Total Synthesis of Gonytolides C and G, Lachnone C, and Formal Synthesis of Blennolide C and Diversonol

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Electronic Supplementary Information

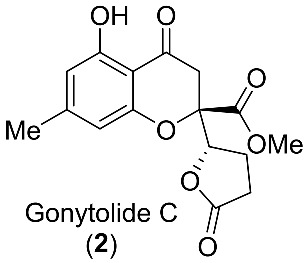
Contents

1. General Experimental Procedure:

Anhydrous solvents were dried and distilled by standard methods prior to use. Commercially available reagents were used without further purification unless otherwise specified. All the reactions were performed under an atmosphere of nitrogen or argon in oven-dried glassware with magnetic stirring. Column chromatography was carried out using silica gel (60-120 or 100-200 or 230-400 mesh) and the column was eluted with ethyl acetate-petroleum ether/CH_2Cl_2. Analytical thin layer chromatography (TLC) was performed on precoated silica gel-60 F_{254} (0.5 mm) glass plates. Visualization of the spots on TLC plates was achieved either by UV light or by staining the plates in methanolic anisaldehyde-sulphuric acid-acetic acid or in aqueous ceric sulphate-phosphomolybdic acid-sulphuric acid, methanol-phosphomolybdic acid-sulphuric acid solution and charring on hot plate.^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ and Acetone-d_6 solvent on 600 MHz, 500 MHz, 400 MHz, 300 MHz and 125 MHz and 75 MHz spectrometer, respectively at ambient temperature. Chemical shifts are reported as δ values in ppm relative to internal $CHCl_3$ δ 7.26 or TMS δ 0.0 and Acetone-d_6 δ 2.05 for ^{1}H NMR and $CHCl_3$ δ 77.0 and Acetone-d_6 δ 30.83 for ^{13}C NMR. ^{1}H NMR data is recorded as follows: chemical shift [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublet; ddd = doublet of doublet of doublet; m = multiplet; brs = broad singlet, brd = broad doublet. FTIR spectra were recorded as KBr thin films or neat. Mass spectra were recorded on Micro Mass VG-7070H mass spectrometer for ESI and are given in mass units (m/z). High resolution mass spectra (HRMS) [ESI+] were obtained using either a TOF or a double focusing spectrometer or using Thermo Exactive^{TM} orbitrap (Thermo fisher scientific, Berlin, Germany).

2. Comparison Tables of Natural and Synthetic Compounds (^1H & ^{13}C NMR)

a) Gonytolide C (2):

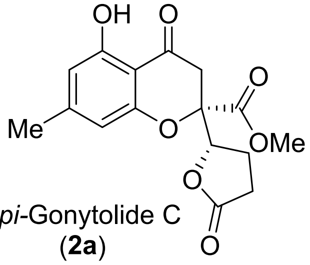


Gonytolide C
(**2**)

Atom No.	**Gonytolide C (2):** δ_H [ppm] (multiplicity; J [Hz], relative integral)	
	Natural (600 MHz, $CDCl_3$)	**Synthetic** (600 MHz, $CDCl_3$)
3	3.12 (d, J = 16.7 Hz, 1H) 2.95 (d, J = 16.7 Hz, 1H)	3.11 (d, J = 16.9 Hz, 1H) 2.95 (d, J = 16.9 Hz, 1H)
6	6.40 (s, 1H)	6.40 (s, 1H)
8	6.38 (s, 1H)	6.37 (s, 1H)
9	4.85 (dd, J = 8.0, 5.9 Hz, 1H)	4.85 (dd, J = 7.9, 6.0 Hz, 1H)
10	2.50-2.35 (m, 2H)	2.50-2.36 (m, 2H)
11	2.71 (ddd, J = 18.0, 9.8, 7.2 Hz, 1H) 2.58 (ddd, J = 18.0, 10.2, 6.7 Hz, 1H)	2.70 (ddd, J = 18.0, 10.1, 7.1 Hz, 1H) 2.58 (ddd, J = 18.0, 10.1, 6.7 Hz, 1H)
14	2.30 (s, 3H)	2.30 (s, 3H)
15	3.72 (s, 3H)	3.73 (s, 3H),
5-OH	11.38 (s, 1H)	11.38 (s, 1H)

Atom No.	**Gonytolide C (2):** δ_C [ppm]	
	Natural (150 MHz, $CDCl_3$)	**Synthetic** (75 MHz, $CDCl_3$)
2	84.0	84.0
3	39.4	39.4
4	193.0	193.0
4a	105.6	105.6
5	161.7	161.7
6	108.4	108.4
7	151.6	151.6
8	111.0	111.0
8a	159.0	159.0
9	80.9	80.9
10	22.0	22.0
11	27.6	27.6
12	175.4	175.5
13	168.9	168.9
14	22.6	22.6
15	53.6	53.6

b) *epi*-**Gonytolide C (2a):**

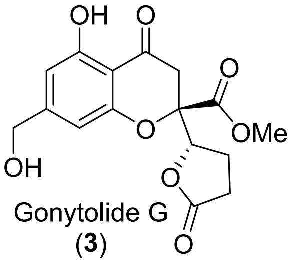


epi-Gonytolide C
(**2a**)

Atom No.	*epi*-**Gonytolide C (2a):** δ_{H} [ppm] (multiplicity; J [Hz], relative integral)	
	Reference 12 (500 MHz, $CDCl_3$)	**Synthetic** (600 MHz, $CDCl_3$)
3	3.42 (d, J = 17.2 Hz, 1H), 3.04 (d, J = 17.3 Hz, 1H),	3.43 (d, J = 17.3 Hz, 1H), 3.04 (d, J = 17.3 Hz, 1H)
6 & 8	6.34 (s, 2H),	6.35 (s, 1H), 6.33 (s, 1H)
9	4.75 (dd, J = 8.5, 4.2 Hz, 1H)	4.75 (dd, J = 8.6, 4.1 Hz, 1H)
10	2.47 (m, 1H), 2.32 (m, 1H),	2.47 (m, 1H), 2.31 (m, 1H),
11	2.78 (m, 1H), 2.55 (m, 1H),	2.78 (ddd, J = 18.0, 10.5, 8.3 Hz, 1H), 2.55 (ddd, J = 18.0, 10.5, 5.3 Hz, 1H),
14	2.28 (s, 3H)	2.28 (s, 3H)
15	3.72 (s, 3H)	3.72 (s, 3H),
5-OH	11.39 (s, 1H)	11.39 (s, 1H)

Atom No.	*epi*-**Gonytolide C (2a):** δ_{C} [ppm]	
	Reference 12 (100 MHz, $CDCl_3$)	**Synthetic** (75 MHz, $CDCl_3$)
2	84.5	84.6
3	40.2	40.3
4	194.0	194.0
4a	105.4	105.5
5	161.6	161.7
6	108.2	108.3
7	151.1	151.2
8	110.9	111.0
8a	158.8	158.9
9	79.6	79.7
10	21.6	21.7
11	27.7	27.7
12	176.0	175.9
13	169.0	169.1
14	22.5	22.6
15	53.6	53.6

c) **Gonytolide G (3):**

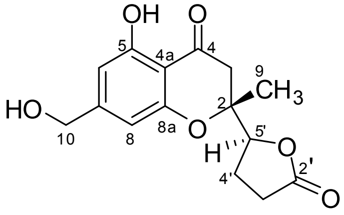


Gonytolide G
(**3**)

Atom No.	**Gonytolide G (3):** δ_H [ppm] (multiplicity; J [Hz]), relative integral	
	Natural (600 MHz, $CDCl_3$)	**Synthetic** (500 MHz, $CDCl_3$)
3	3.13 (d, J = 17.0 Hz, 1H) 2.98 (d, J = 17.0 Hz, 1H)	3.14 (d, *J* = 17.0 Hz, 1H) 2.98 (d, *J* = 17.0 Hz, 1H)
6	6.56 (s, 1H)	6.56 (s, 1H)
8	6.59 (s, 1H)	6.60 (s, 1H)
9	4.87 (dd, J = 7.8, 6.1 Hz, 1H)	4.87 (dd, *J* = 7.9, 5.9 Hz, 1H)
10	2.51-2.40 (m, 2H)	2.49-2.39 (m, 2H)
11	2.71 (ddd, J = 17.4, 9.5, 7.3 Hz, 1H) 2.58 (ddd, J = 17.4, 9.9, 6.8 Hz, 1H)	2.72 (ddd, *J* = 17.8, 9.7, 7.3 Hz, 1H), 2.60 (ddd, *J* = 17.8, 10.0, 6.4 Hz, 1H)
14	4.66 (s, 2H)	4.67 (s, 2H)
15	3.74 (s, 3H)	3.74 (s, 3H)
5-OH	11.42 (s, 1H)	11.43 (s, 1H)

Atom No.	**Gonytolide G (3):** δ_C [ppm]	
	Natural (150 MHz, $CDCl_3$)	**Synthetic** (75 MHz, $CDCl_3$)
2	84.1	84.2
3	39.5	39.5
4	193.3	193.3
4a	106.6	106.6
5	162.1	162.1
6	107.7	107.7
7	153.8	153.8
8	105.1	105.1
8a	159.4	159.4
9	80.9	80.9
10	22.0	22.0
11	27.6	27.6
12	175.5	175.5
13	168.9	168.9
14	66.4	64.4
15	53.7	53.7

d) **Lachnone C (4):**



Atom No	**Lachnone C (4):** δ_H [ppm] (multiplicity; J [Hz]), relative integral)		
	Natural (300 MHz, $CDCl_3$)	**Synthetic**[14] (500 MHz, $CDCl_3$)	**Synthetic (present)** (500 MHz, $CDCl_3$)
5-OH	11.57 (s, 1H)	11.56 (s, 1H)	11.56 (s, 1H)
H-6	6.52 (brs, 1H)	6.51 (s, 1H)	6.51 (s, 1H)
H-8	6.45 (brs, 1H)	6.45 (s, 1H)	6.45 (s, 1H)
H-10	4.63 (brs, 2H)	4.63 (bs, 2H)	4.63 (s, 2H)
H-5^1	4.58 (t, J = 7.2 Hz, 1H)	4.58 (t, J = 7.0 Hz, 1H)	4.58 (t, J = 7.3 Hz 1H)
H-3α	2.98 (d, J = 17.1 Hz, 1H)	2.98 (d, J = 17.5 Hz, 1H)	2.98 (d, J = 17.1 Hz, 1H)
H-3β	2.61 (d, J = 17.1 Hz, 1H)	2.68-2.25 (m, 3H)	2.61 (d, J = 17.1 Hz, 1H)
H-3^1	2.60 (m, 2H)		2.71-2.55 (m, 2H)
H-4^1	2.32 (m, 2H)	2.42-2.25 (m, 2H)	2.38-2.27 (m, 2H)
H-9	1.43 (s, 3H)	1.45 (s, 3H)	1.45 (s, 3H)

Atom No	**Lachnone C (4):** δ_C [ppm]		
	Natural (125 MHz, $CDCl_3$)	**Synthetic**[14] (125 MHz, $CDCl_3$)	**Synthetic (present)** (125 MHz, $CDCl_3$)
C-4	195.8	195.8	195.7
C-2^1	176.1	176.1	176.1
C-5	162.0	162.0	161.9
C-8a	158.9	158.9	158.8
C-7	153.2	153.2	153.1
C-4a	106.9	106.9	106.8
C-6	106.4	106.4	106.3
C-8	105.3	105.3	105.2
C-5^1	82.6	82.6	82.5
C-2	80.9	80.8	80.8
C-10	64.5	64.4	64.4
C-3	42.9	42.8	42.8
C-3^1	28.2	28.2	28.1
C-4^1	22.3	22.3	22.3
C-9	19.1	19.1	19.1

3. Crystallographic data for 16a: X-ray data for the compound **16a** were collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite monochromated Mo-Kα radiation (λ=0.71073Å) with ω-scan method.[1] Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Unit cell dimensions were determined using 7449 reflections for **16a** data. Integration and scaling of intensity data were accomplished using SAINT program.[1] The structures were solved by Direct Methods using SHELXS97[2] and refinement was carried out by full-matrix least-squares technique using SHELXL97.[2] Anisotropic displacement parameters were included for all non-hydrogen atoms. All H atoms were positioned geometrically and treated as riding on their parent C atoms, with C-H distances of 0.93--0.97 Å, and with $U_{iso}(H) = 1.2U_{eq}$ (C) or $1.5U_{eq}$ for methyl atoms. The O bound H atoms were located from the difference Fourier map. The friedel pair reflections were merged (using MERG4) in the final cycle of refinement.

Crystal data for **16a**: $C_7H_{10}O_6$, $M = 190.15$, colourless block, 0.48 × 0.41 × 0.29 mm^3, orthorhombic, space group $P2_12_12_1$ (No. 19), $a = 6.7699(4)$, $b = 8.2068(5)$, $c = 15.1001(9)$ Å, $V = 838.95(9)$ Å^3, $Z = 4$, $D_c = 1.505$ g/cm^3, $F_{000} = 400$, CCD area detector, MoKα radiation, $\lambda = 0.71073$ Å, $T = 293(2)$K, $2\theta_{max} = 50.0°$, 7978 reflections collected, 877 unique ($R_{int} = 0.0183$). Final $GooF = 1.201$, $R1 = 0.0295$, $wR2 = 0.0830$, R indices based on 871 reflections with $I > 2\sigma(I)$ (refinement on F^2), 127 parameters, $\mu = 0.134$ mm^{-1}. CCDC 974676 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].

1. SMART & SAINT. Software Reference manuals. Versions 6.28a & 5.625, Bruker Analytical X-ray Systems Inc., Madison, Wisconsin, U.S.A., 2001.
2. Sheldrick, G. M. SHELXS97 and SHELXL97, Programs for crystal structure solution and refinement; University of Gottingen: Germany, 1997.

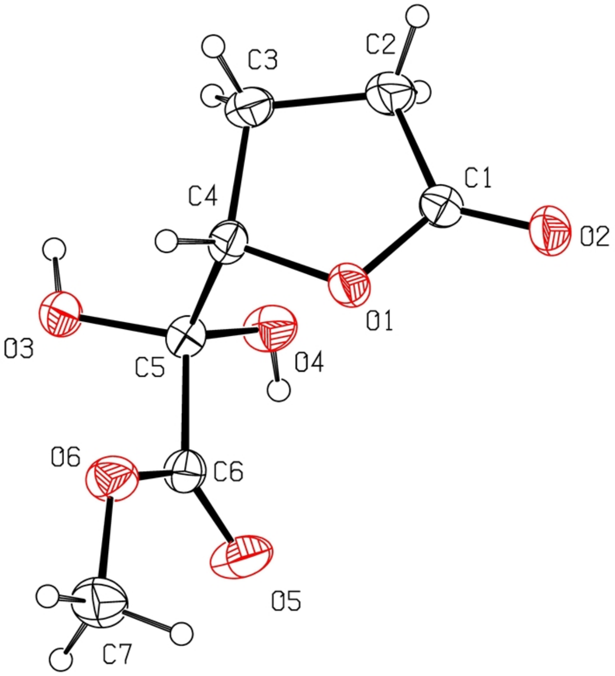
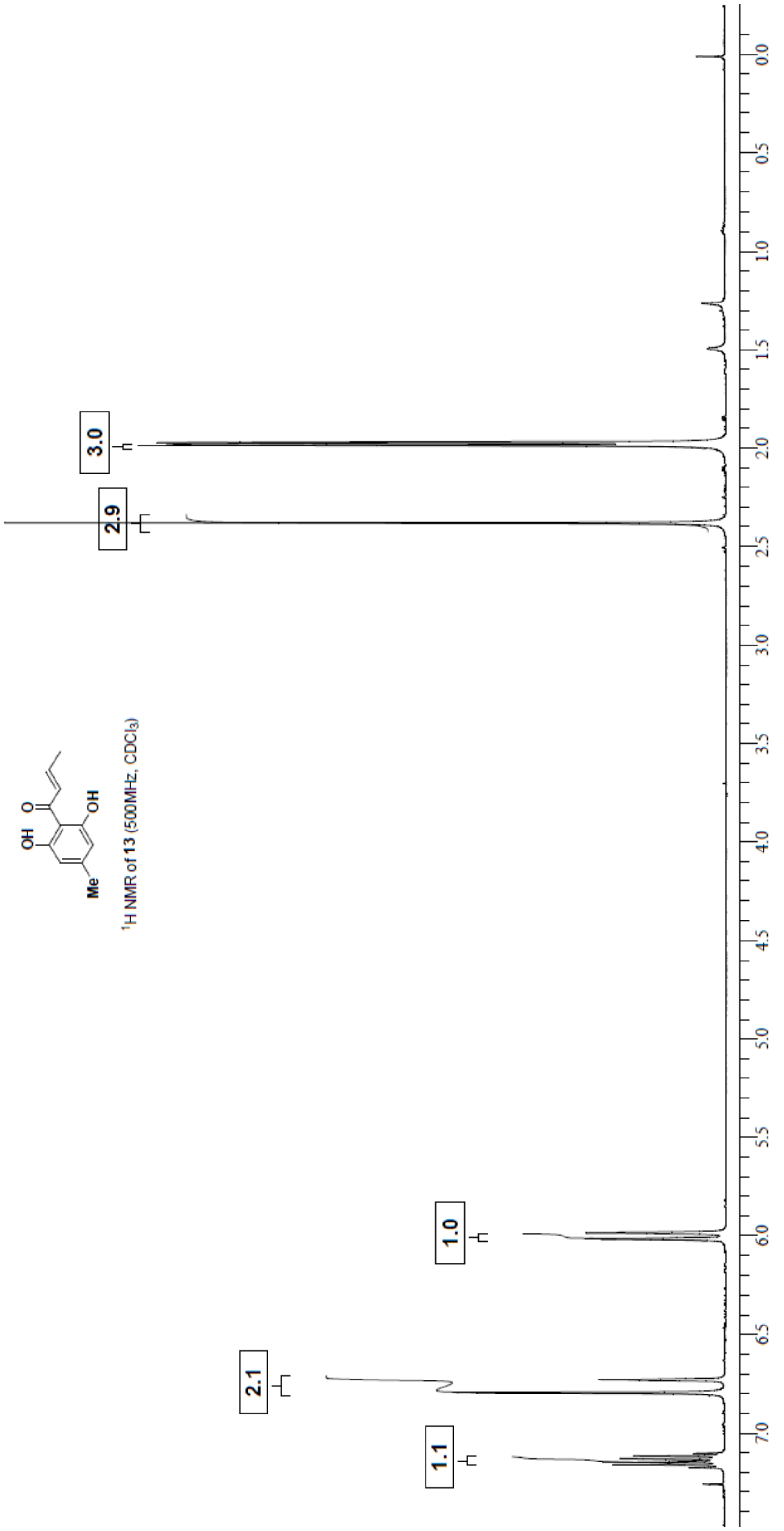
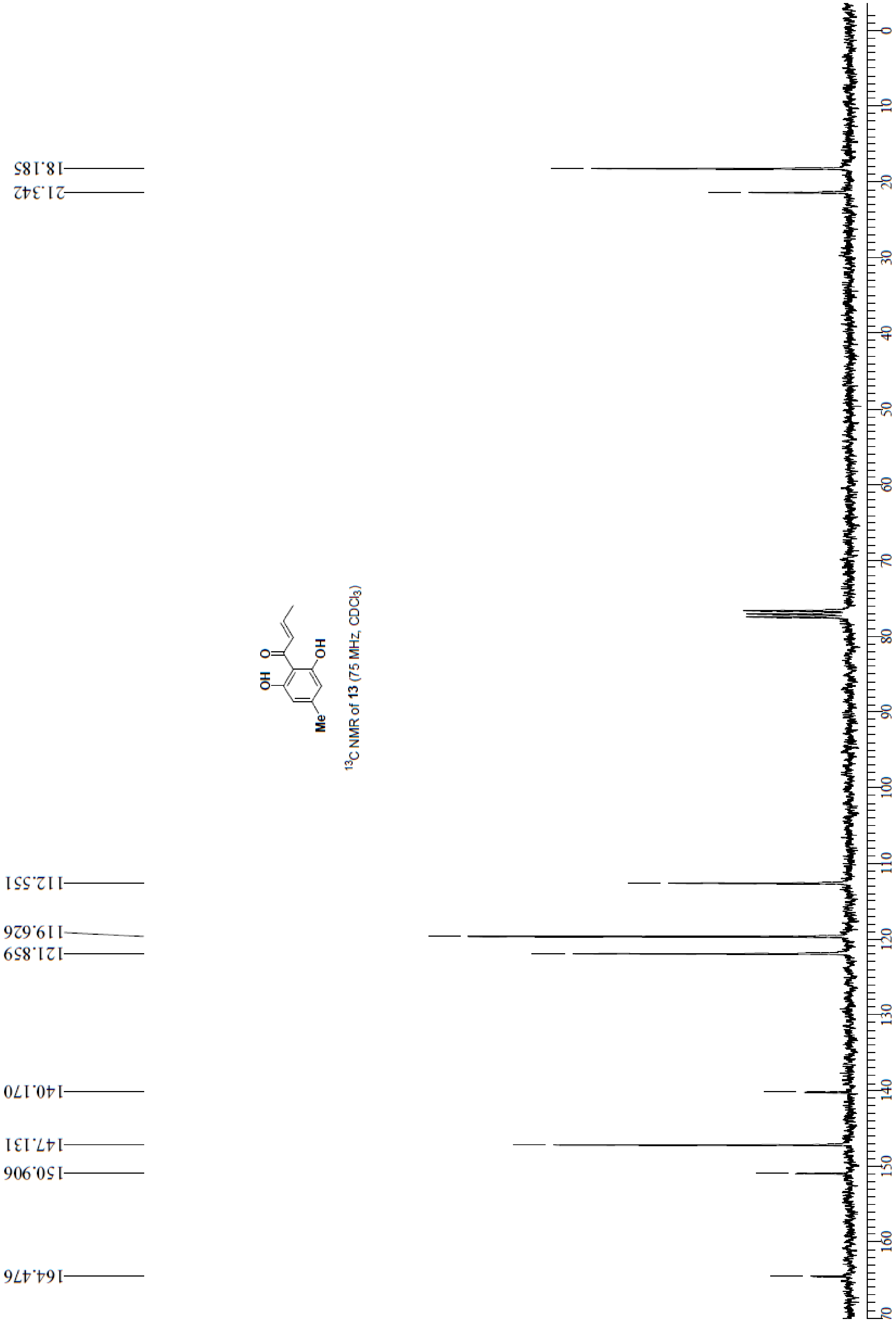


Figure caption: The molecular structure of AP45 with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radius.

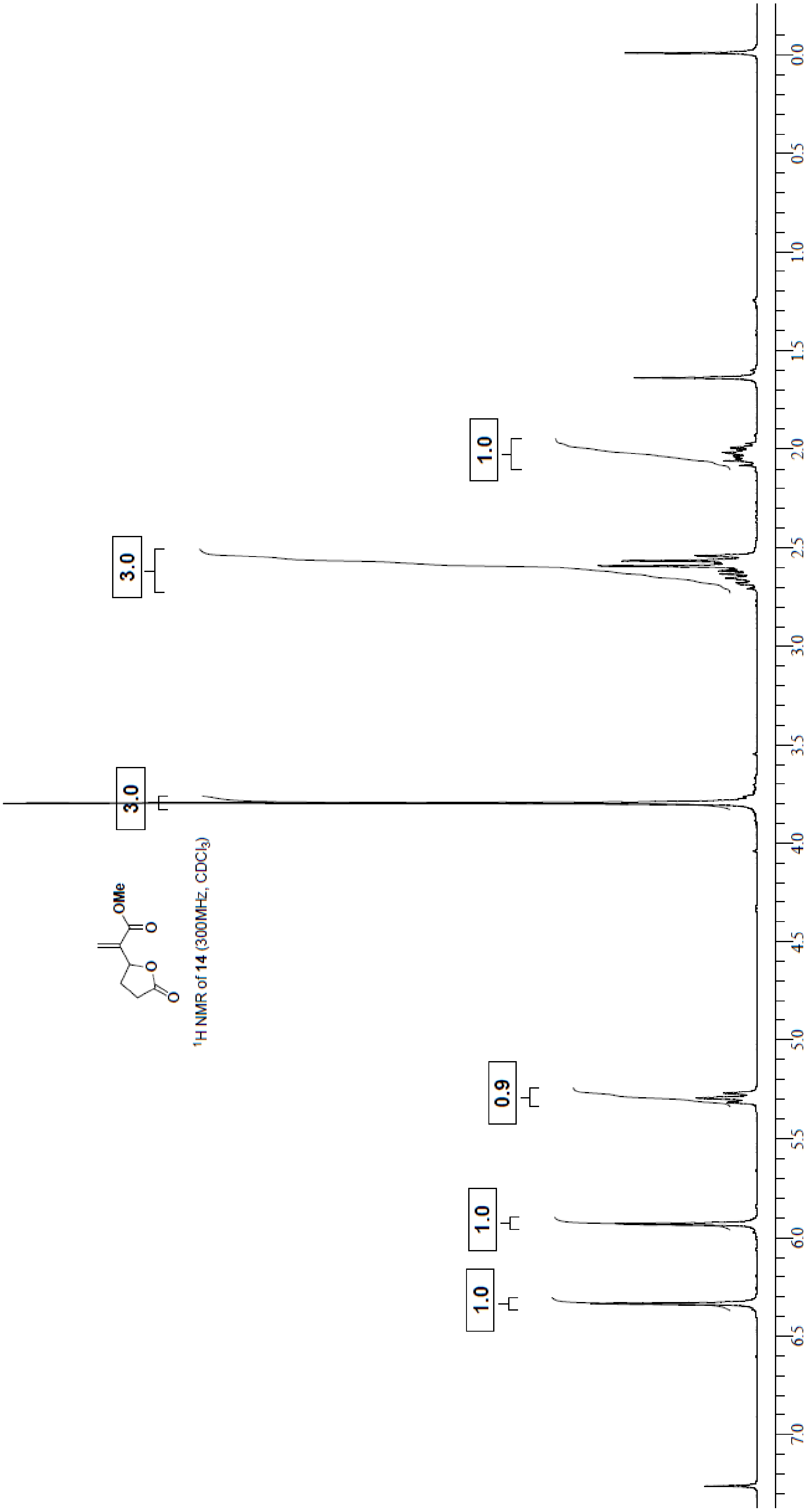
4. ^{1}H and ^{13}C NMR Spectra:



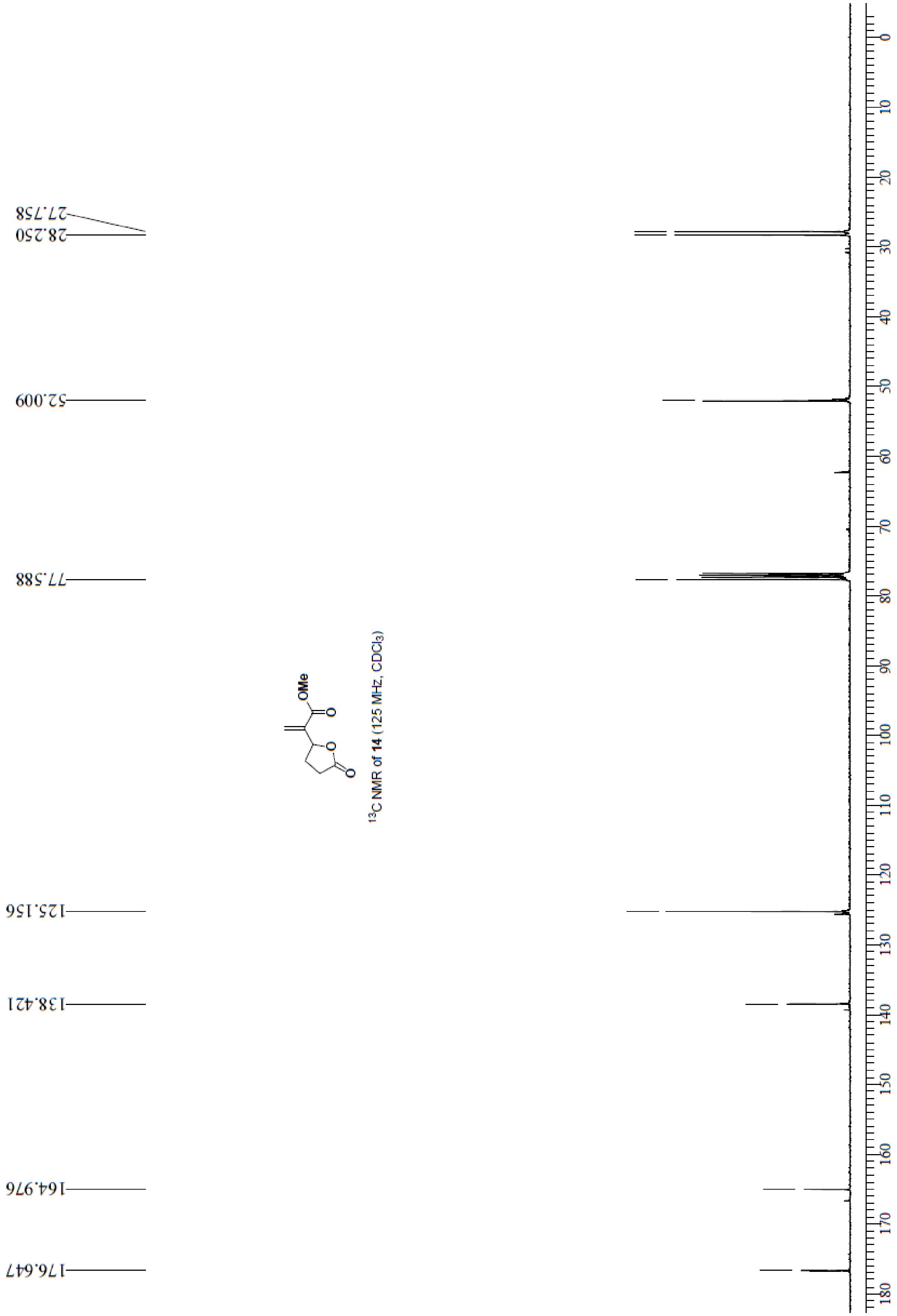
^{1}H NMR of **13** (500MHz, $CDCl_3$)



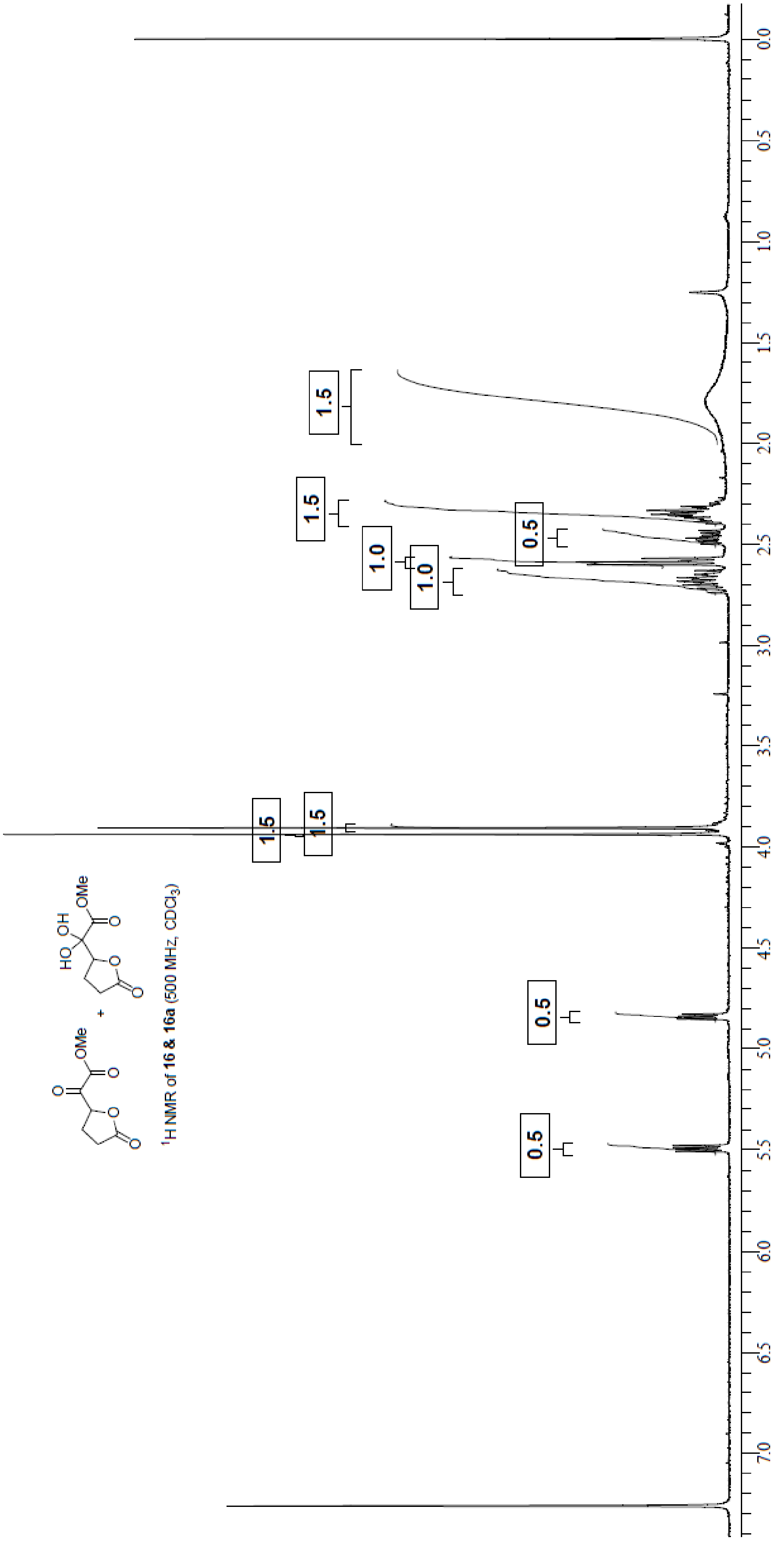
^{13}C NMR of **13** (75 MHz, CDCl$_3$)



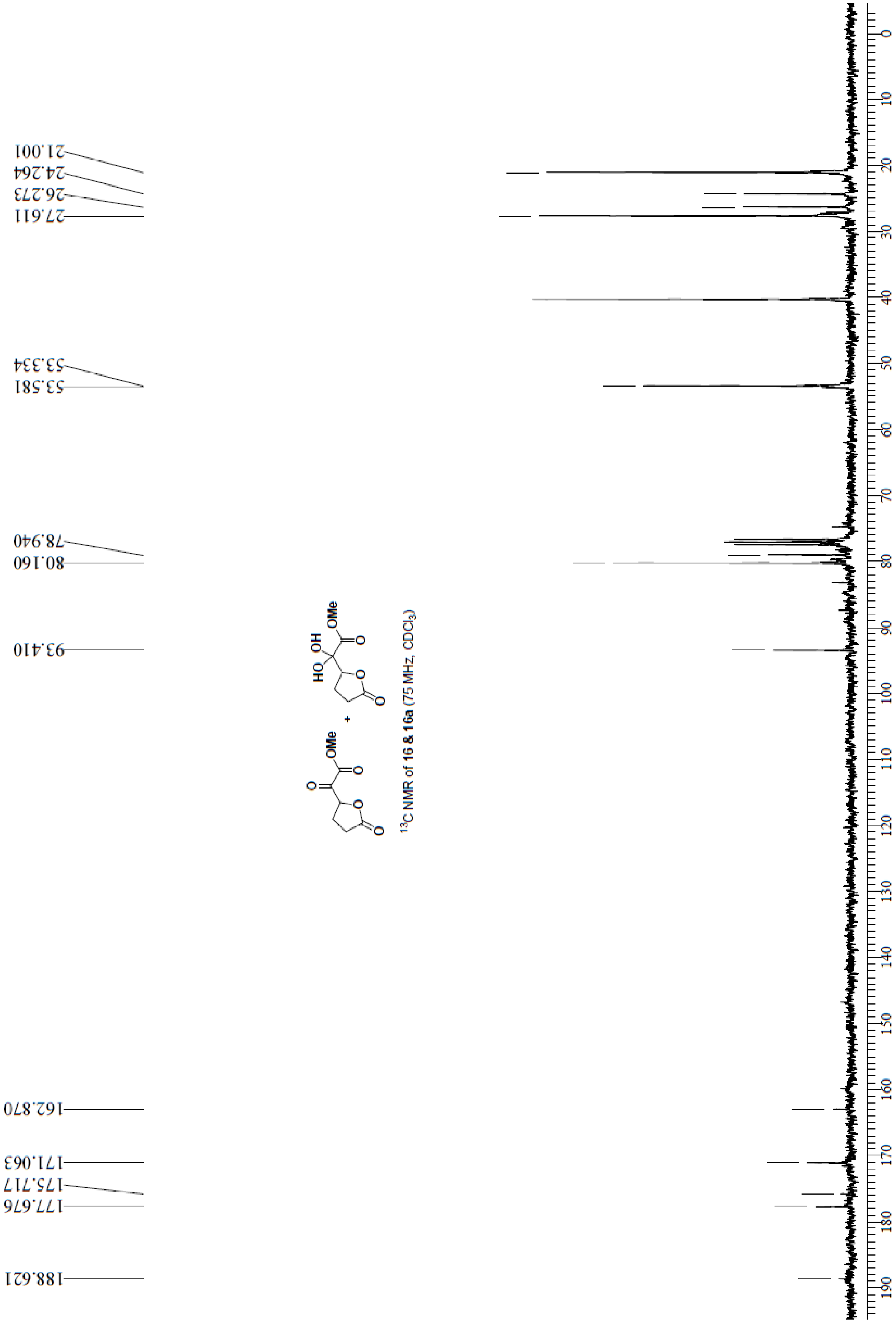
^{1}H NMR of **14** (300MHz, $CDCl_3$)



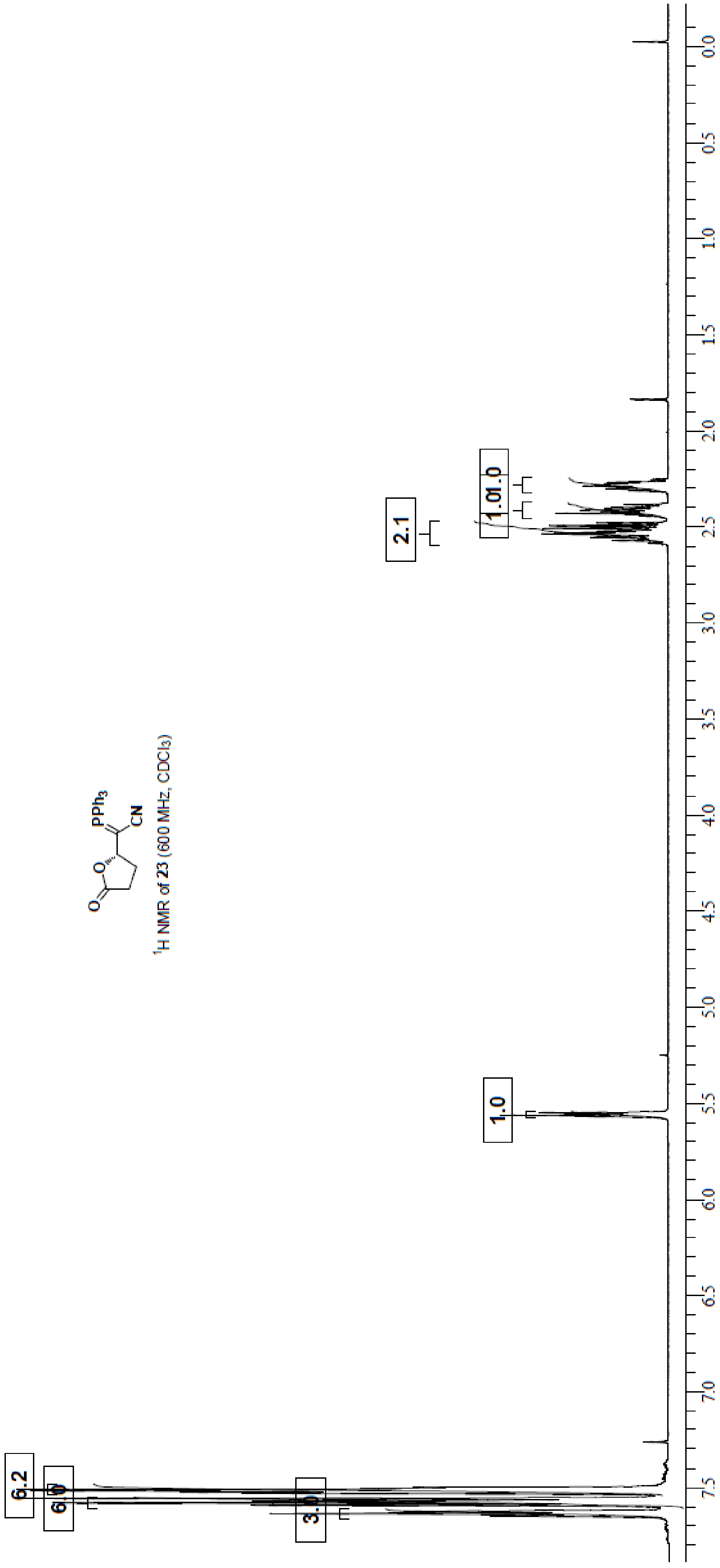
^{13}C NMR of **14** (125 MHz, CDCl$_3$)



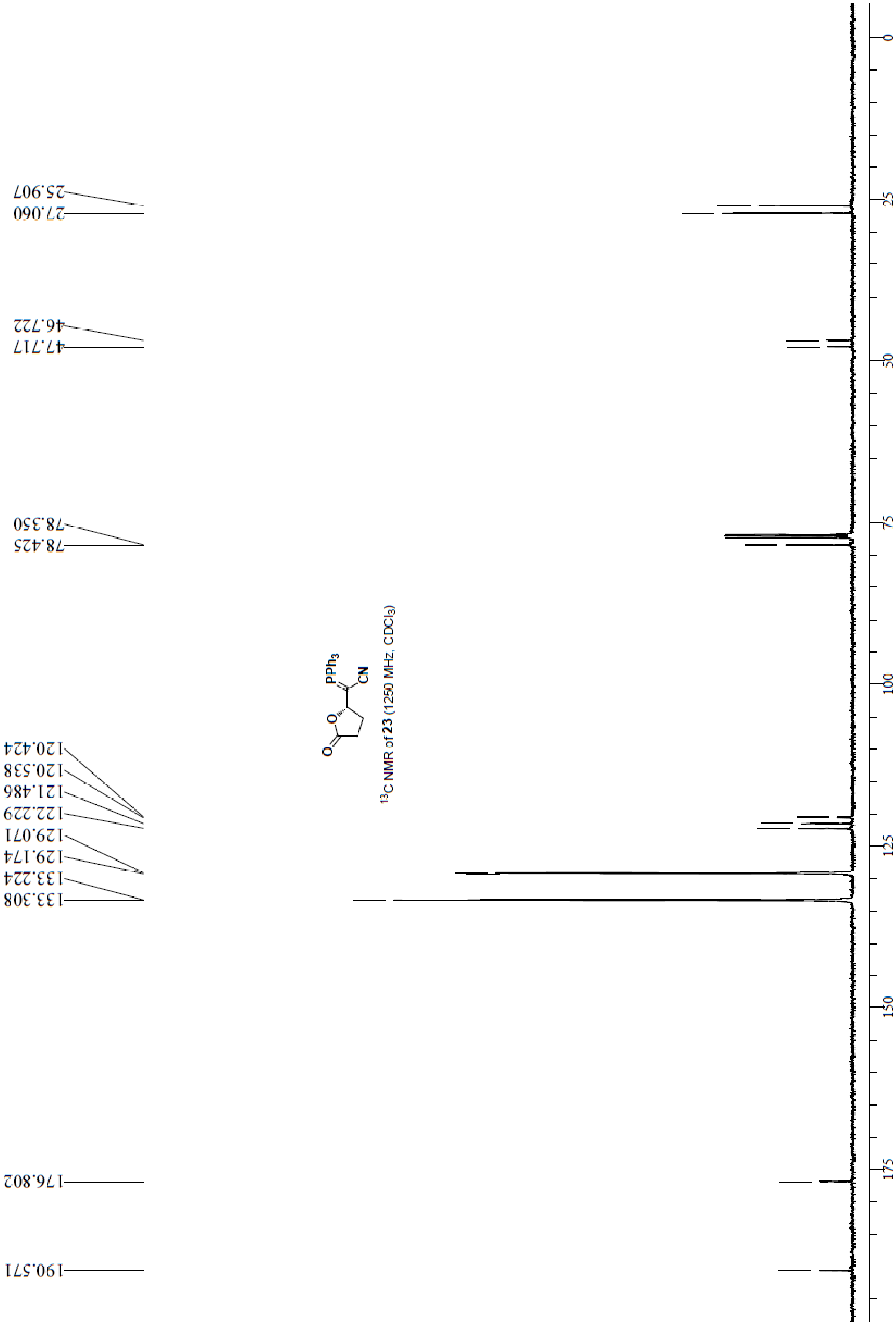
^{1}H NMR of **16 & 16a** (500 MHz, $CDCl_3$)



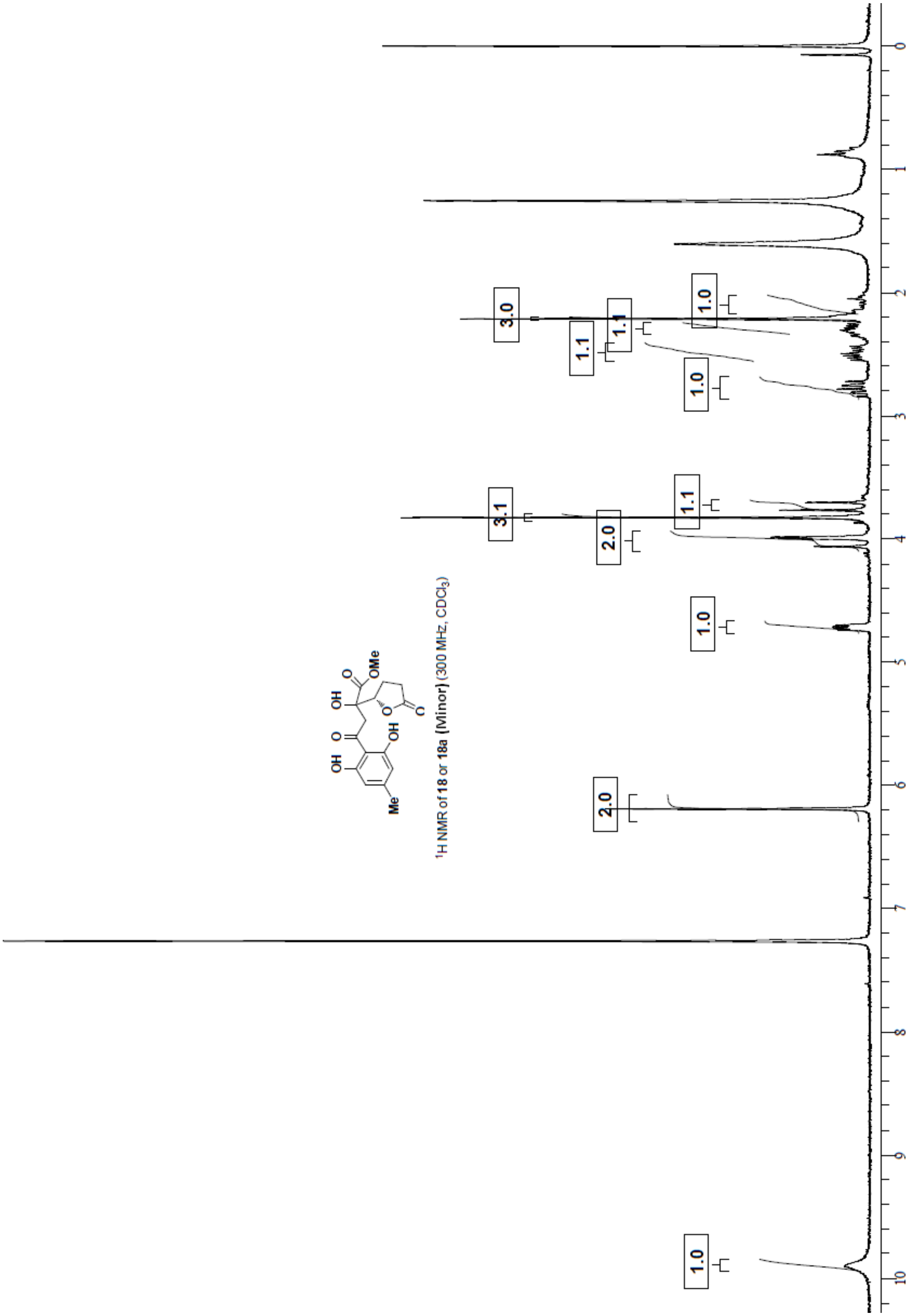
^{13}C NMR of **16 & 16a** (75 MHz, CDCl$_3$)



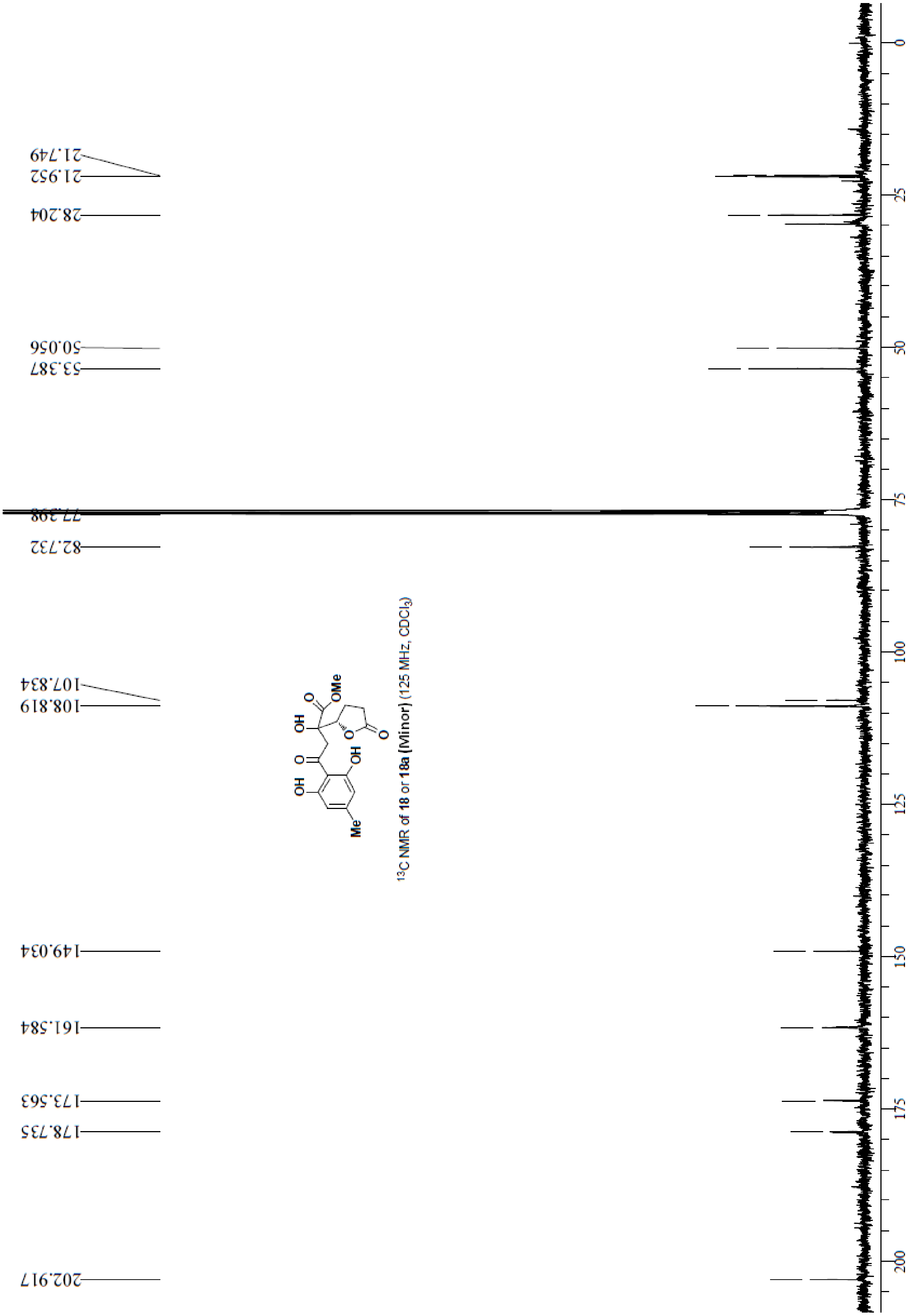
^{1}H NMR of **23** (600 MHz, $CDCl_3$)



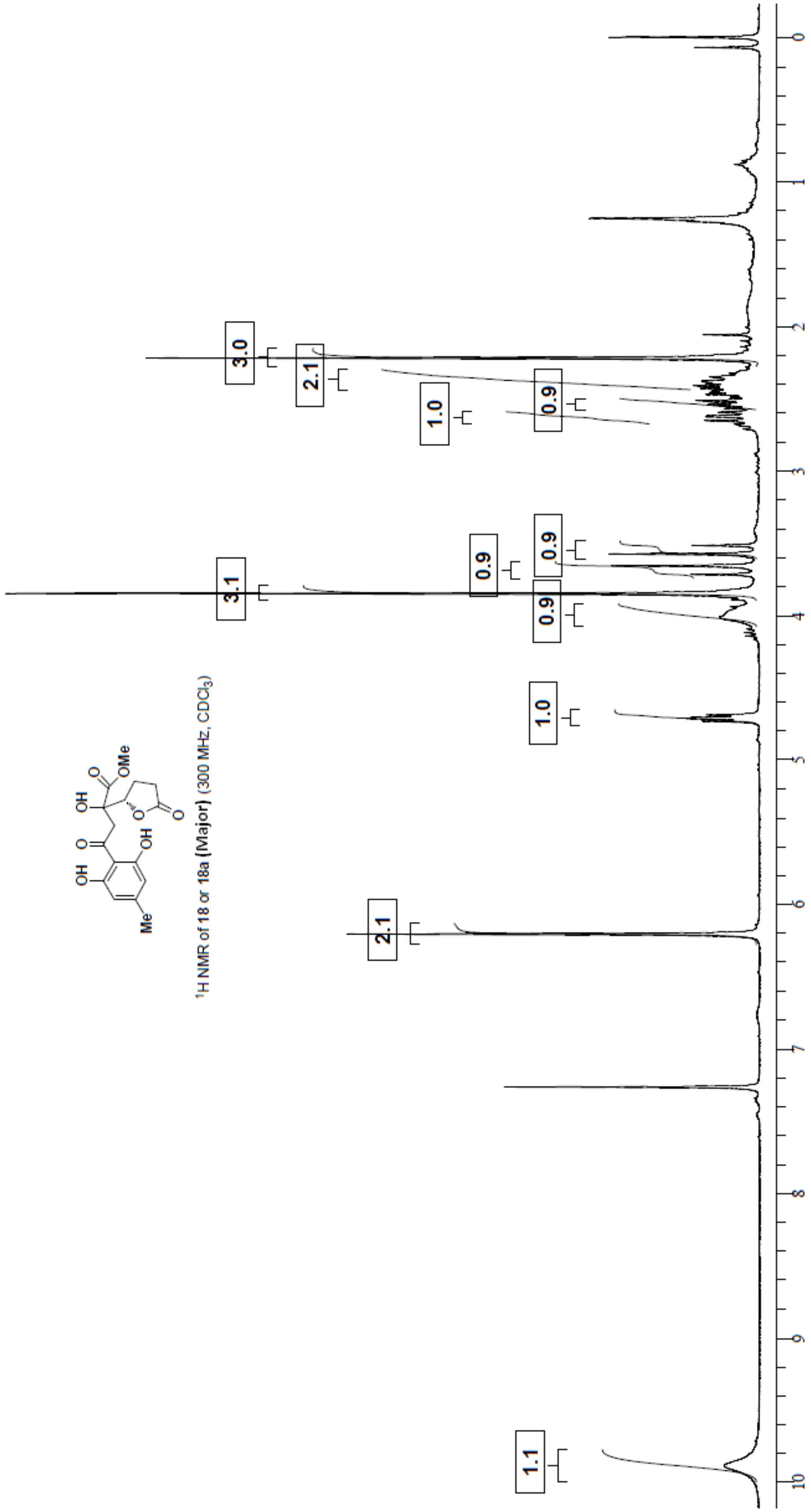
^{13}C NMR of **23** (1250 MHz, CDCl$_3$)



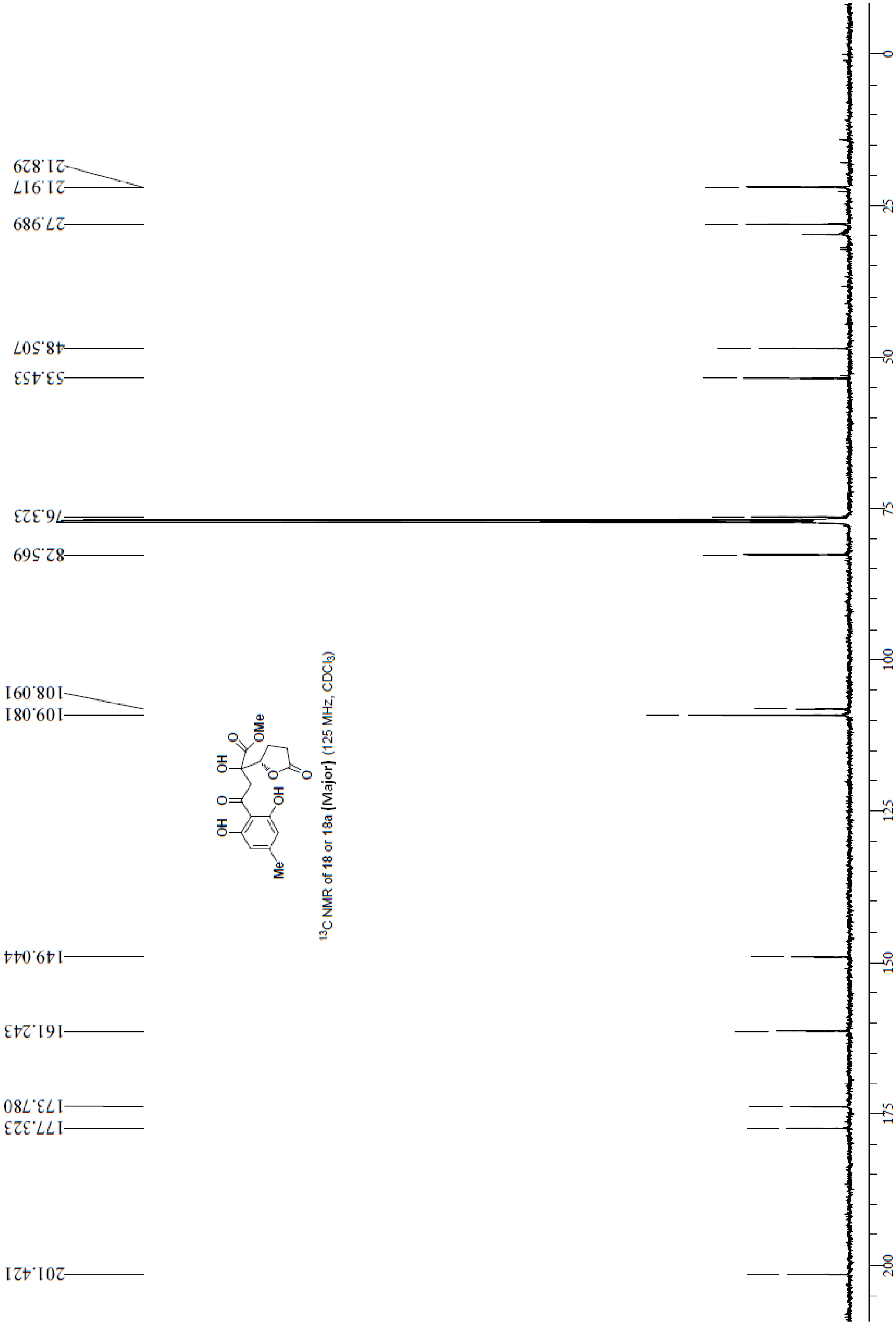
^{1}H NMR of **18** or **18a** (Minor) (300 MHz, CDCl$_3$)



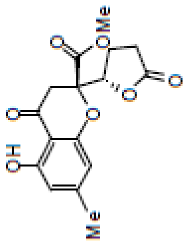
^{13}C NMR of **18** or **18a** **(Minor)** (125 MHz, $CDCl_3$)



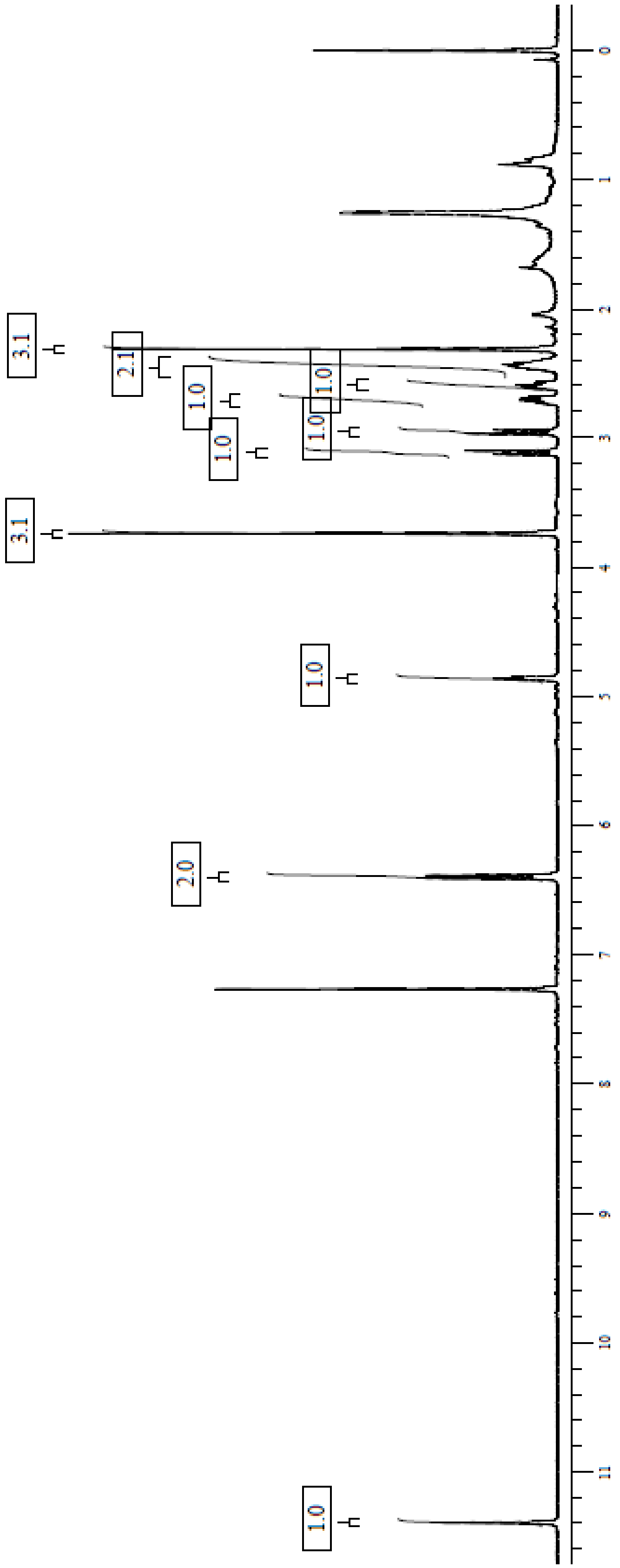
^{1}H NMR of 18 or 18a **(Major)** (300 MHz, CDCl$_3$)

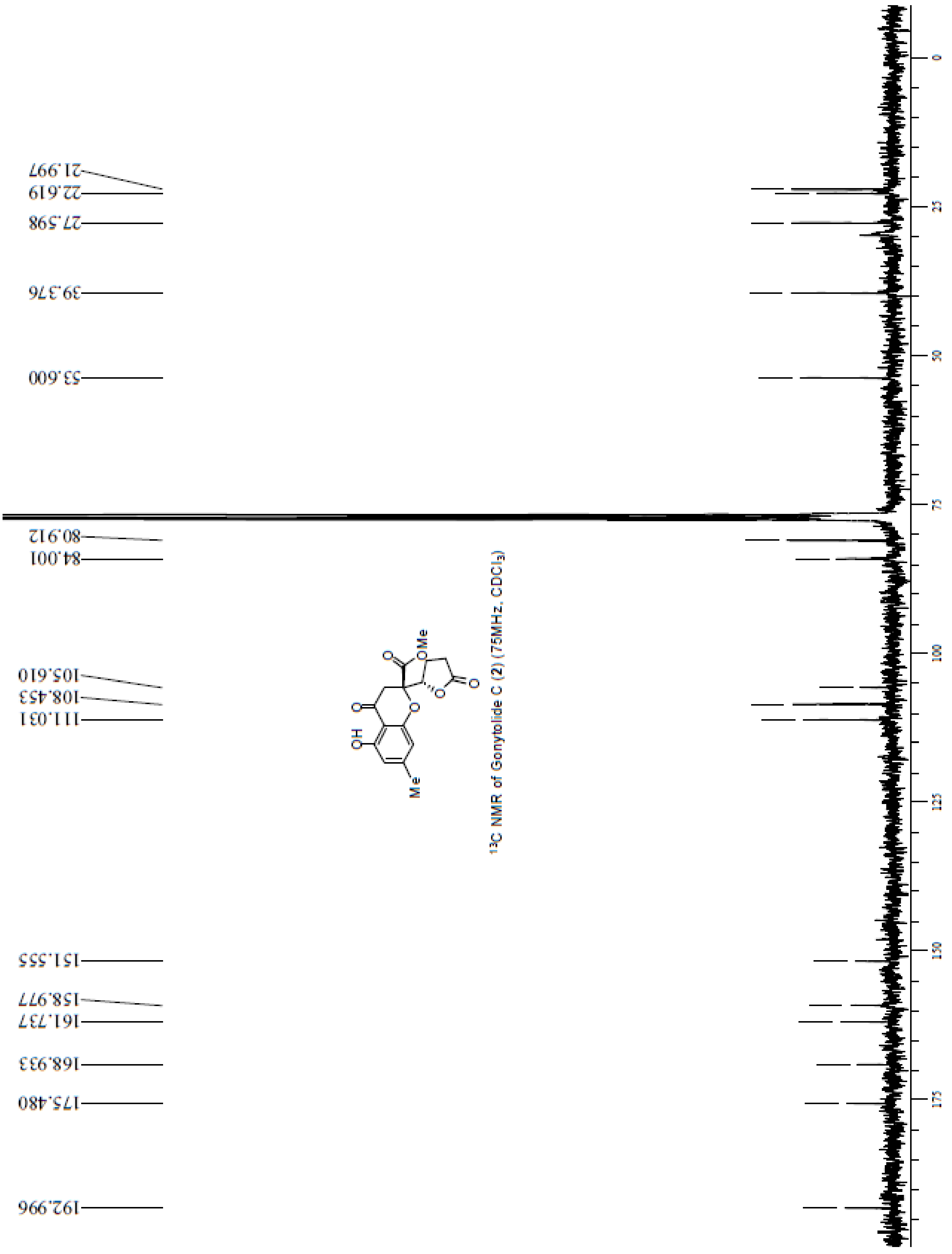


^{13}C NMR of 18 or 18a **(Major)** (125 MHz, CDCl$_3$)

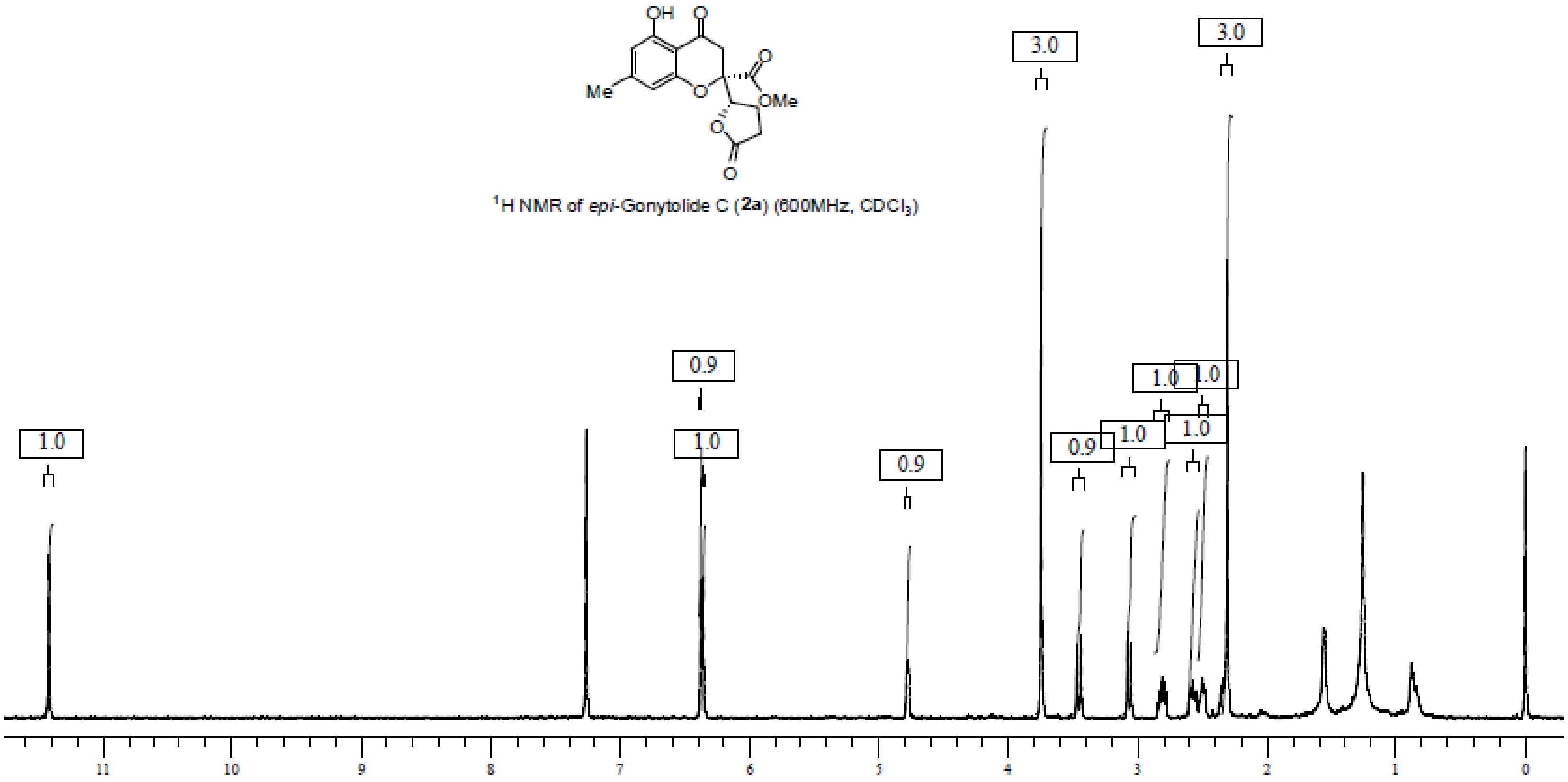


^{1}H NMR of Gonytolide C (2) (600MHz, CDCl$_3$)

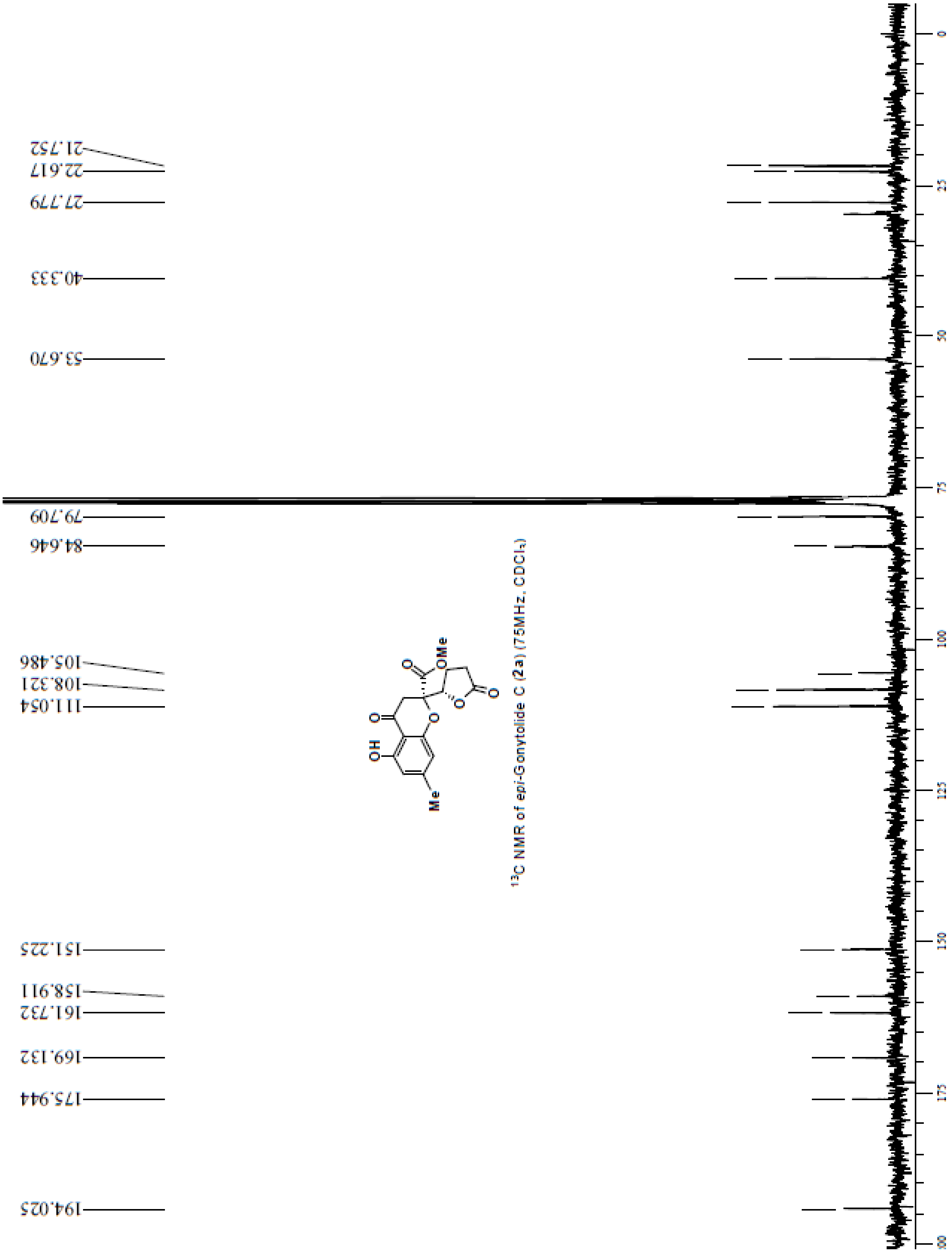




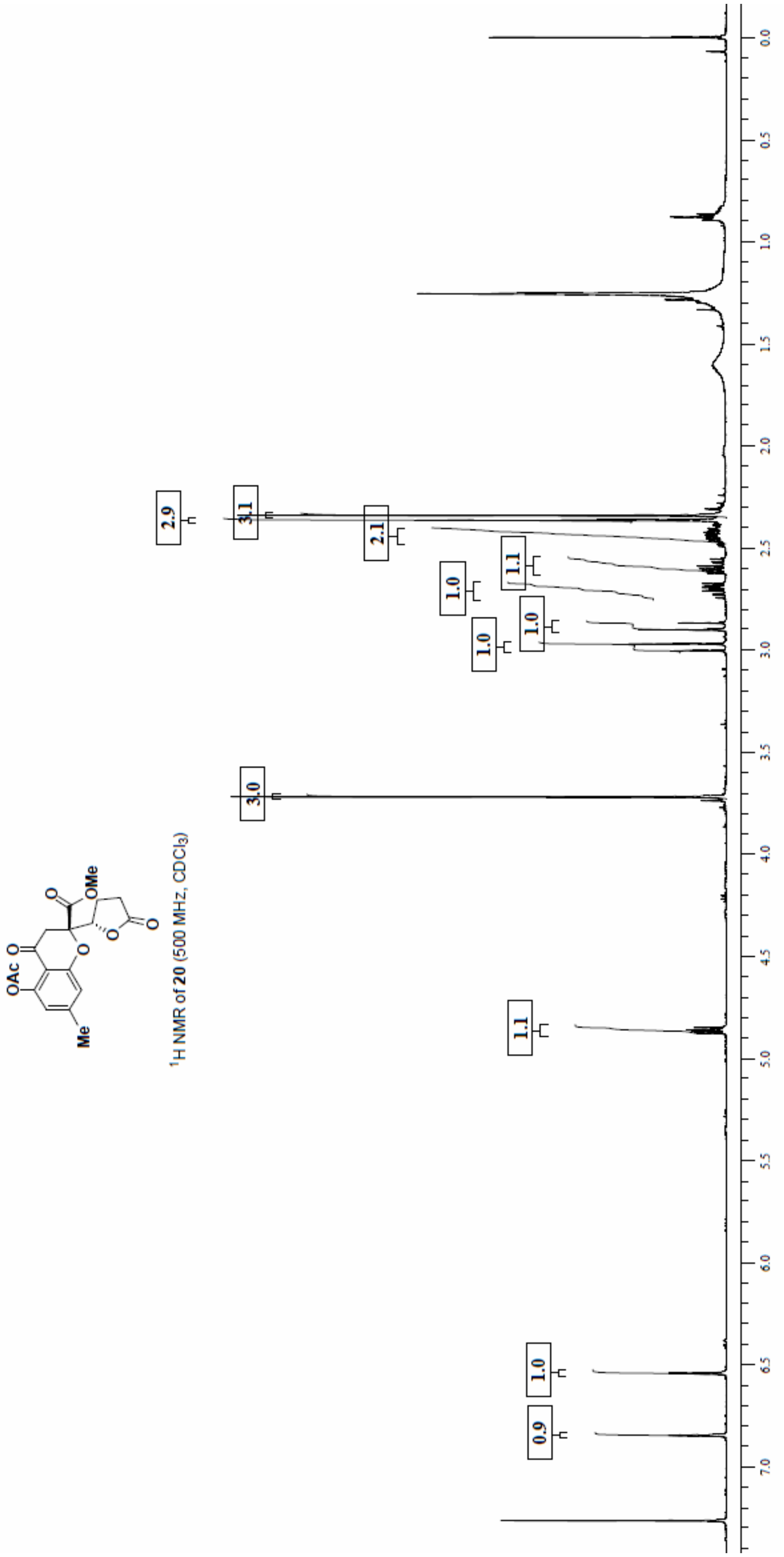
^{13}C NMR of Gonytbolide C (2) (75MHz, CDCl$_3$)



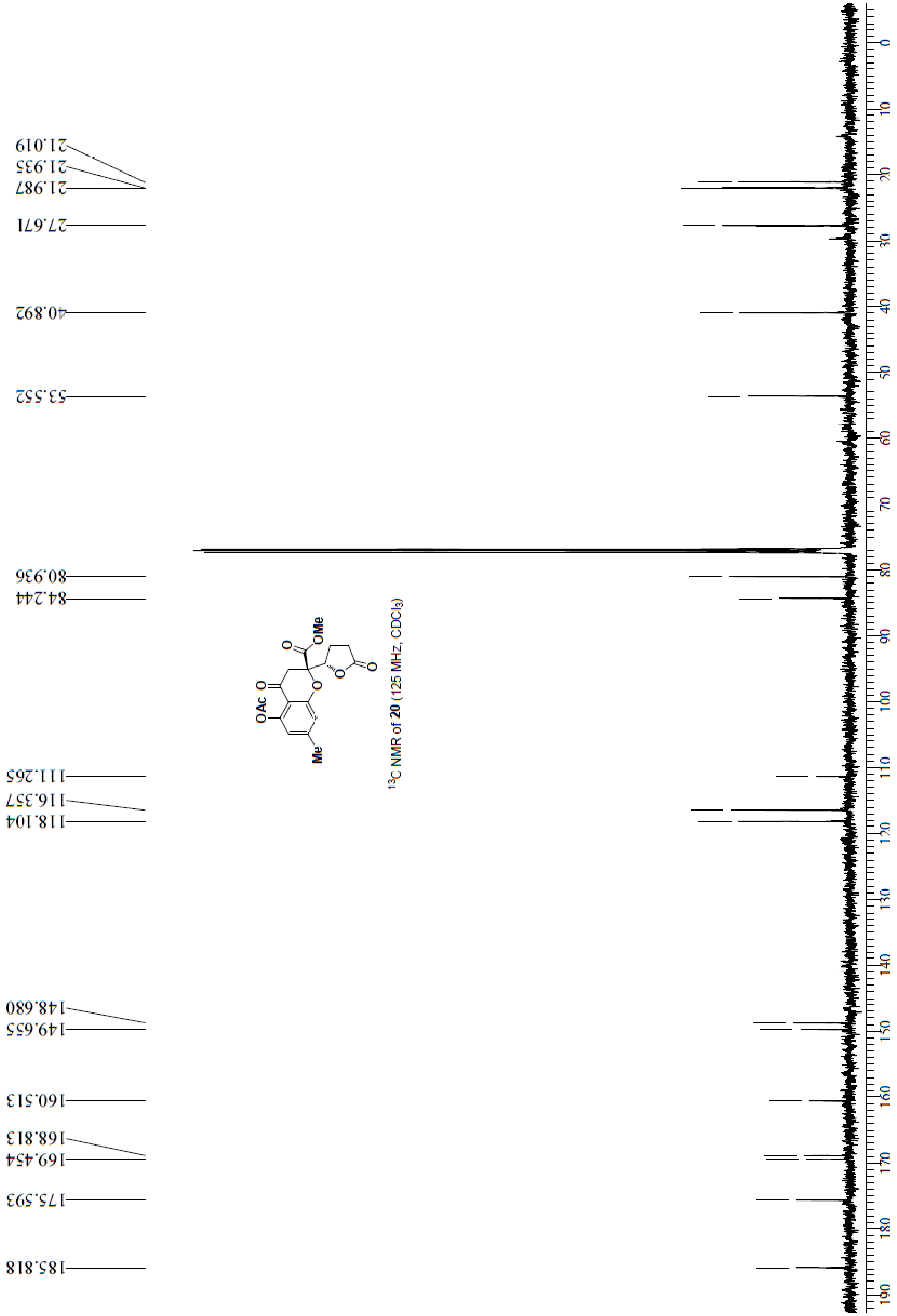
^{1}H NMR of *epi*-Gonytolide C (**2a**) (600MHz, $CDCl_3$)



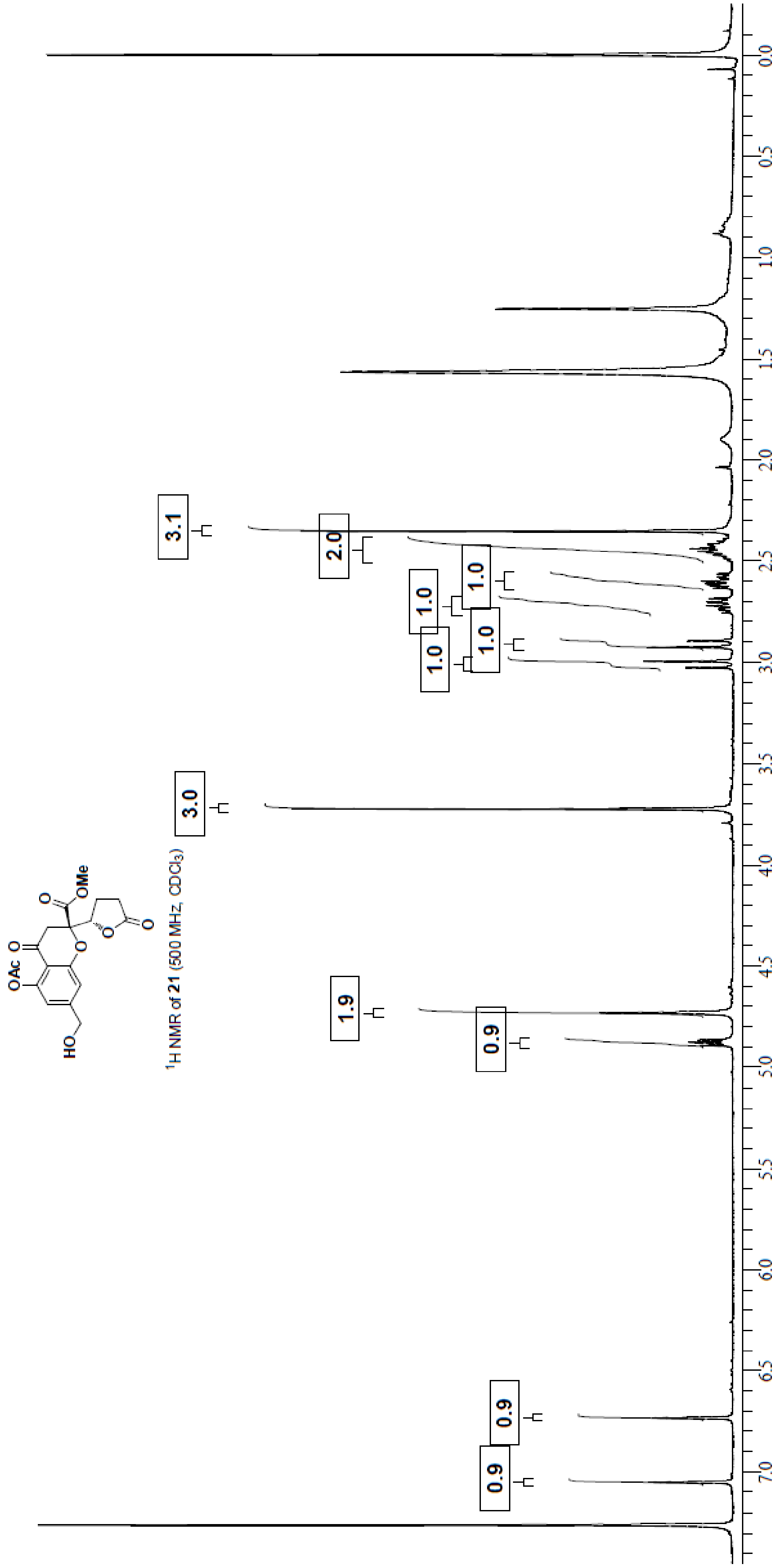
^{13}C NMR of epi-Gonytolide C (**2a**) (75MHz, CDCl$_3$)



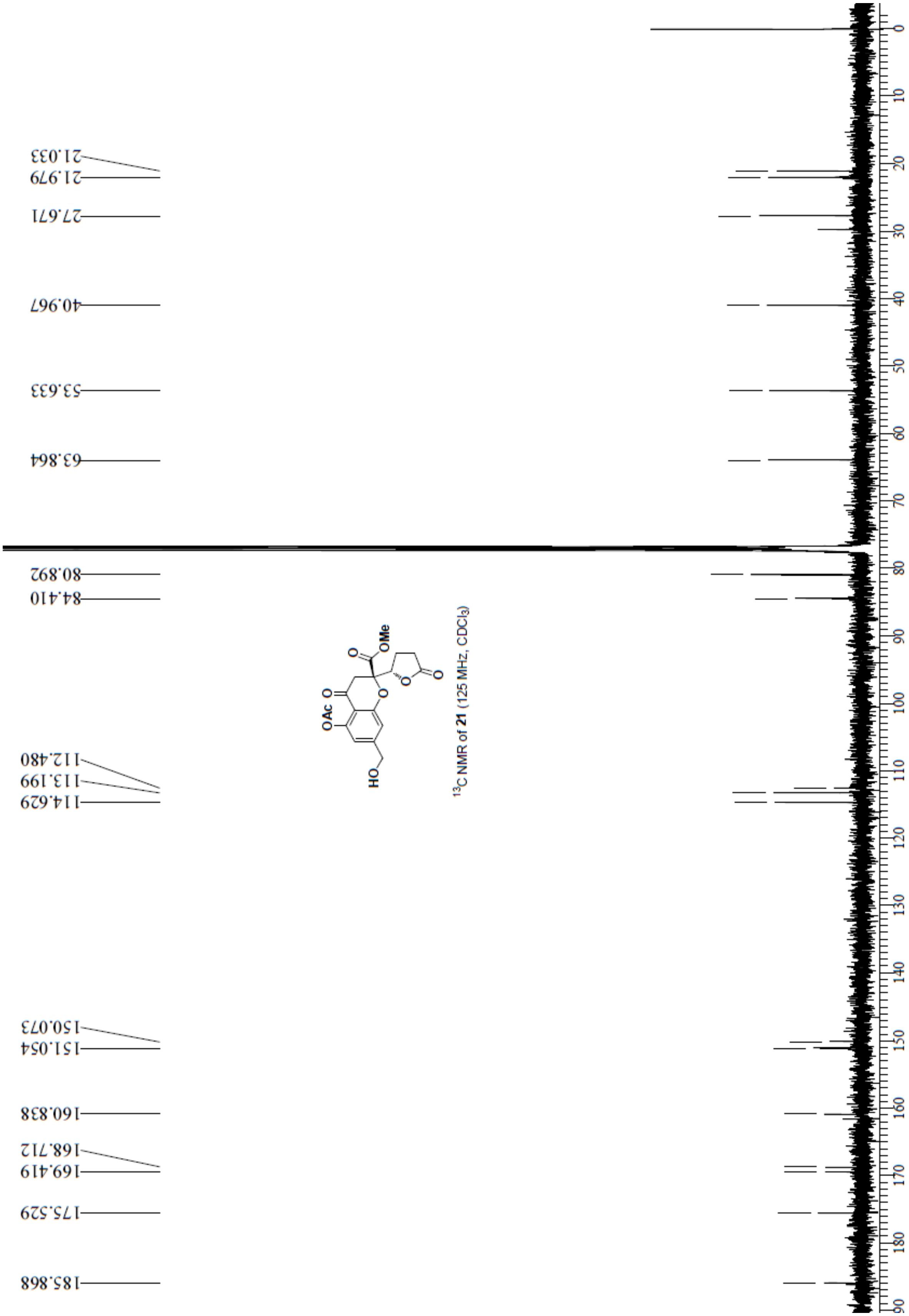
^{1}H NMR of **20** (500 MHz, $CDCl_3$)



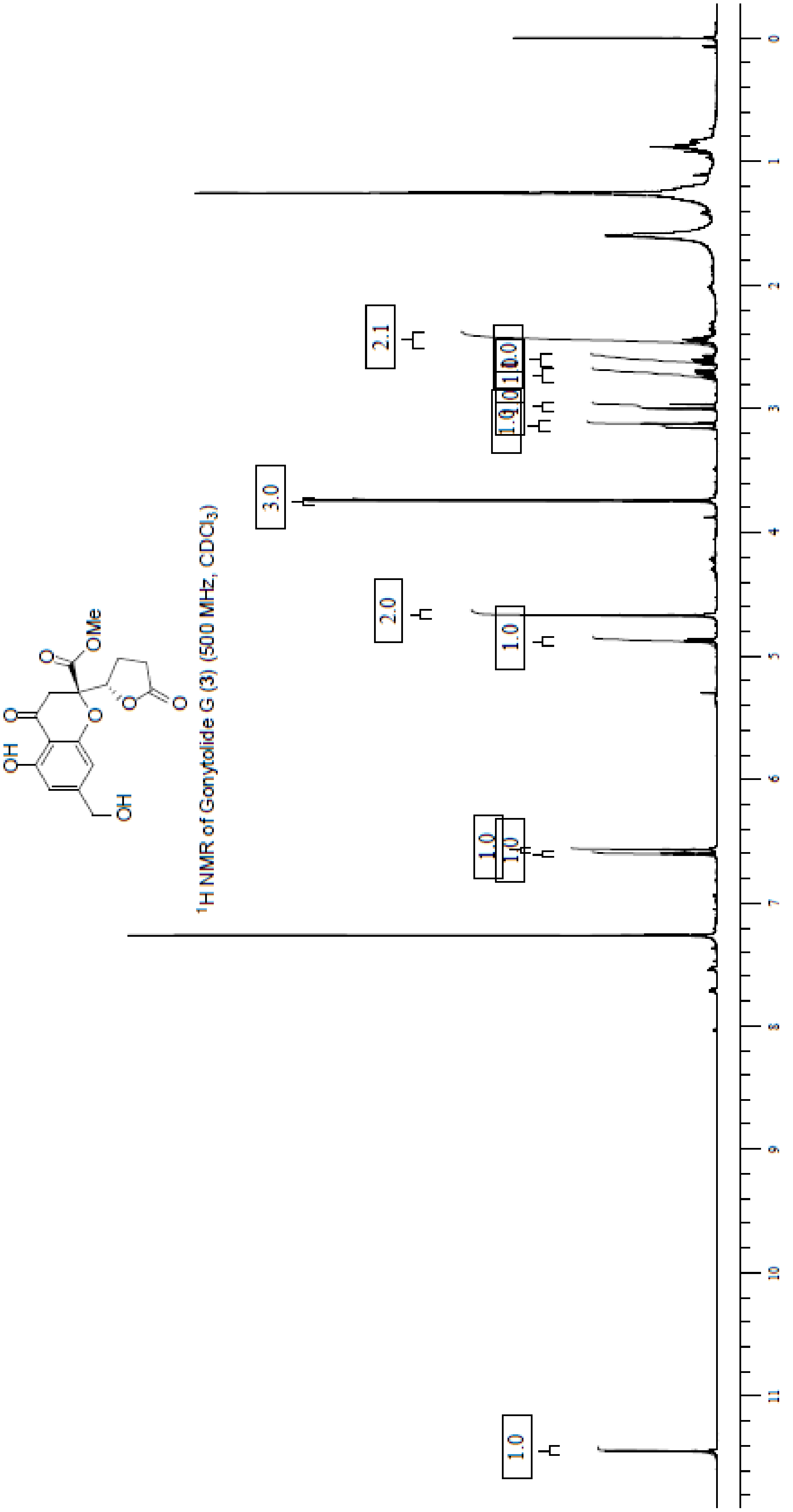
^{13}C NMR of **20** (125 MHz, $CDCl_3$)



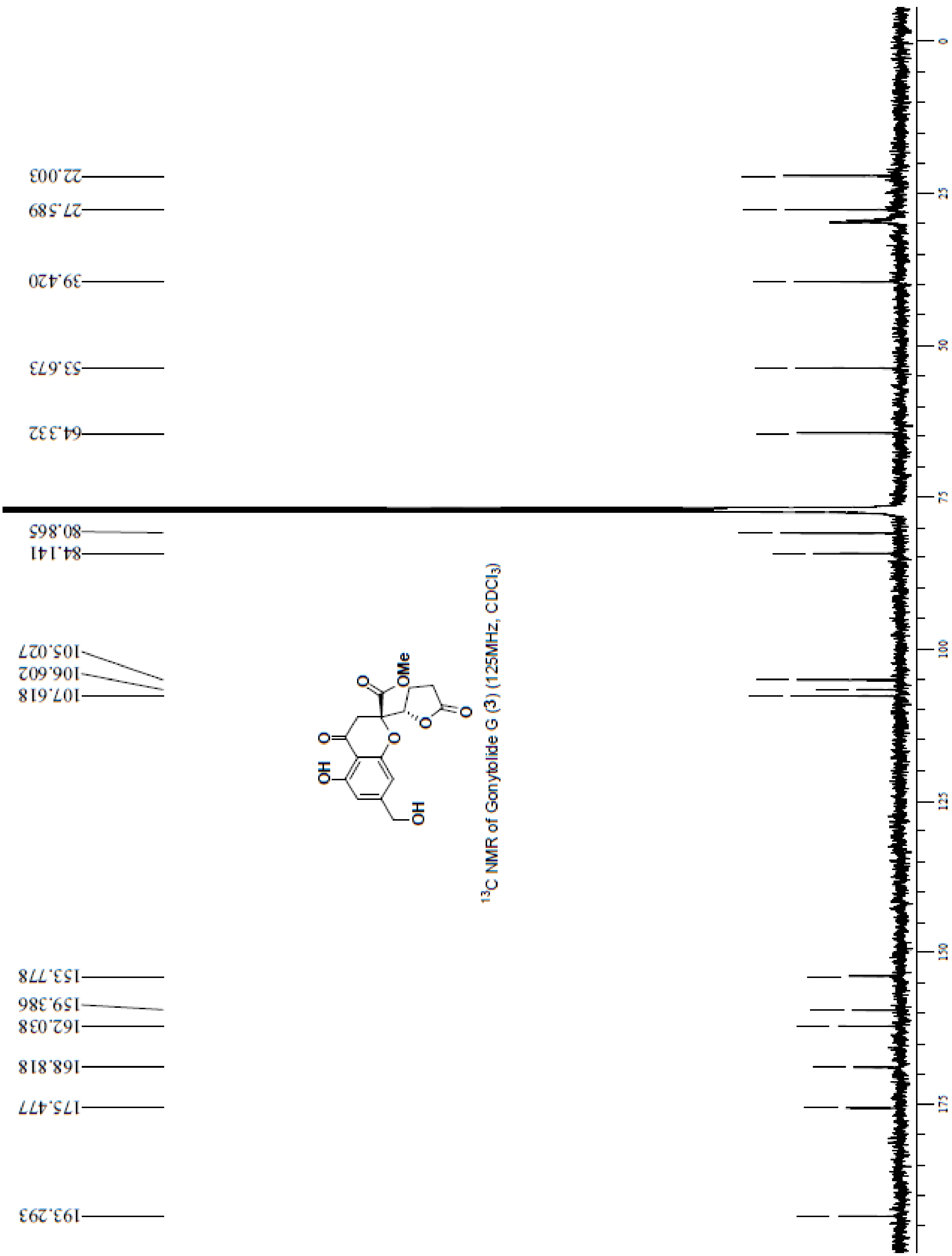
^{1}H NMR of **21** (500 MHz, CDCl$_3$)



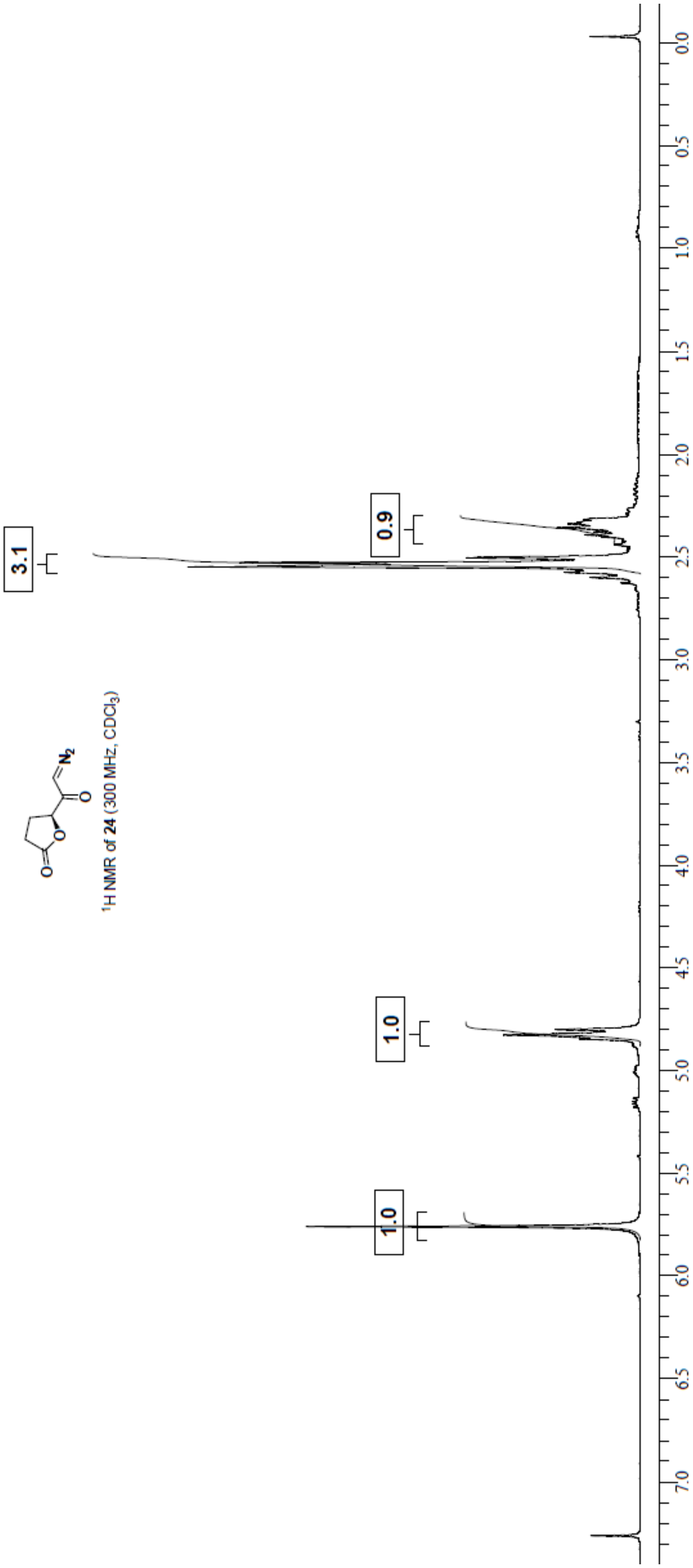
^{13}C NMR of **21** (125 MHz, $CDCl_3$)



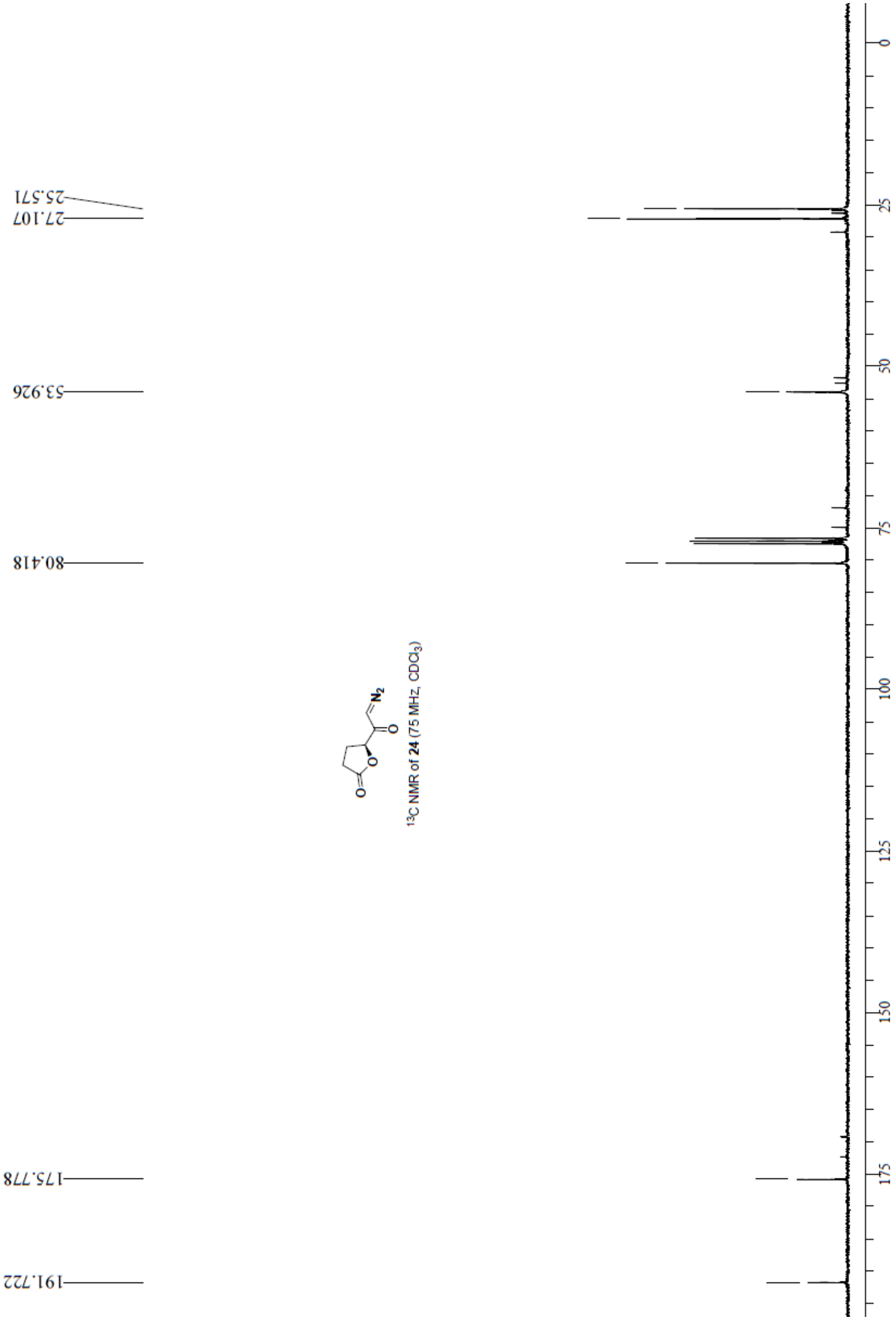
^{1}H NMR of Gonytolide G (3) (500 MHz, CDCl$_3$)



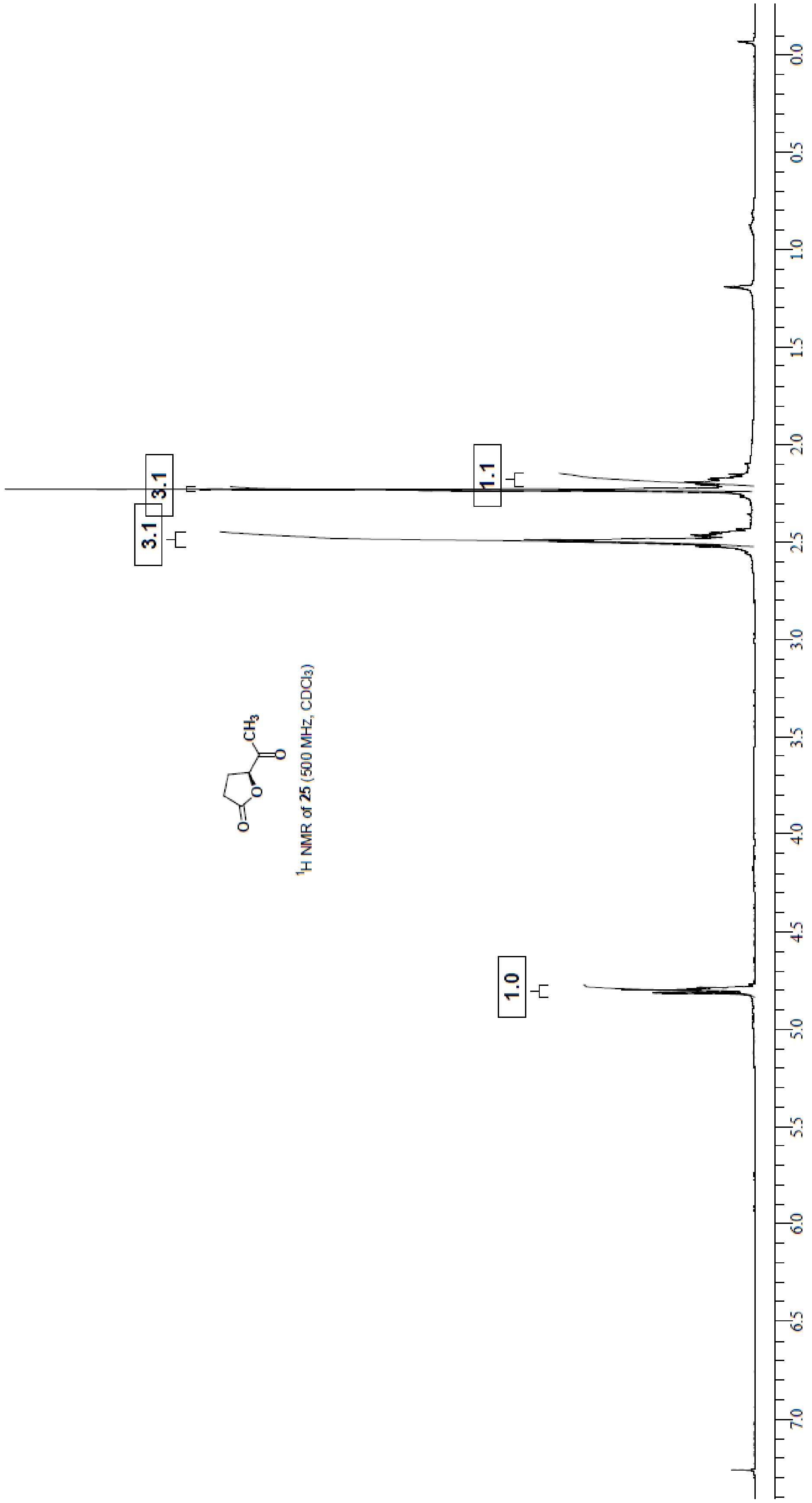
^{13}C NMR of Gonytolide G (3) (125MHz, CDCl$_3$)



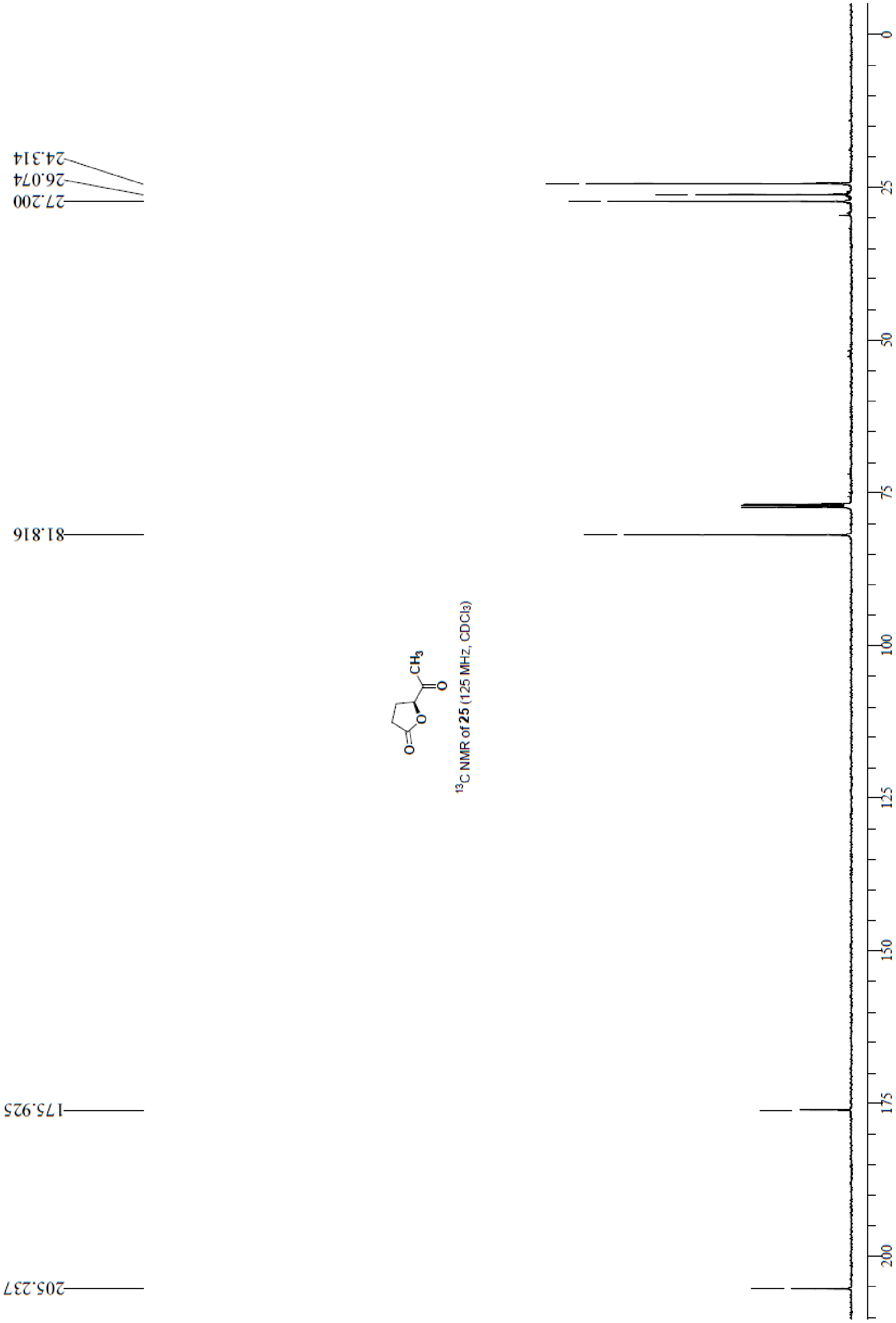
^{1}H NMR of **24** (300 MHz, $CDCl_3$)



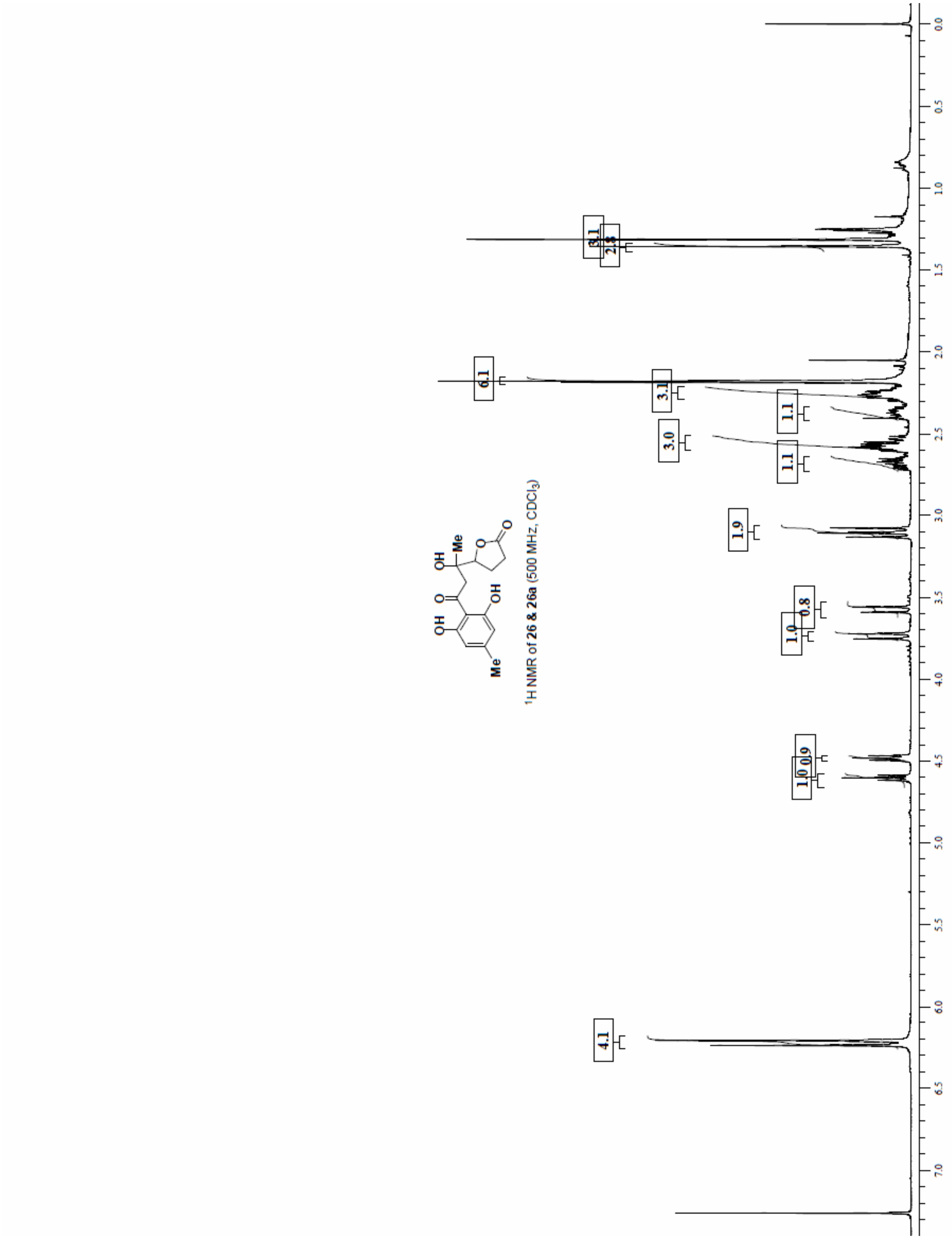
^{13}C NMR of **24** (75 MHz, CDCl$_3$)



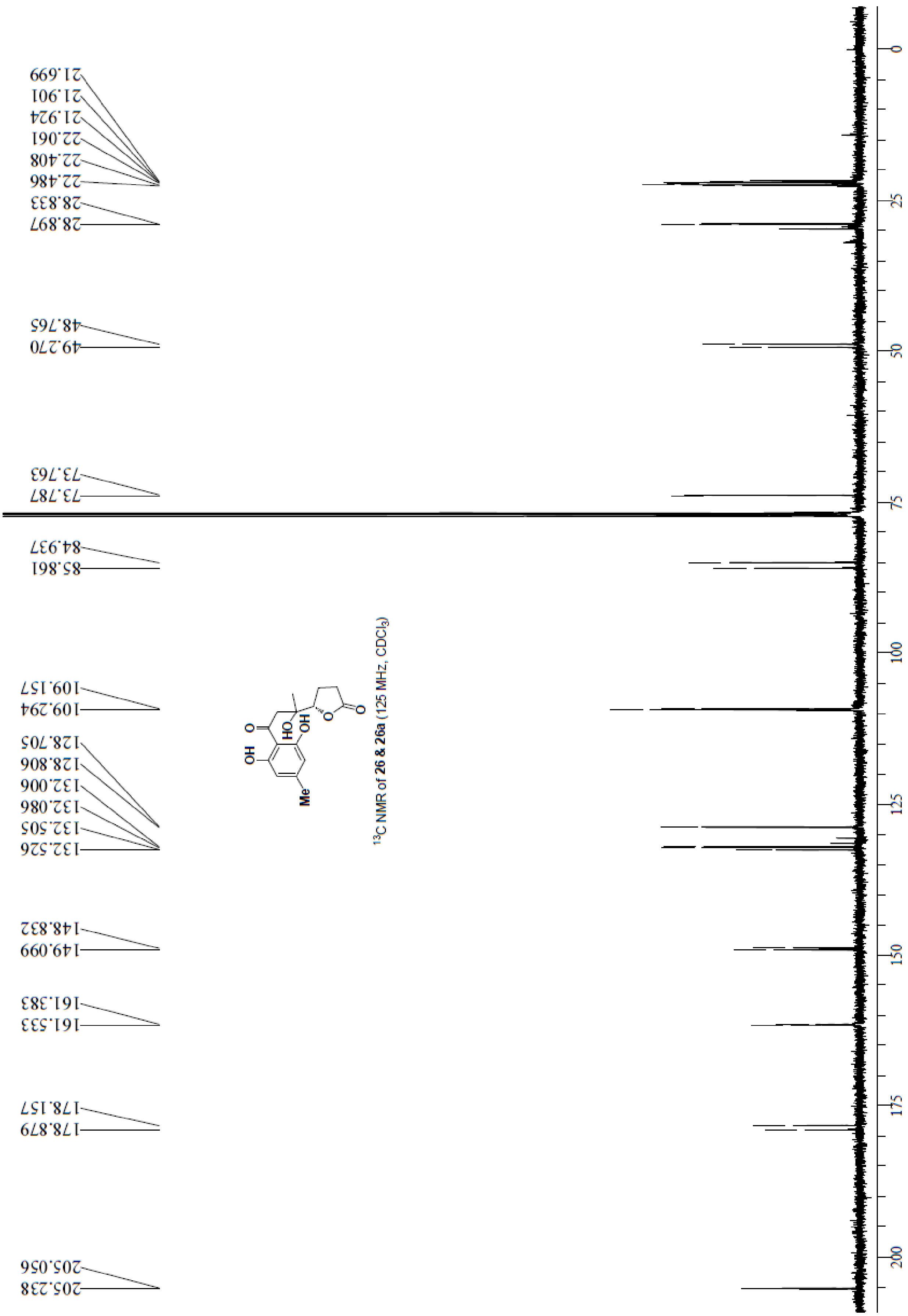
^{1}H NMR of **25** (500 MHz, CDCl$_3$)



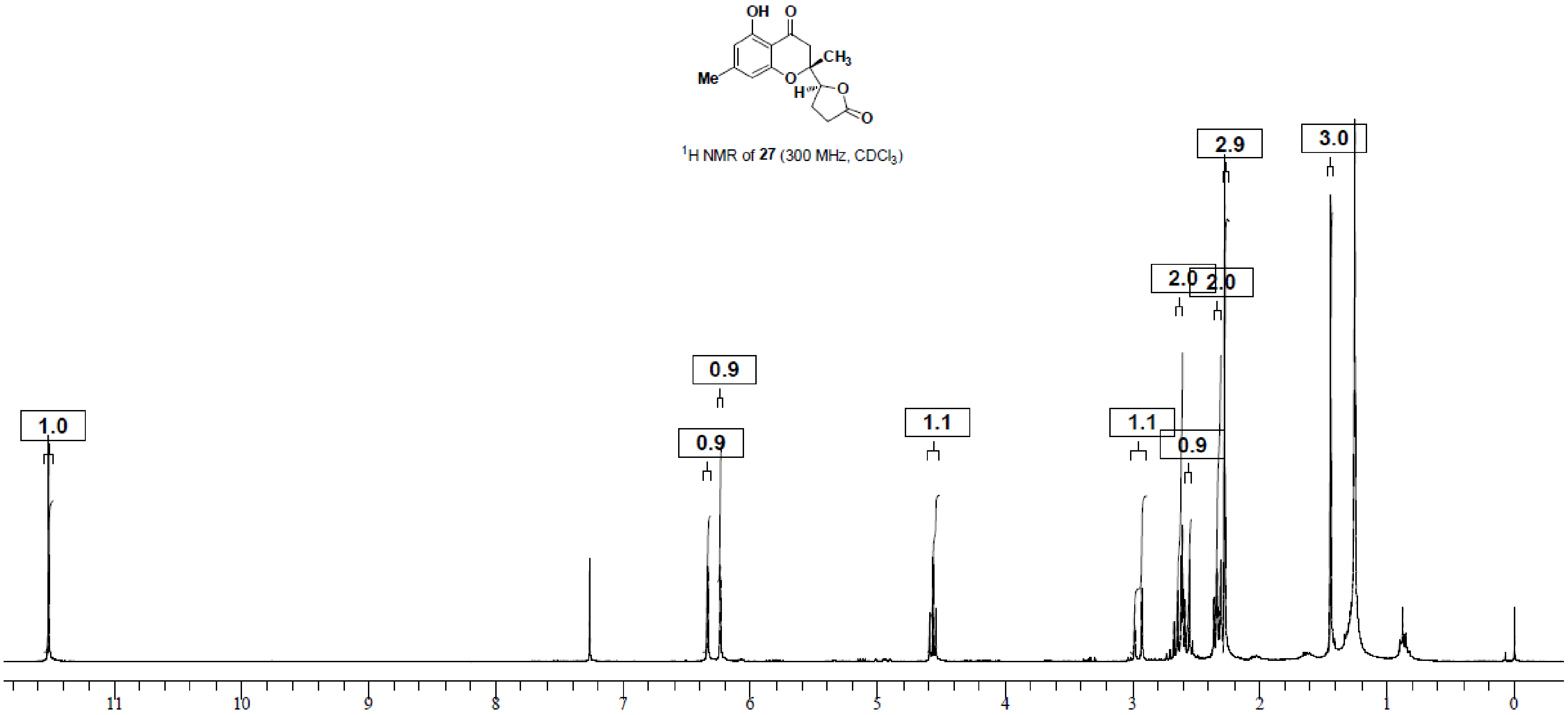
^{13}C NMR of **25** (125 MHz, $CDCl_3$)



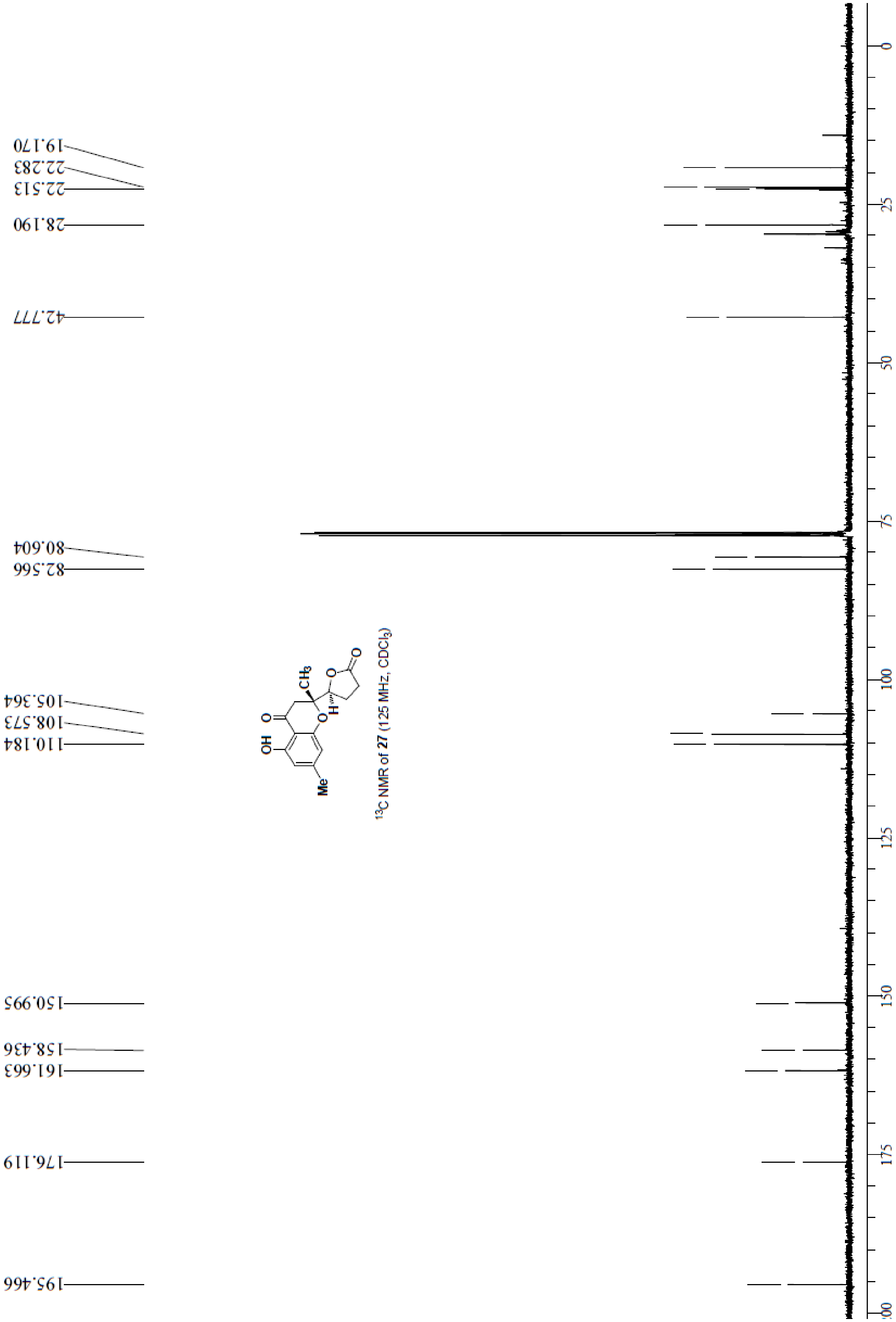
^{1}H NMR of **26 & 26a** (500 MHz, $CDCl_3$)



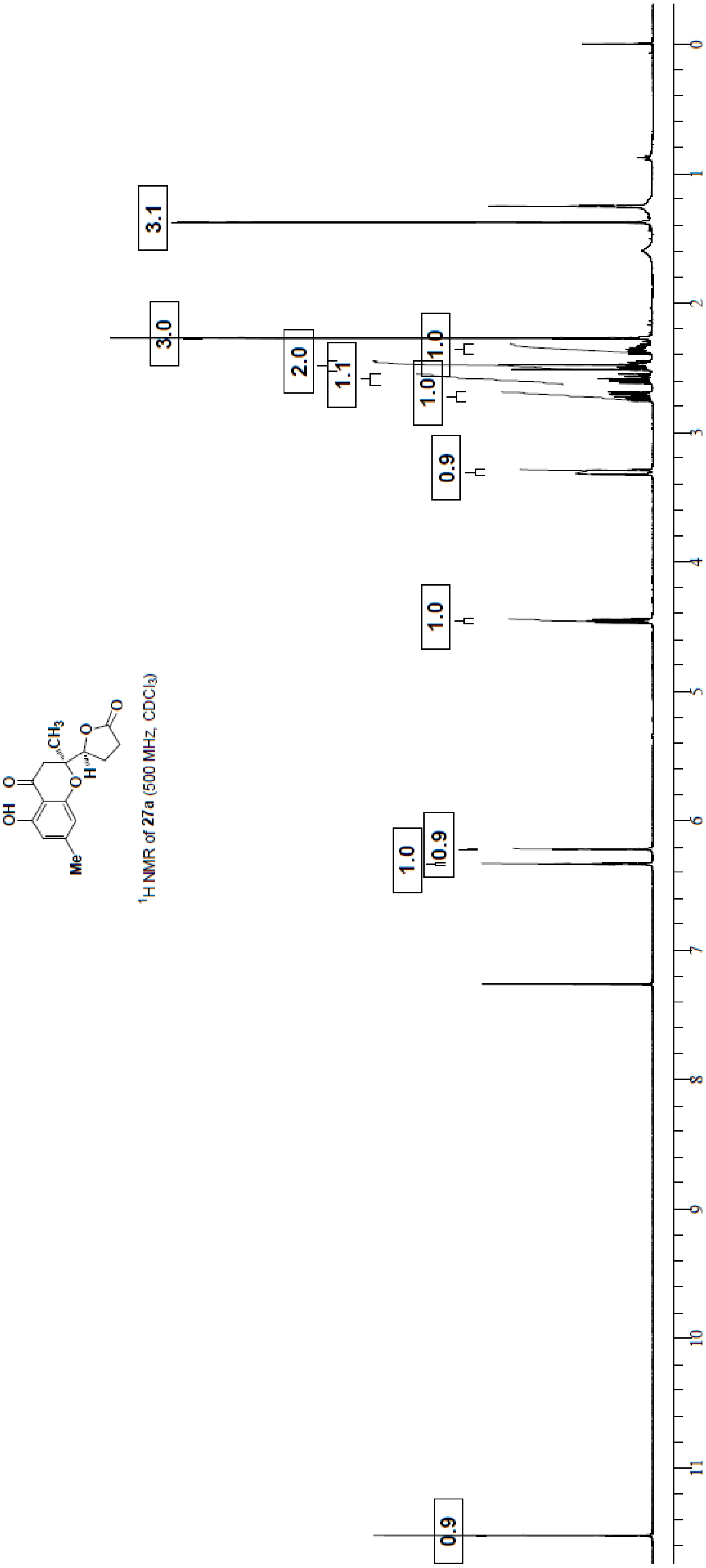
^{13}C NMR of **26 & 26a** (125 MHz, CDCl$_3$)



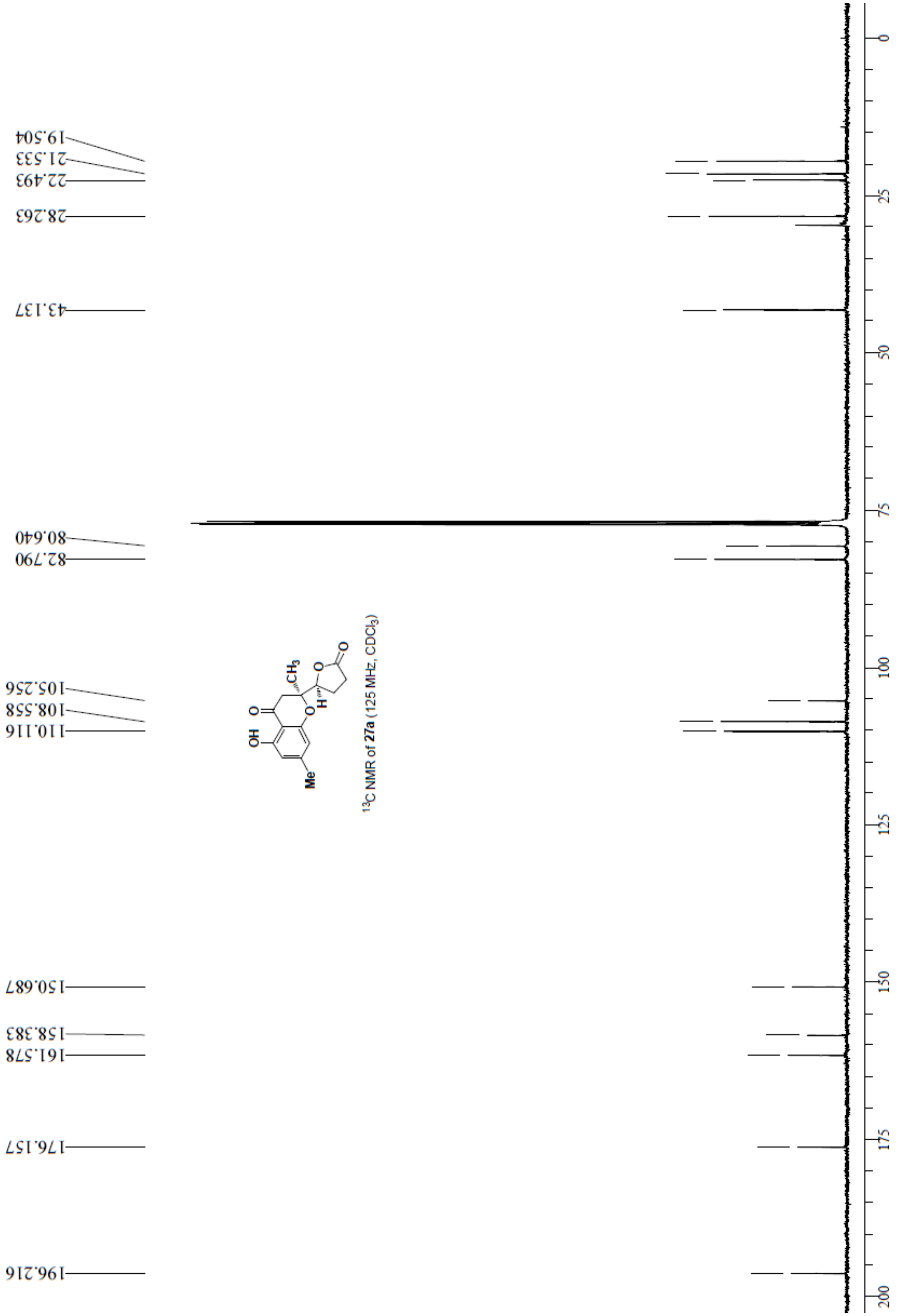
^{1}H NMR of **27** (300 MHz, CDCl$_3$)



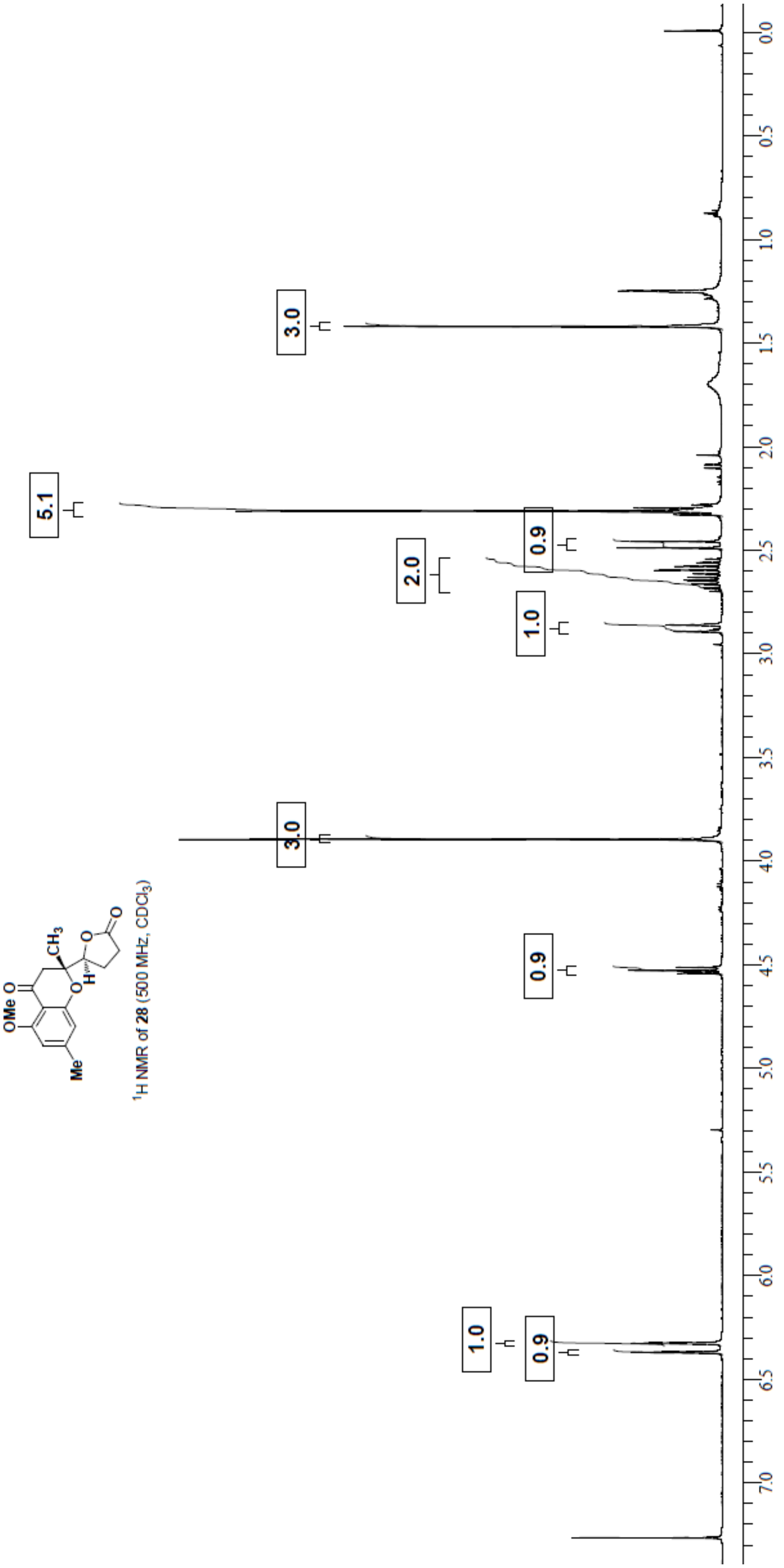
^{13}C NMR of **27** (125 MHz, $CDCl_3$)



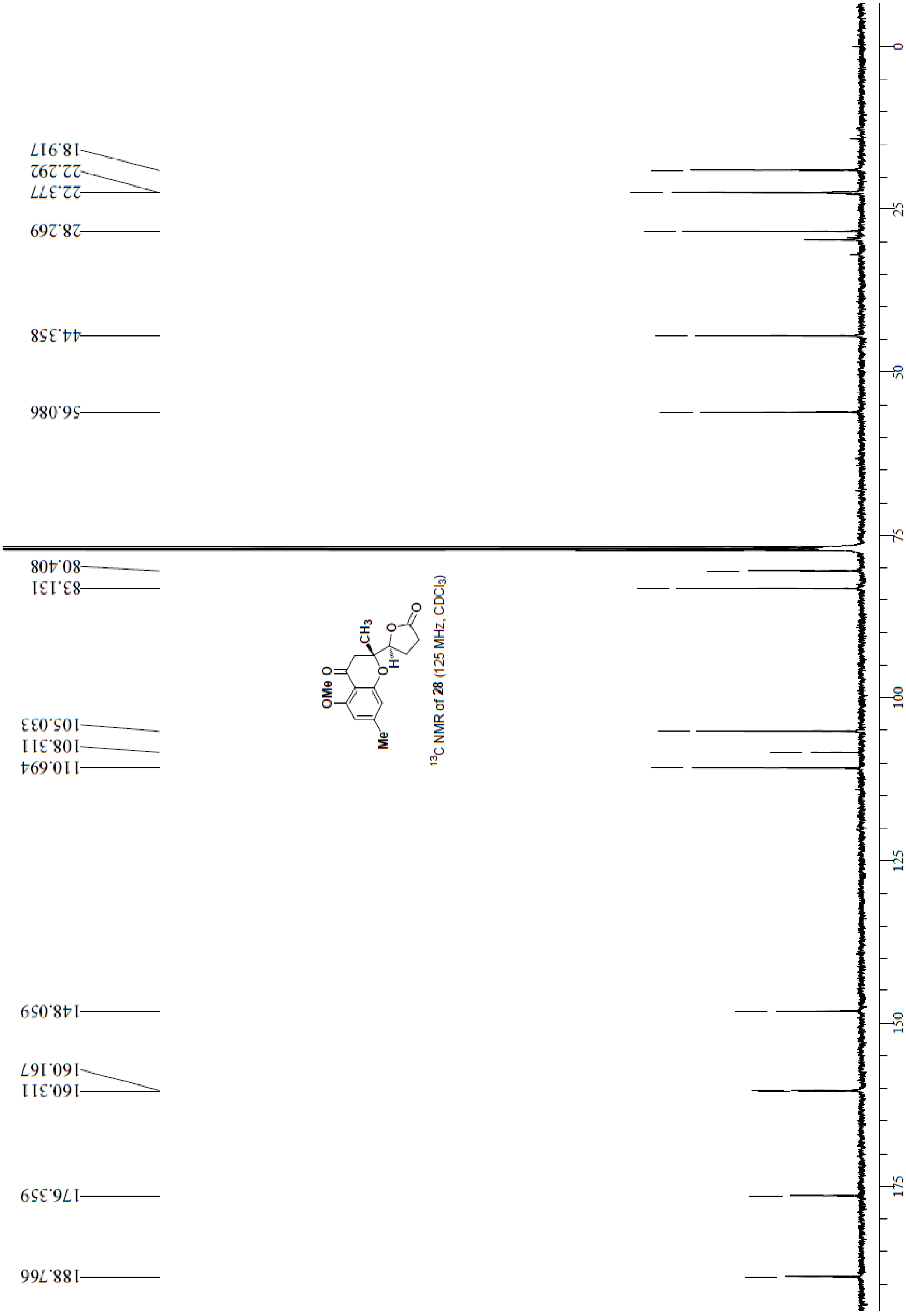
^{1}H NMR of **27a** (500 MHz, CDCl$_3$)



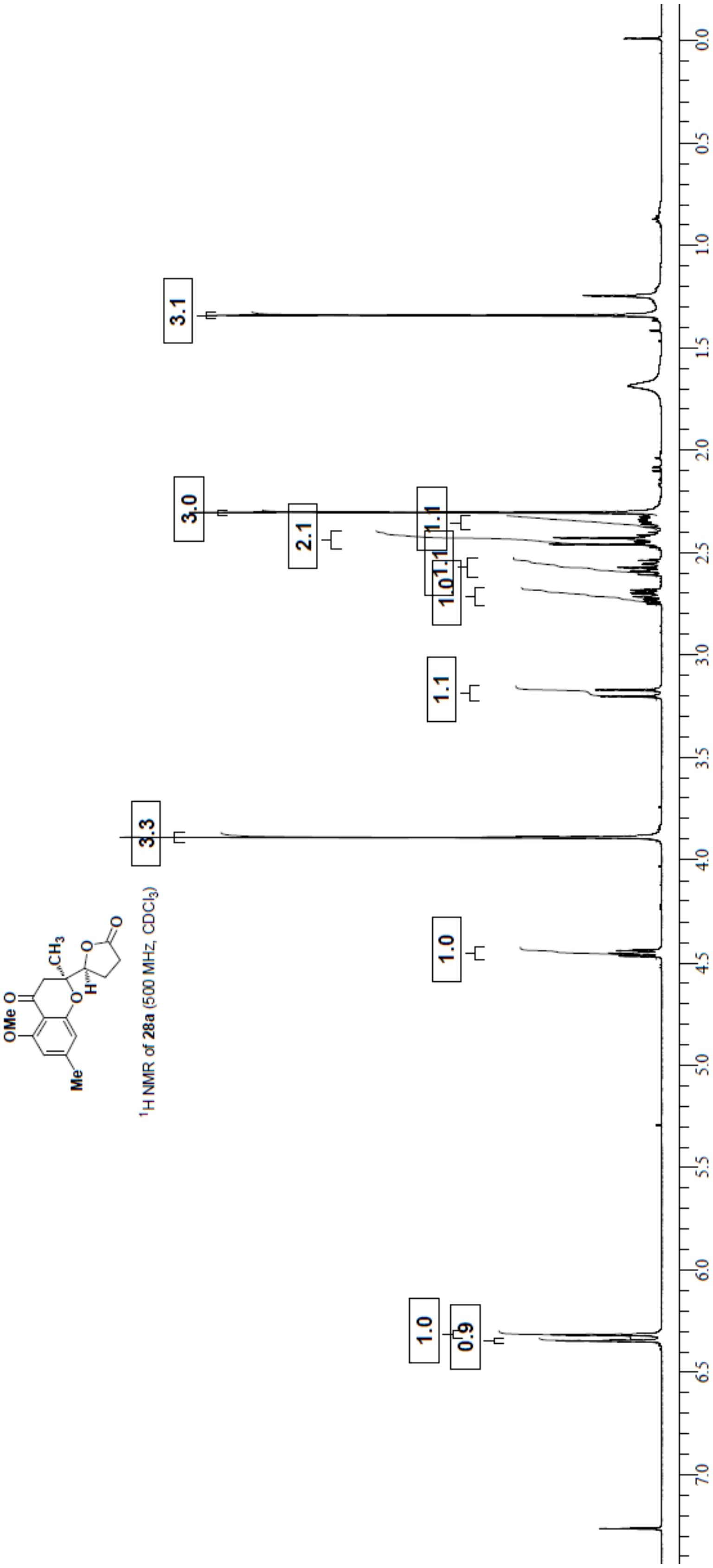
^{13}C NMR of **27a** (125 MHz, CDCl$_3$)



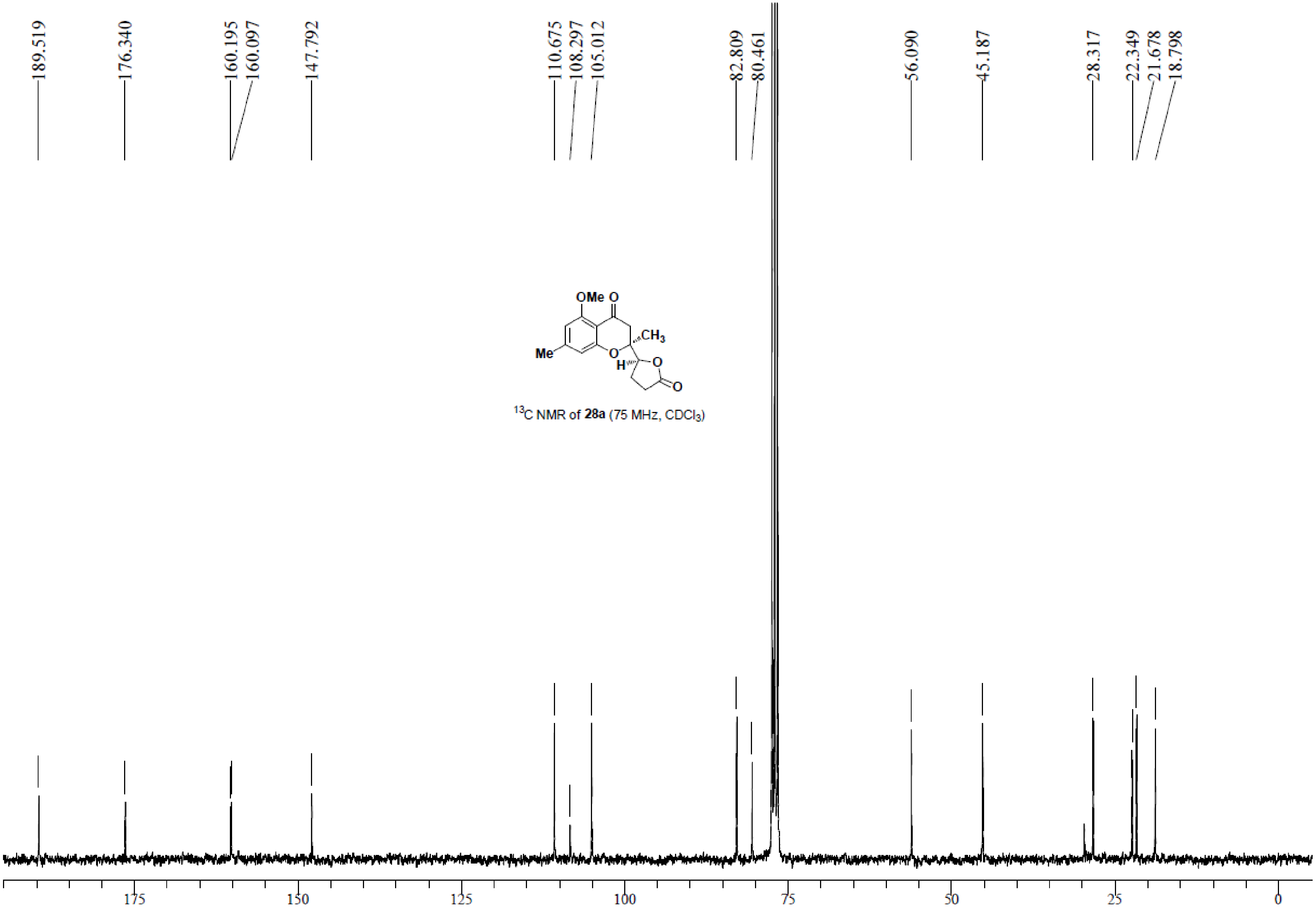
^{1}H NMR of **28** (500 MHz, CDCl$_3$)



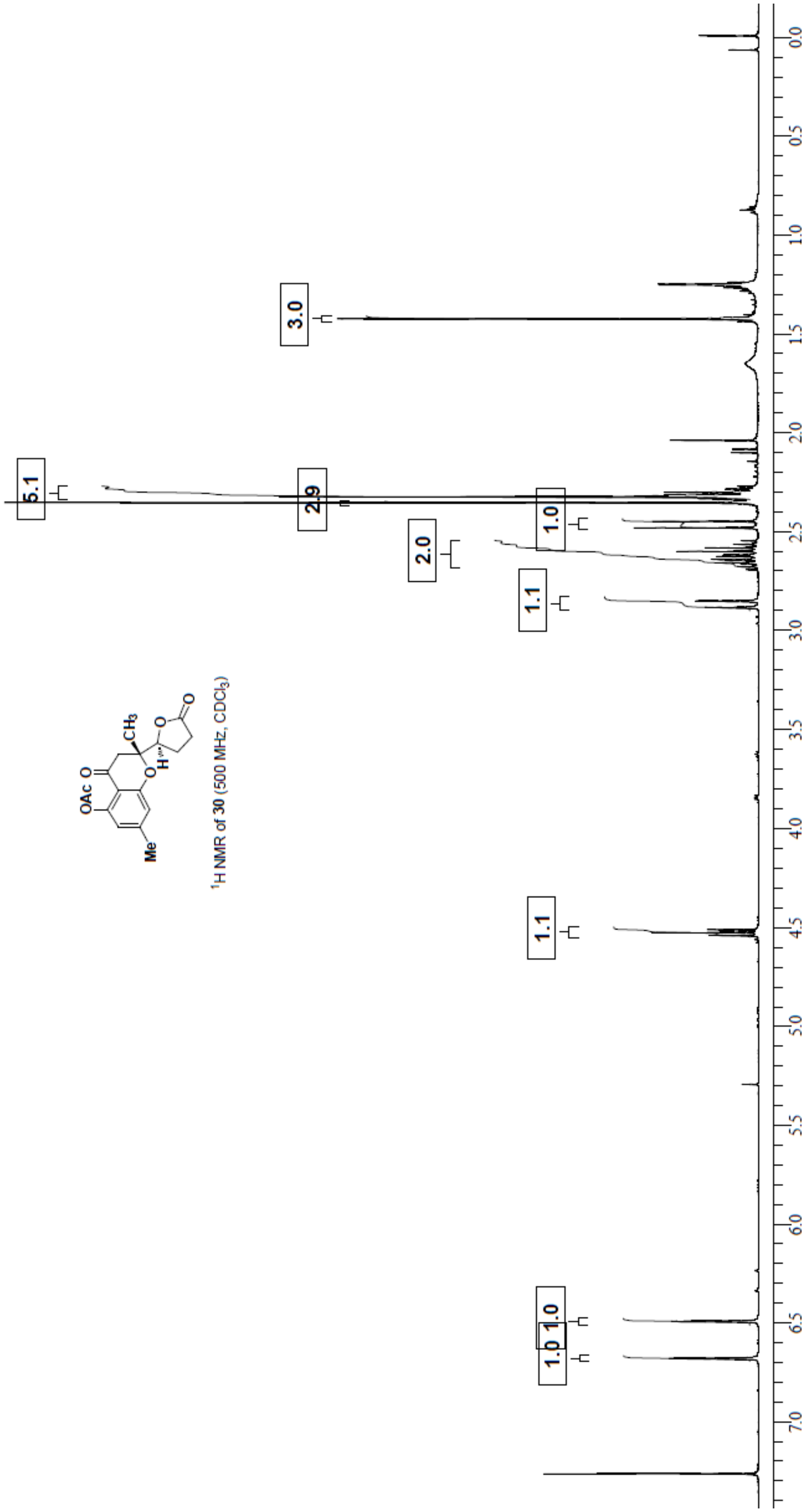
^{13}C NMR of **28** (125 MHz, CDCl$_3$)



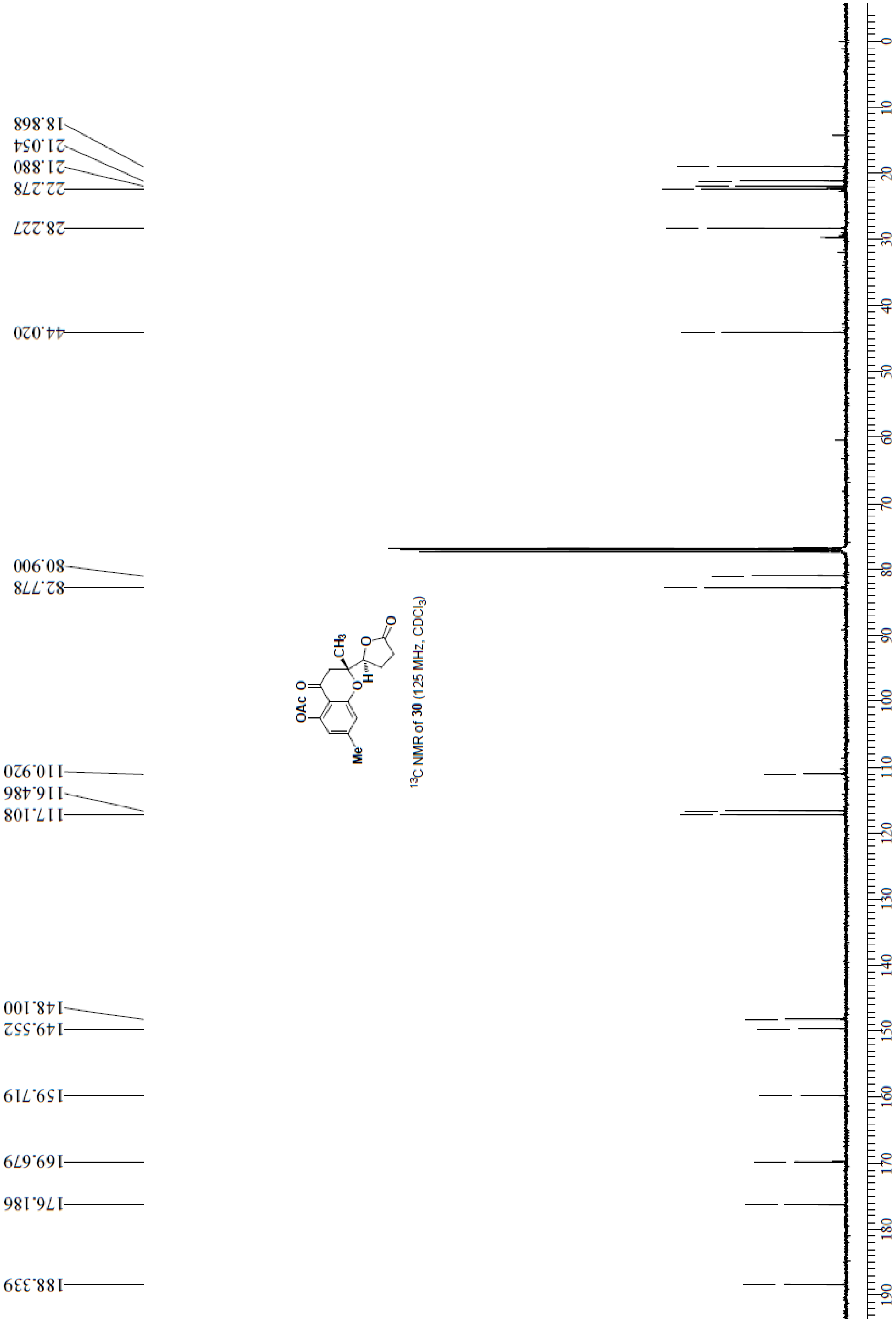
^{1}H NMR of **28a** (500 MHz, CDCl$_3$)



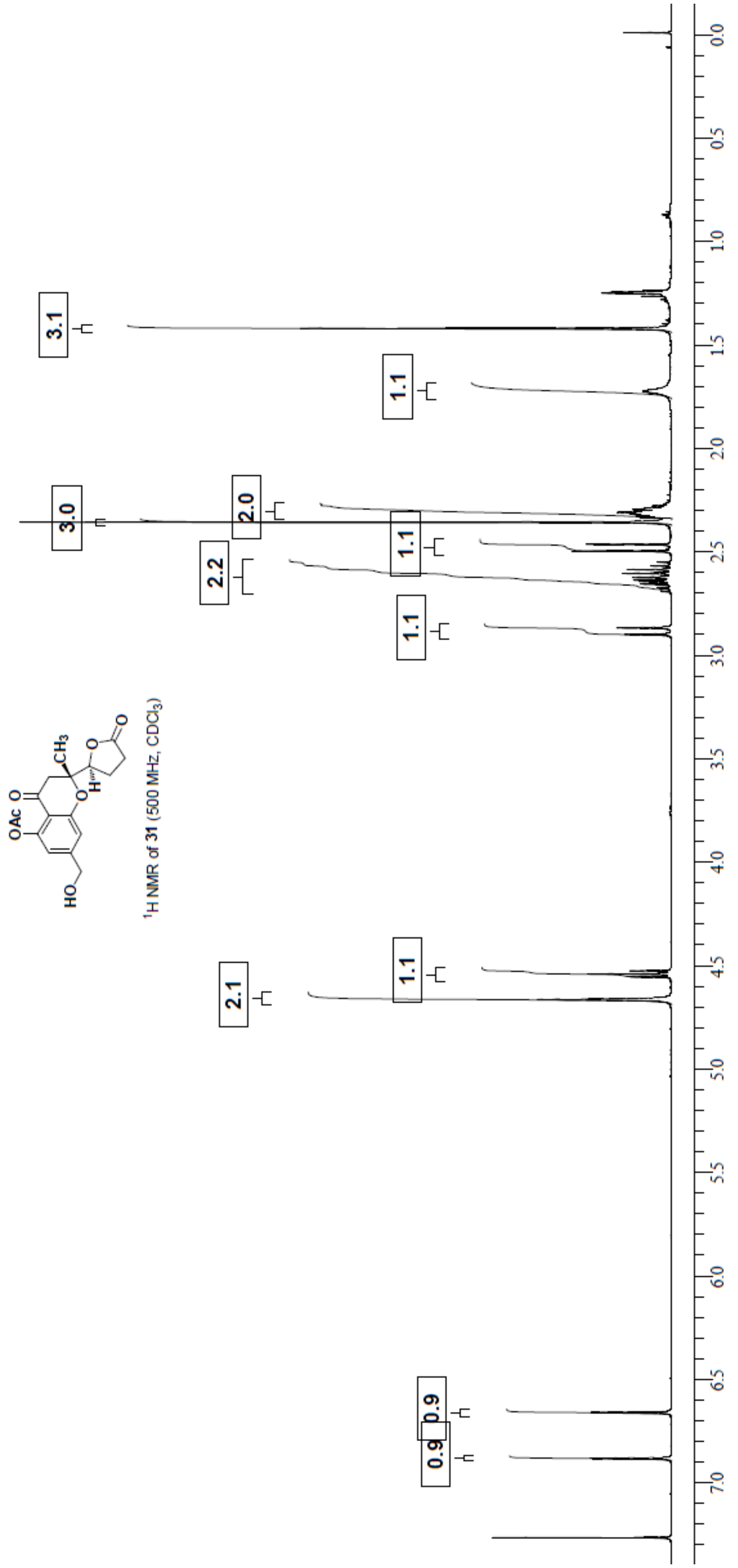
^{13}C NMR of **28a** (75 MHz, CDCl$_3$)



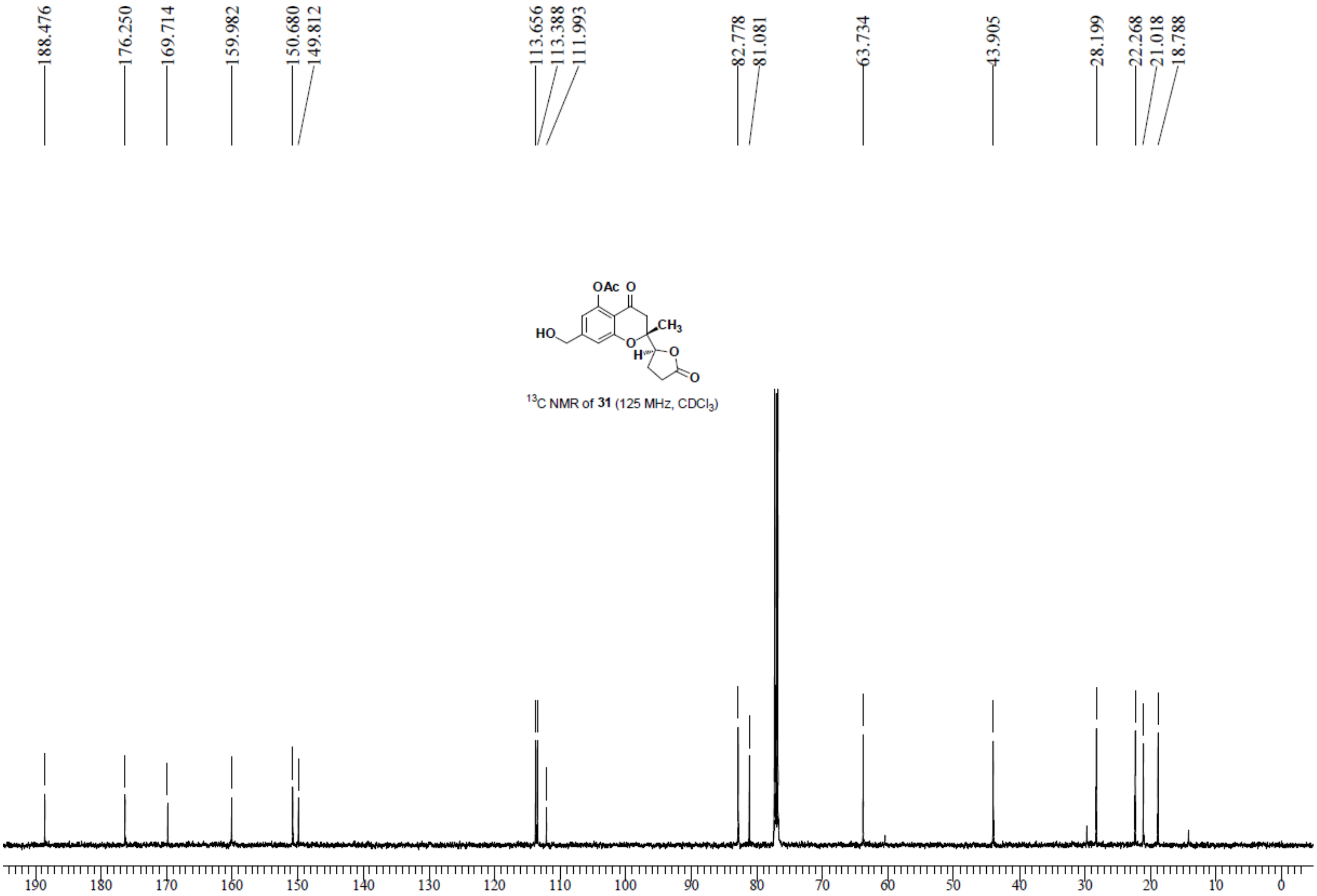
^{1}H NMR of **30** (500 MHz, CDCl$_3$)



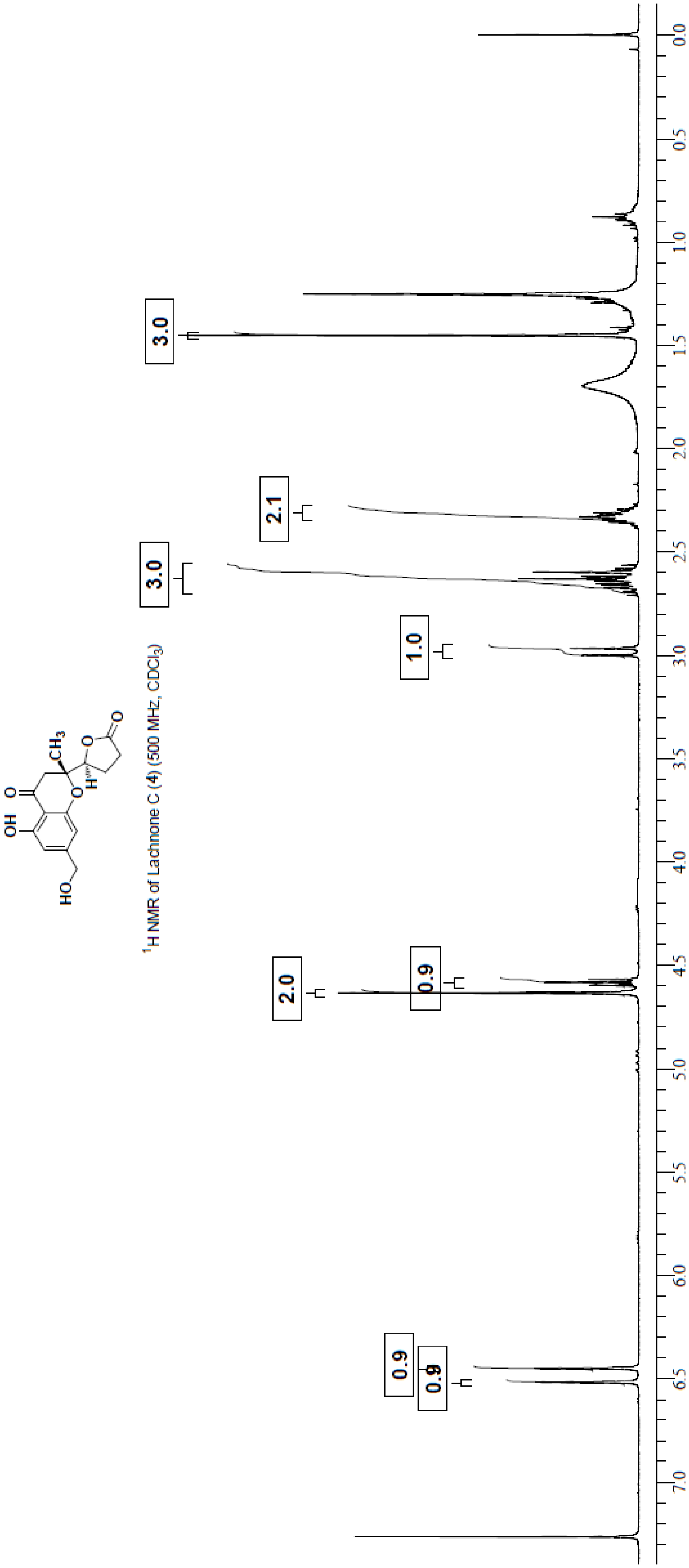
^{13}C NMR of **30** (125 MHz, CDCl$_3$)



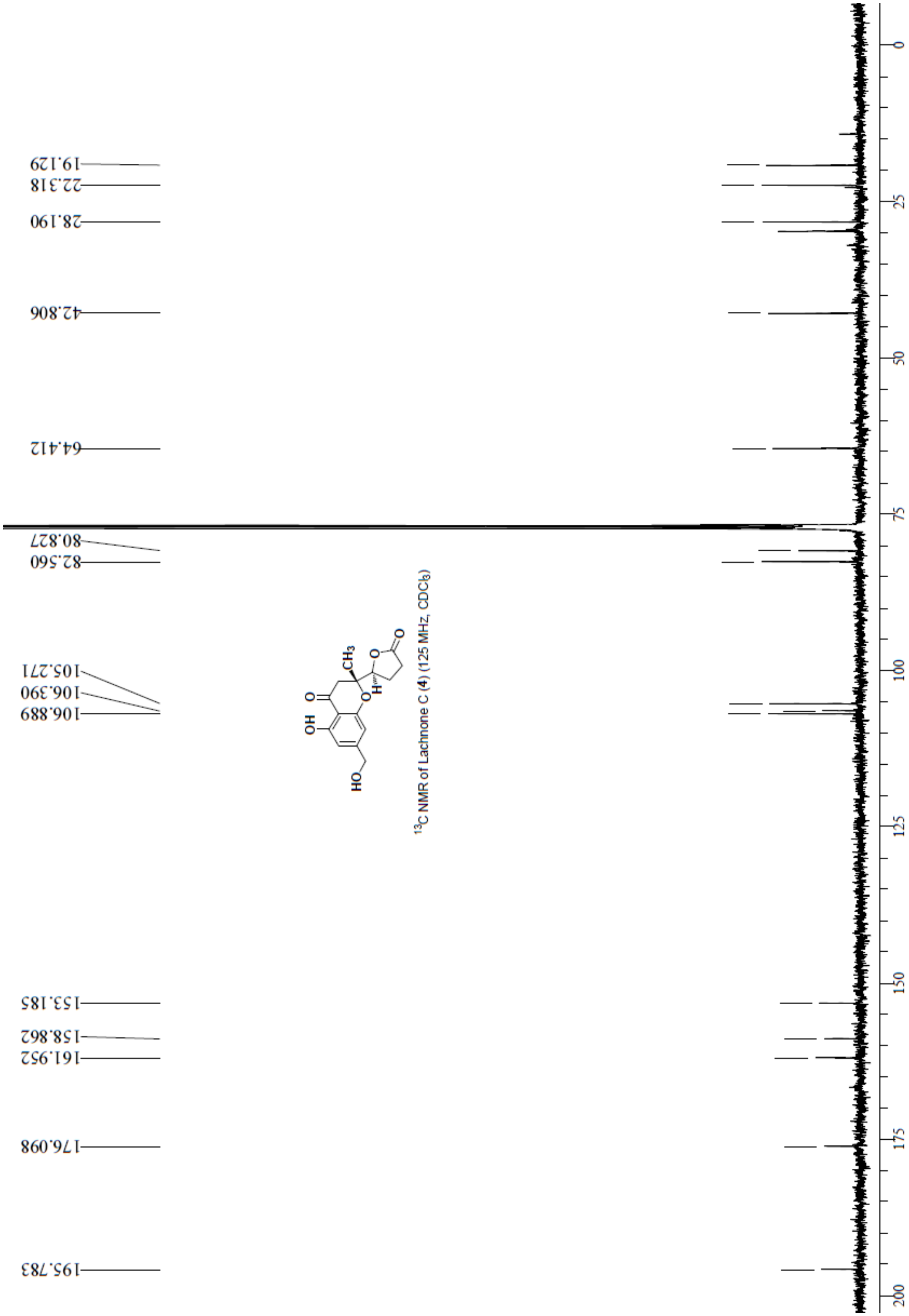
^{1}H NMR of **31** (500 MHz, $CDCl_3$)



^{13}C NMR of **31** (125 MHz, $CDCl_3$)



^{1}H NMR of Lachnone C (4) (500 MHz, CDCl$_3$)



^{13}C NMR of Lachnone C (**4**) (125 MHz, $CDCl_3$)