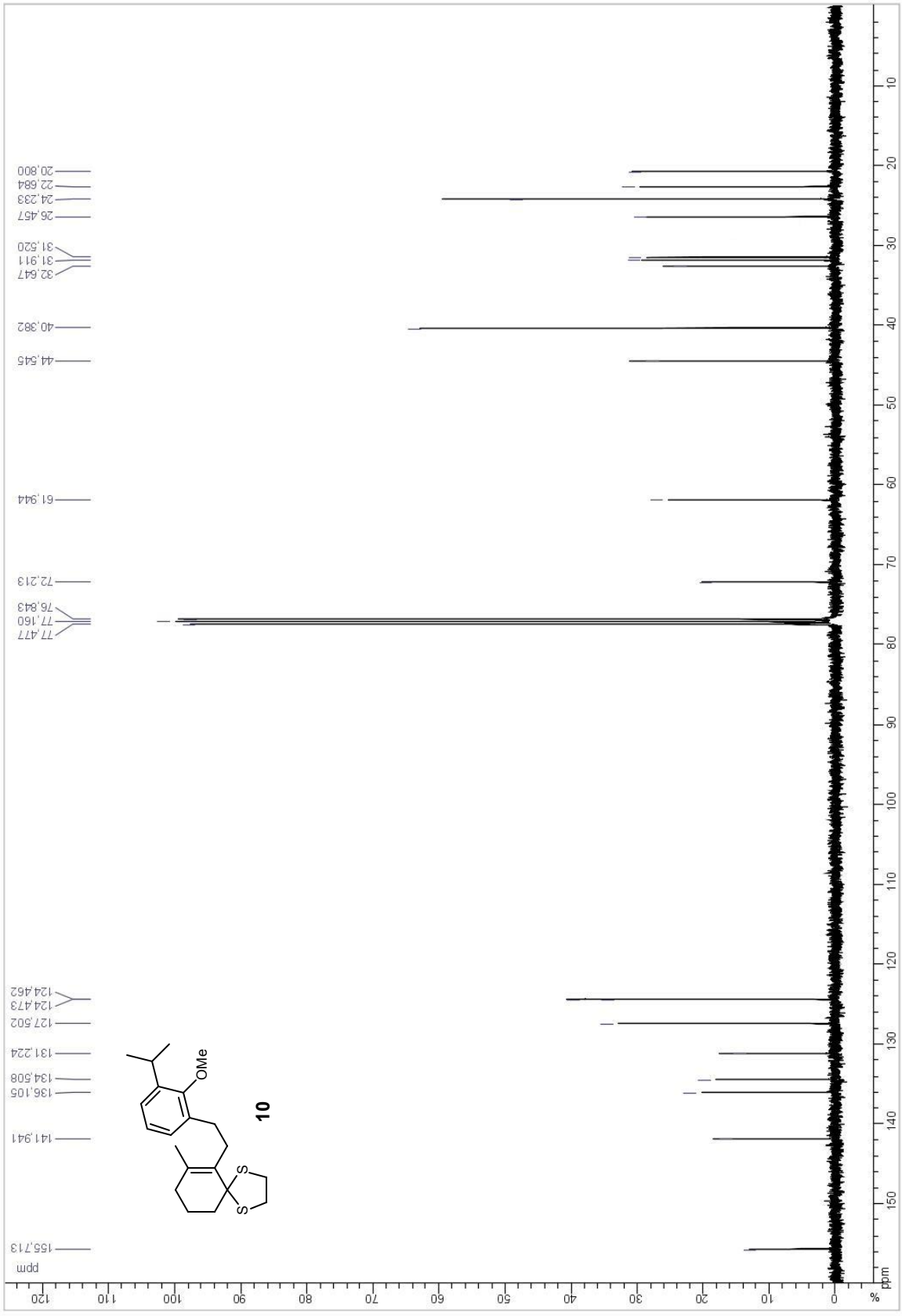

8
ppm
%
6.2
2.0
1.3
2.0
4.0
1.1
1.0
3.3
2.1
1.0

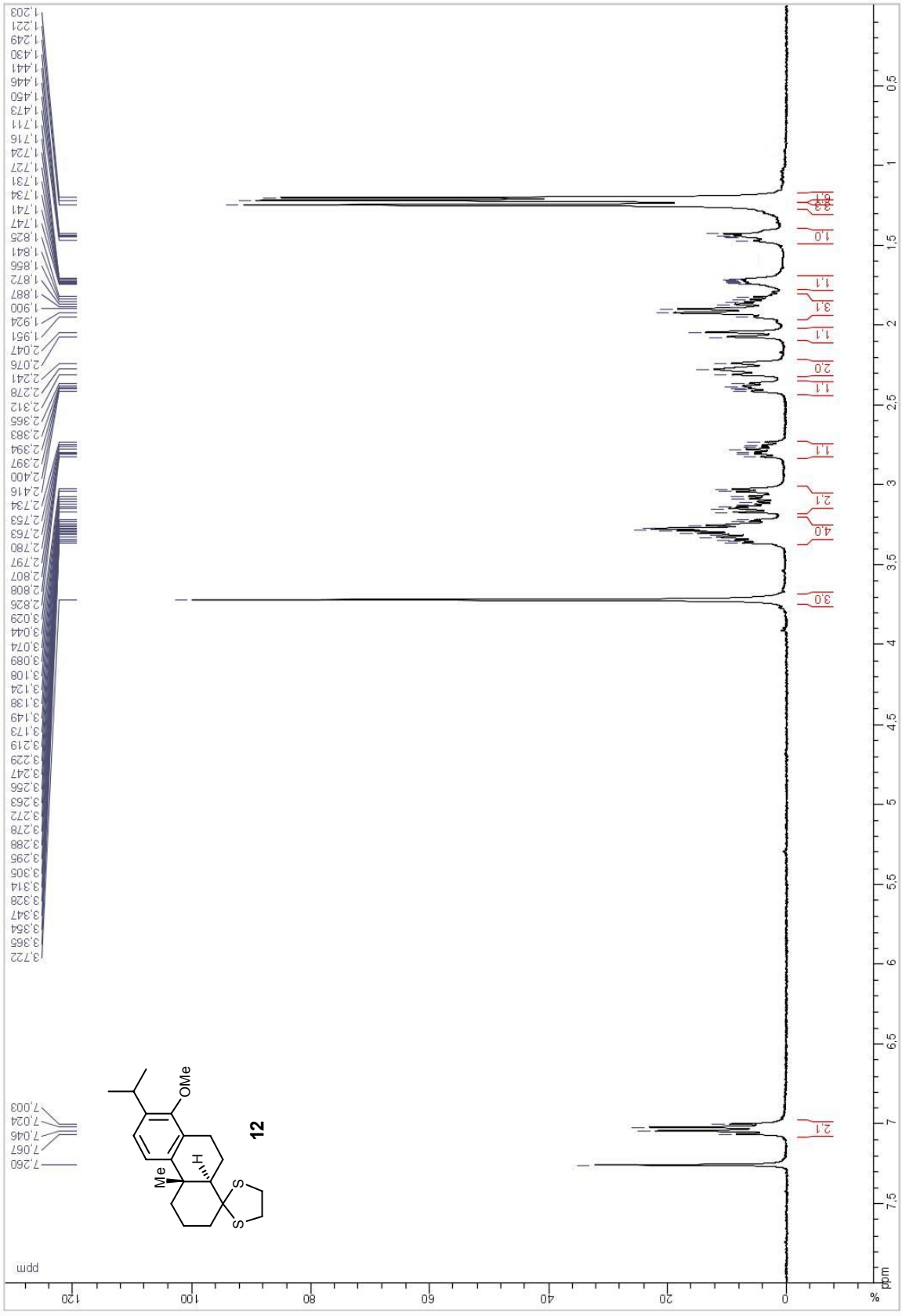

21.951
24.080
24.128
24.434
25.515
29.096
30.033
40.663
41.563
52.485
57.413
61.777
76.843
77.160
77.481
124.498
124.819
127.568
134.399
142.040
155.746
170.160
204.867
207.553
8
ppm
%

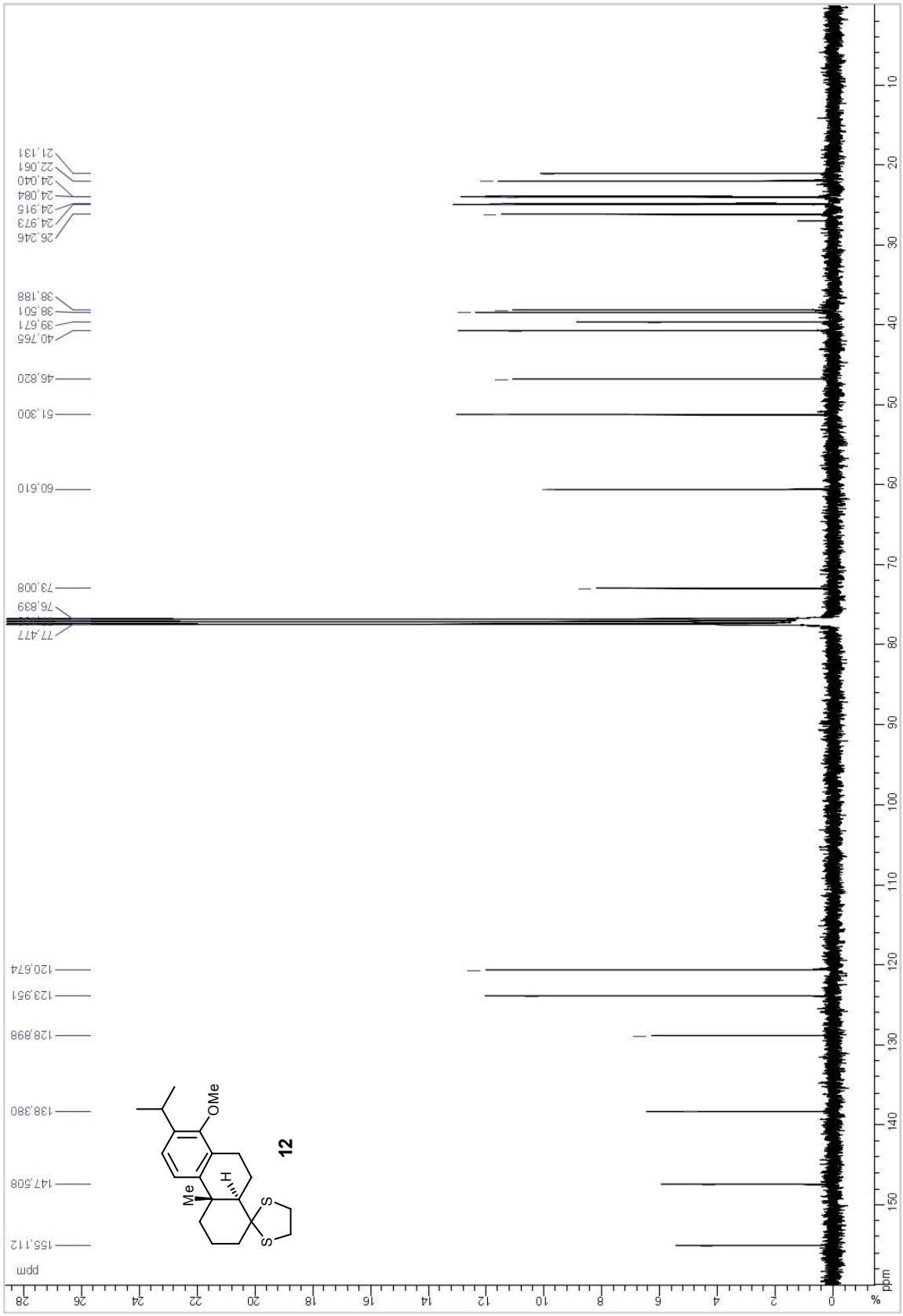

1.210
1.228
1.694
1.893
1.908
1.924
1.941
1.957
2.249
2.264
2.279
2.378
2.396
2.412
2.559
2.564
2.580
2.586
2.600
2.628
2.631
2.642
2.649
3.269
3.286
3.303
3.321
3.338
3.355
3.372
3.741
7.008
7.020
7.090
7.102
7.114
7.260
6.1
3.1
2.1
2.0
2.0
4.1
1.1
3.0
2.0
1.0
5
O
O
ppm
%
ppm

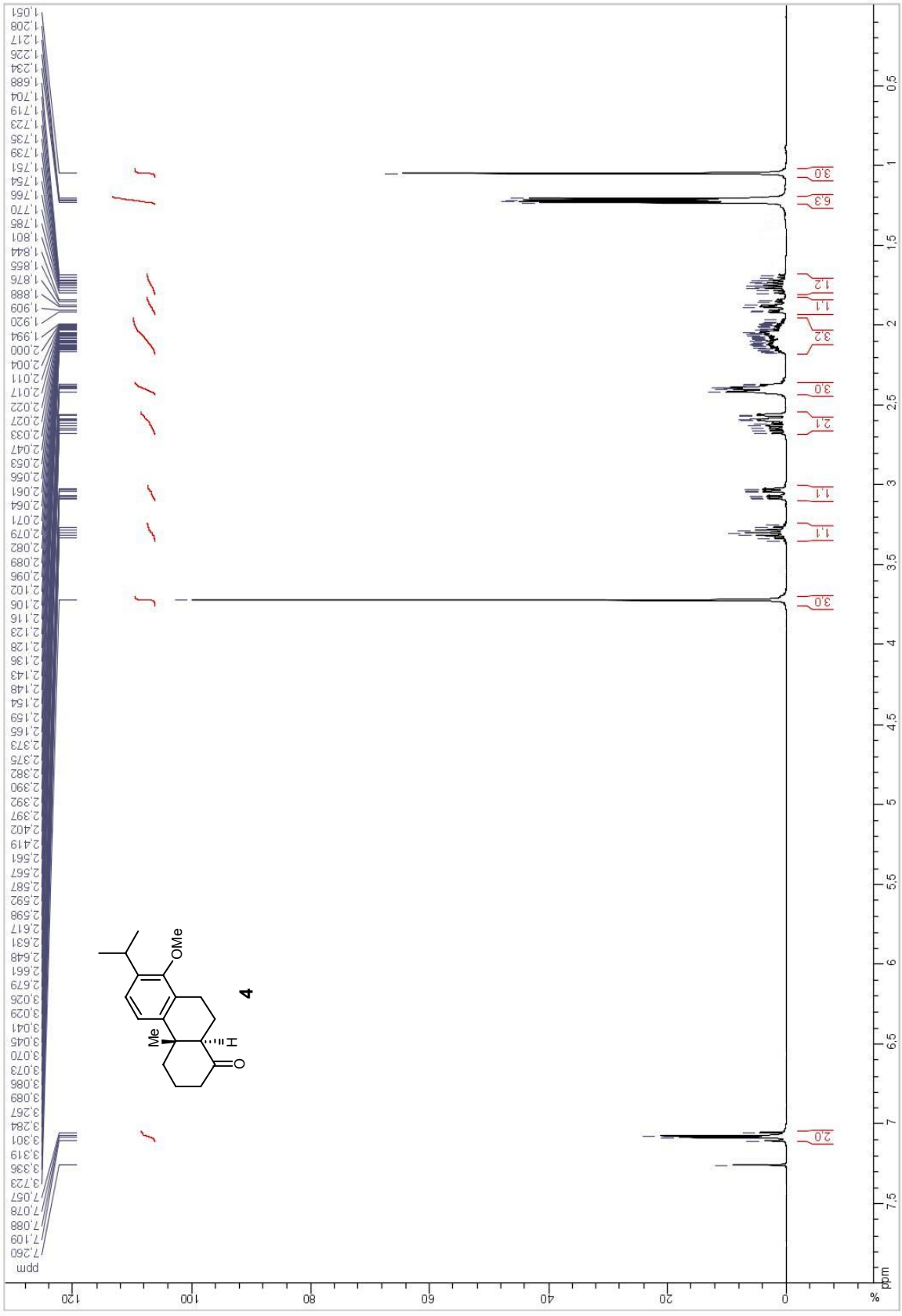

198.874
155.917
155.855
141.832
135.081
134.880
128.260
124.597
124.298
77.477
77.160
76.843
61.799
38.075
33.019
29.621
26.873
26.490
24.131
22.396
20.938
5
ppm
ppm

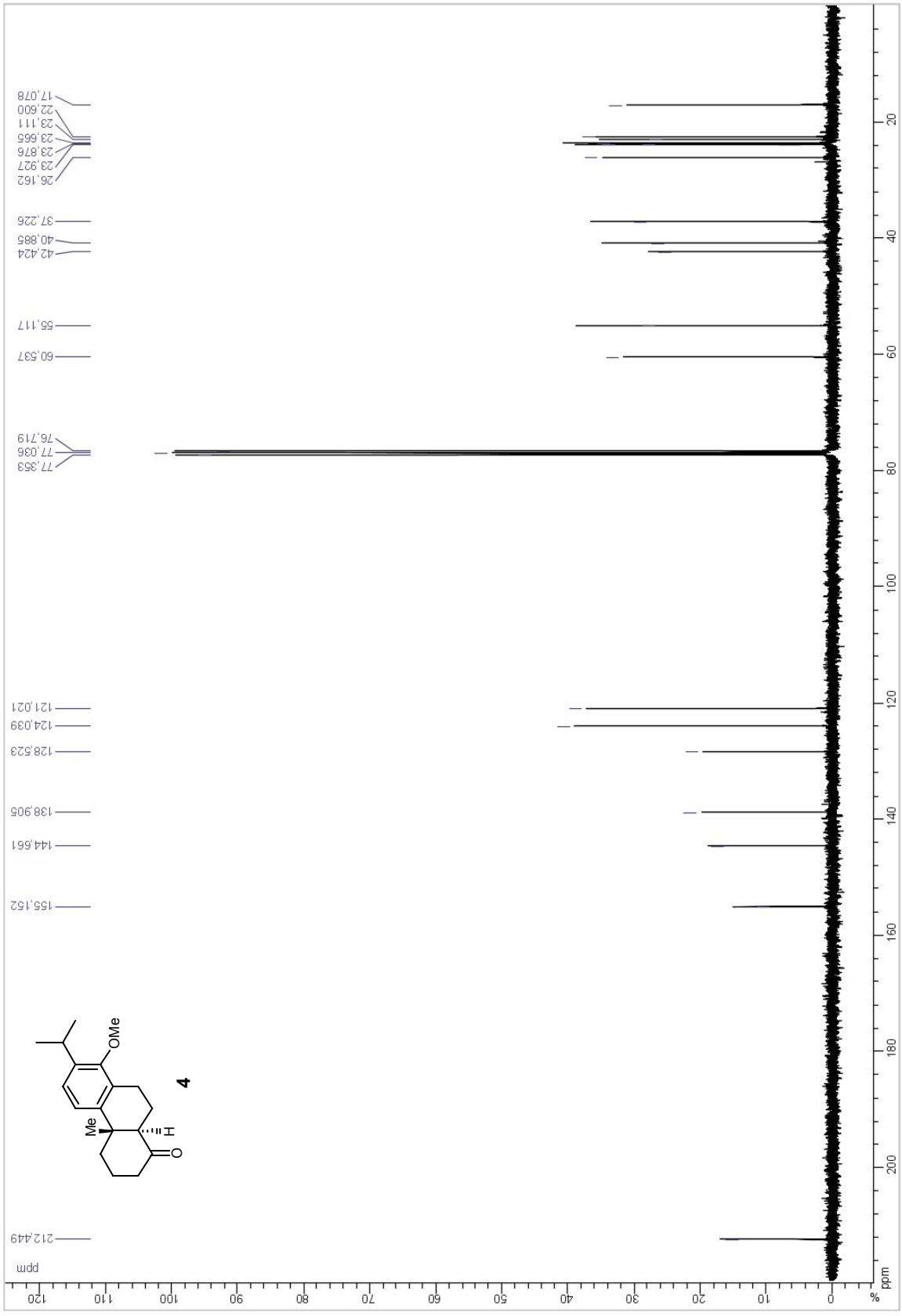

OMe
S
S
10
ppm

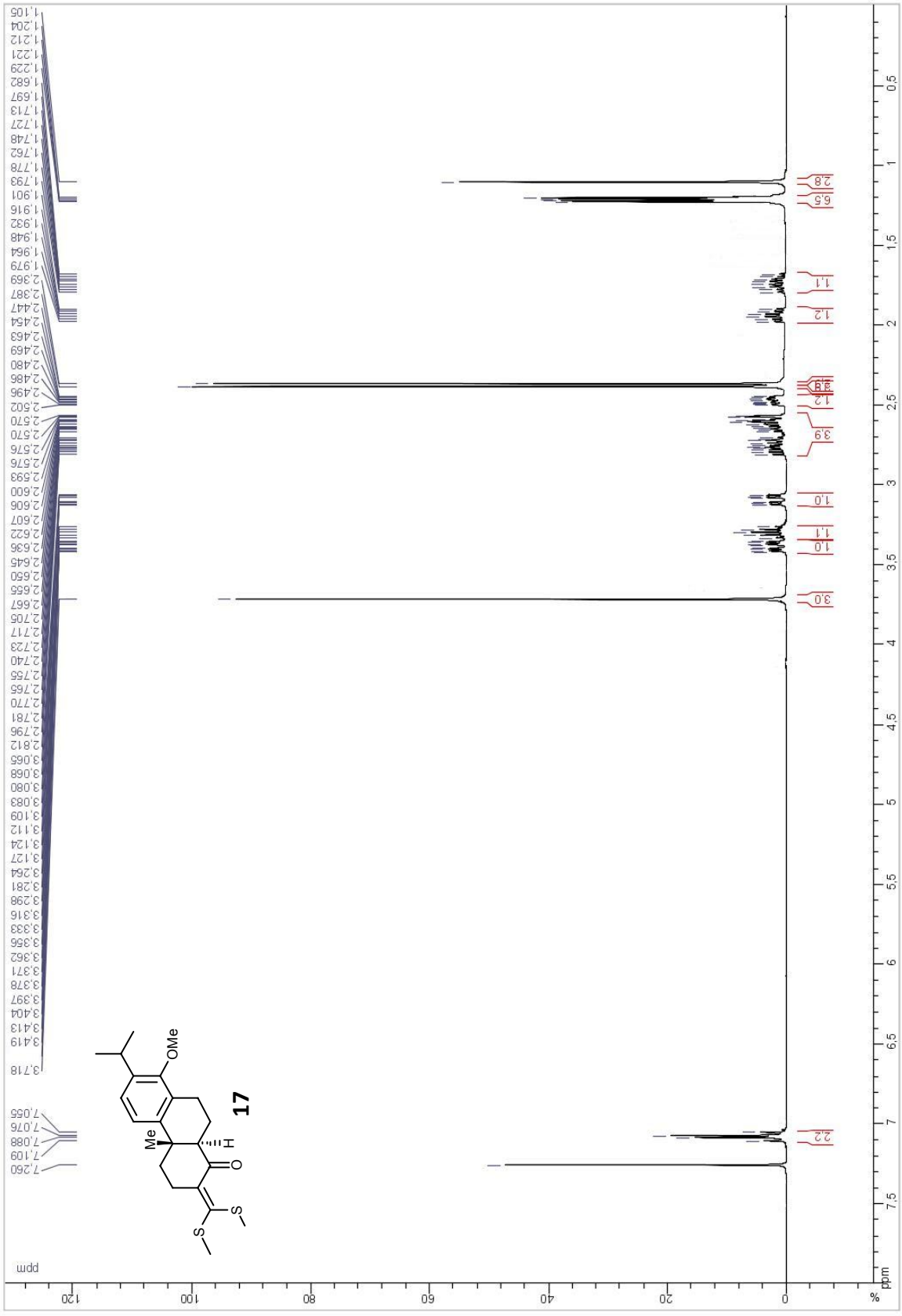

155.713
141.941
136.105
134.508
131.224
127.502
124.473
124.462
77.477
77.160
76.843
72.213
61.944
44.545
40.382
32.647
31.911
31.520
26.457
24.233
22.684
20.800
OMe
S
S
10
ppm
%

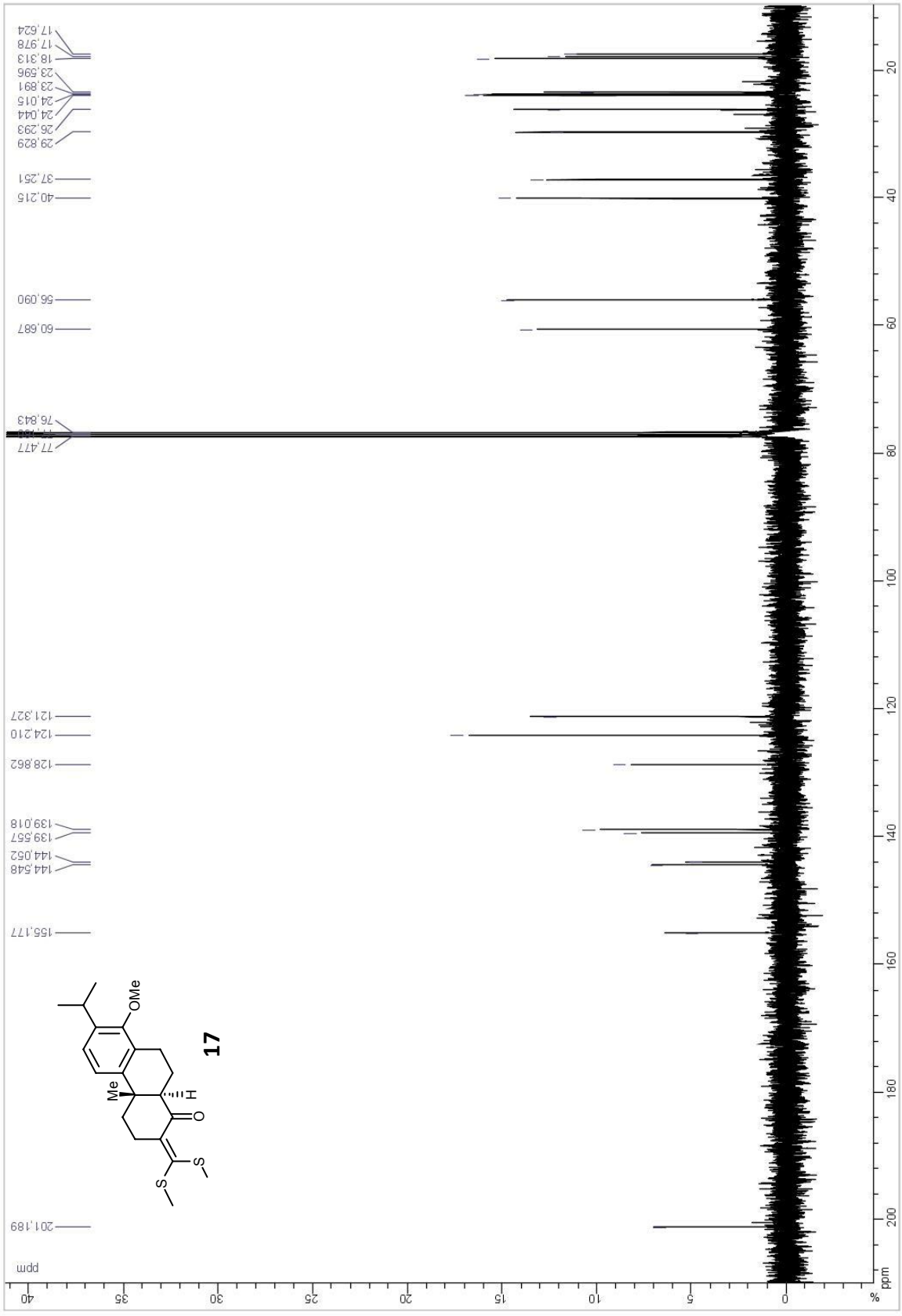

OMe
Me
H
S
S
12
ppm


21.131
22.061
24.040
24.084
24.915
24.973
26.246
38.188
38.501
39.671
40.755
46.820
51.300
60.610
73.008
76.839
77.477
120.574
123.951
128.898
138.380
147.508
155.112
ppm
OMe
Me
H
S
S
12


OMe
Me
H
O
4
3.0
6.3
1.2
1.1
3.2
3.0
2.1
1.1
1.1
3.0
2.0
ppm


17.078
22.600
23.111
23.665
23.876
23.927
26.162
37.226
40.885
42.424
55.117
60.537
76.719
77.036
77.353
121.021
124.039
128.523
138.905
144.661
155.152
212.449
OMe
Me
H
O
4
ppm


OMe
Me
H
O
S
S
17
ppm


17.624
17.978
18.313
23.596
23.891
24.015
24.044
26.293
29.829
37.251
40.215
56.090
60.687
76.843
77.477
121.327
124.210
128.862
139.018
139.557
144.052
144.548
155.177
201.189
OMe
Me
H
O
S
S
17
ppm
40
35
30
25
20
15
10
5
0
%
ppm
20
40
60
80
100
120
140
160
180
200

5. References

1. a) L.M. Deck, E.M. Brazwell, D.L. Vander Jagt, R.E. Royer, *Org. Prep. Proced. Int.* **1990**, *22*, 495-500; b) L.F. Basil, H. Nakano, R. Frutos, M. Kopach, A.I. Meyers, *Synthesis* **2002**, 2064-2074.

2. D. Yang, X.-Y. Ye, X. Ming, *J. Org. Chem.* **2000**, *65*, 2208-2217.