

Electronic Supporting Information

Expanding the Chemical Space of Withaferin A by Incorporating Silicon to Improve its Clinical Potential on Human Ovarian Carcinoma Cells

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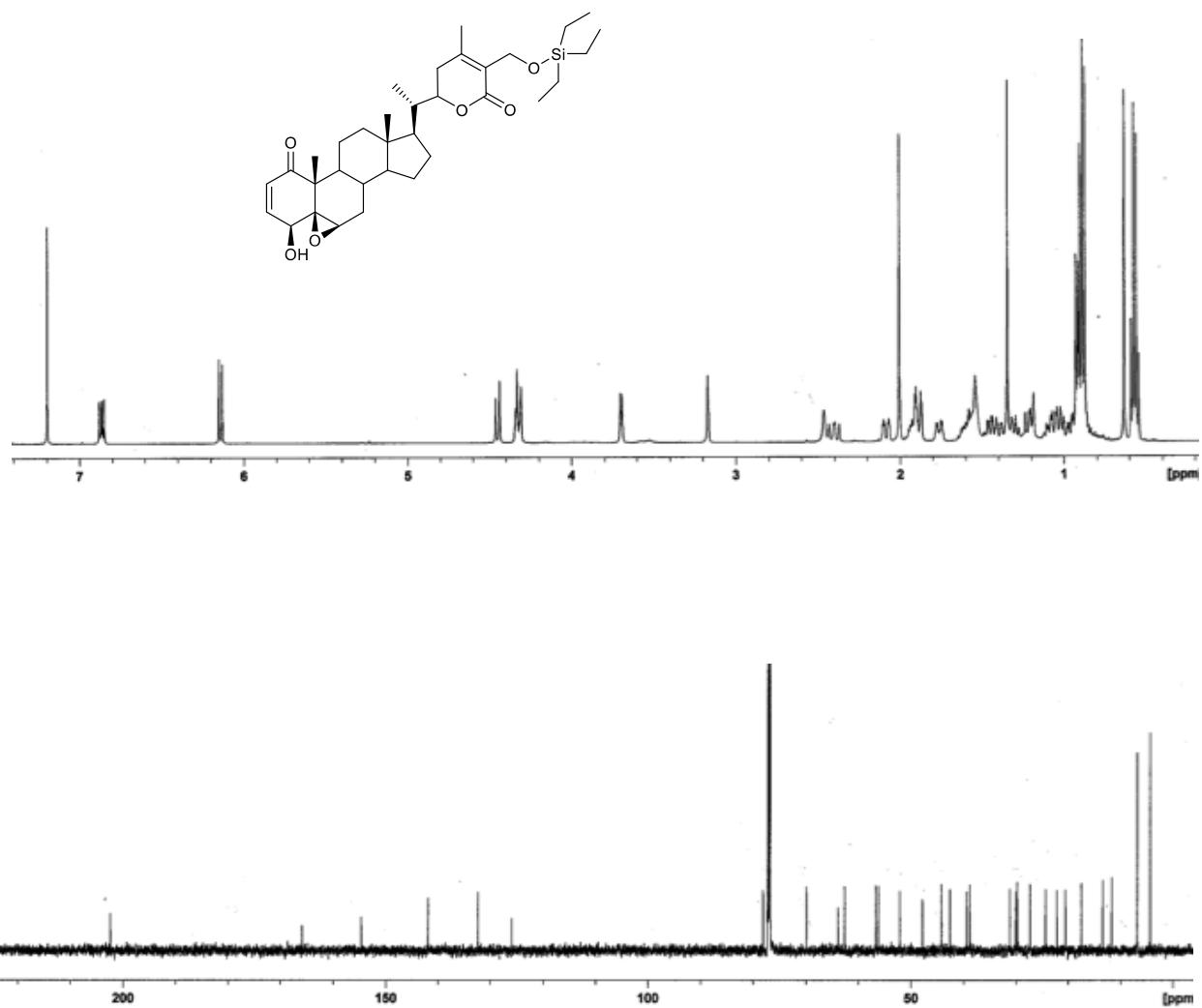
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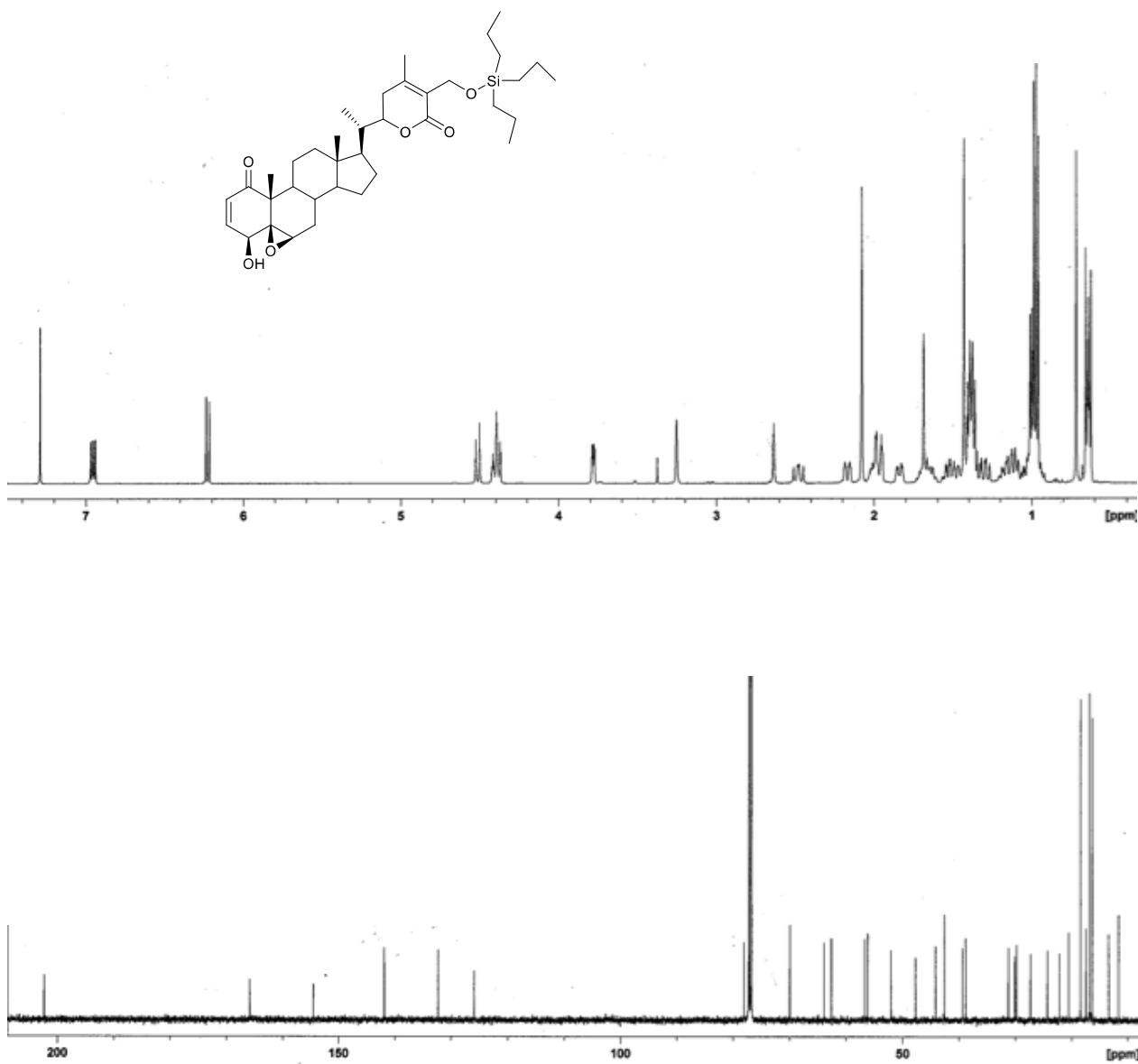
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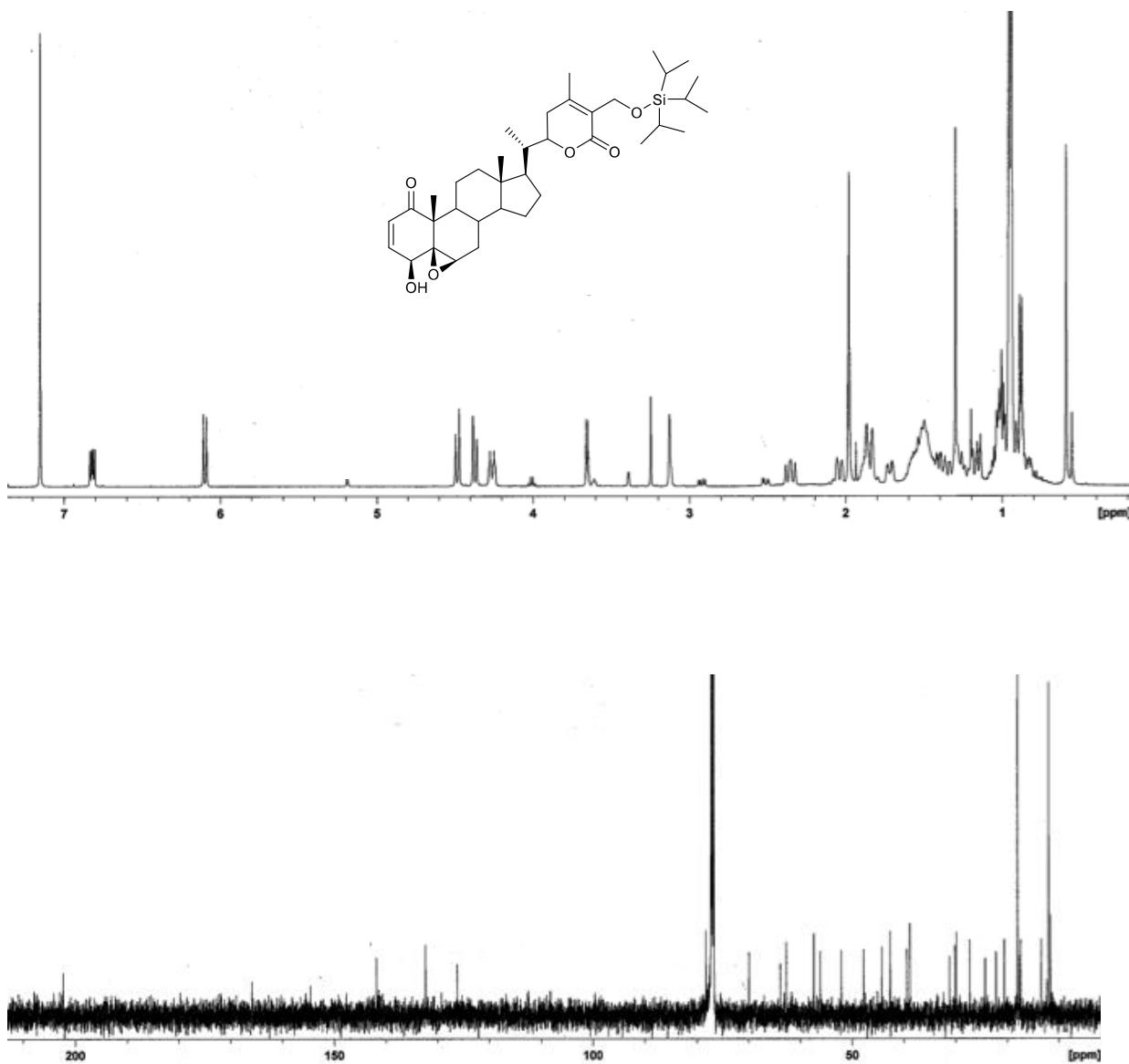
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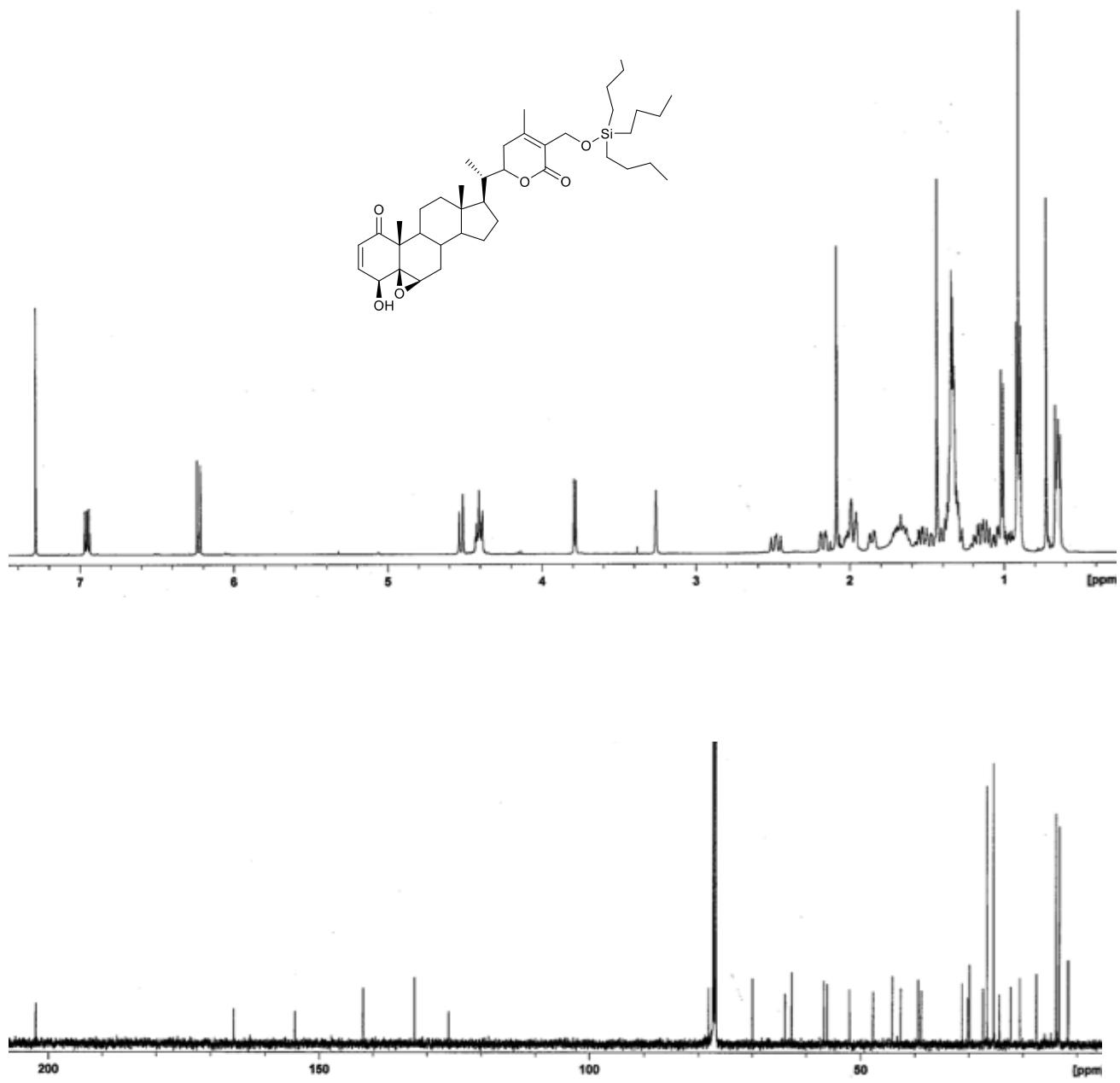
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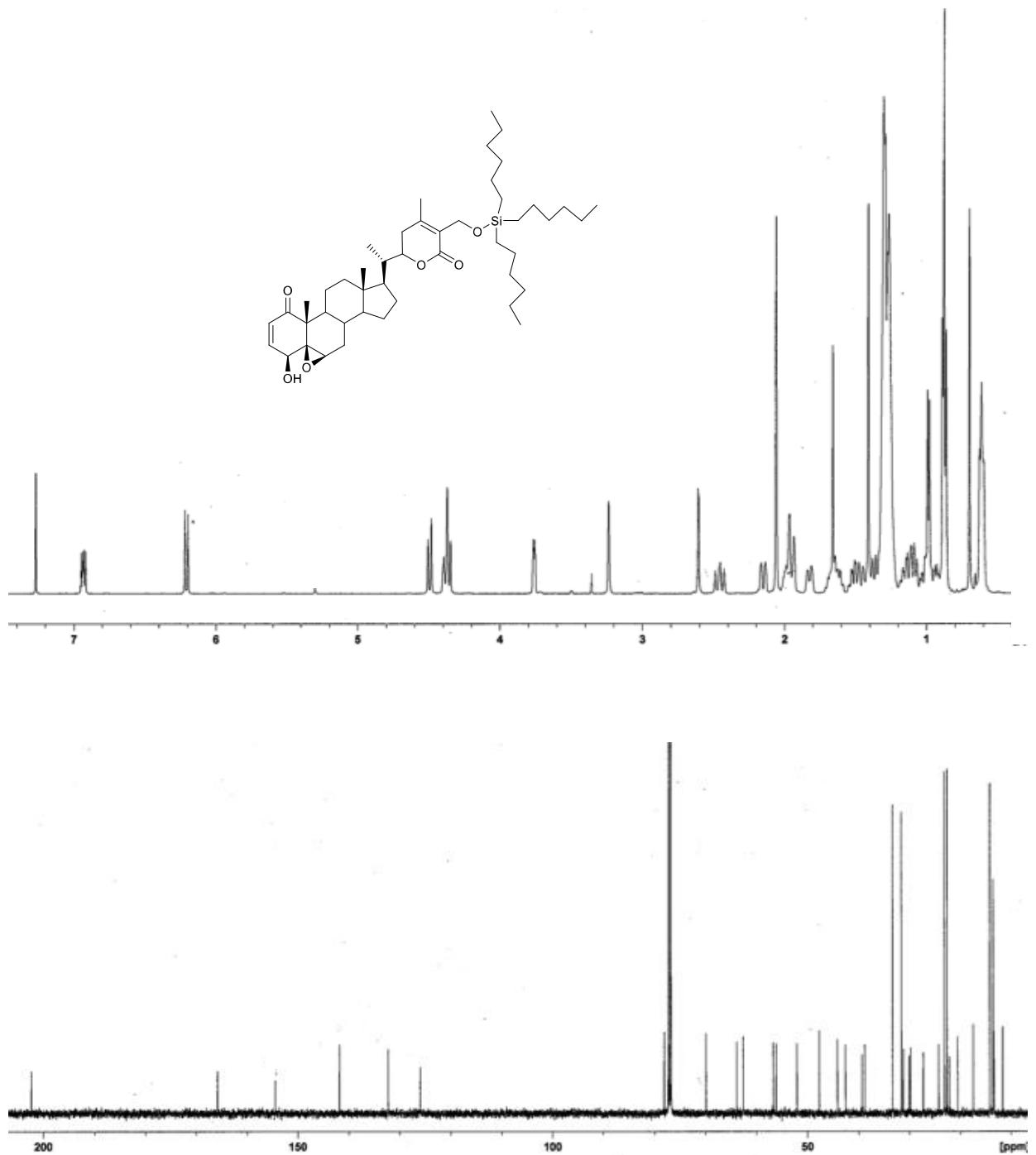
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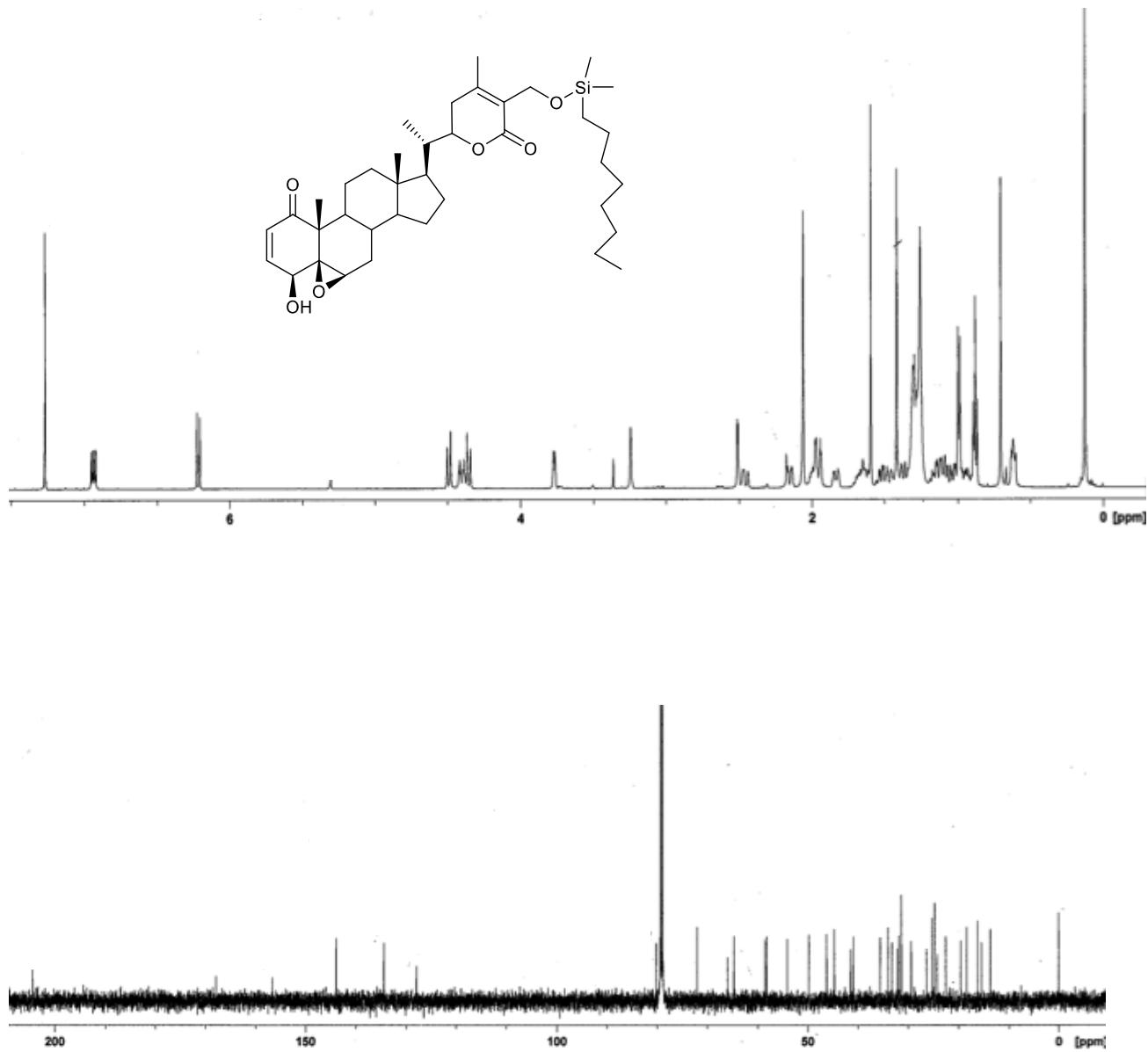
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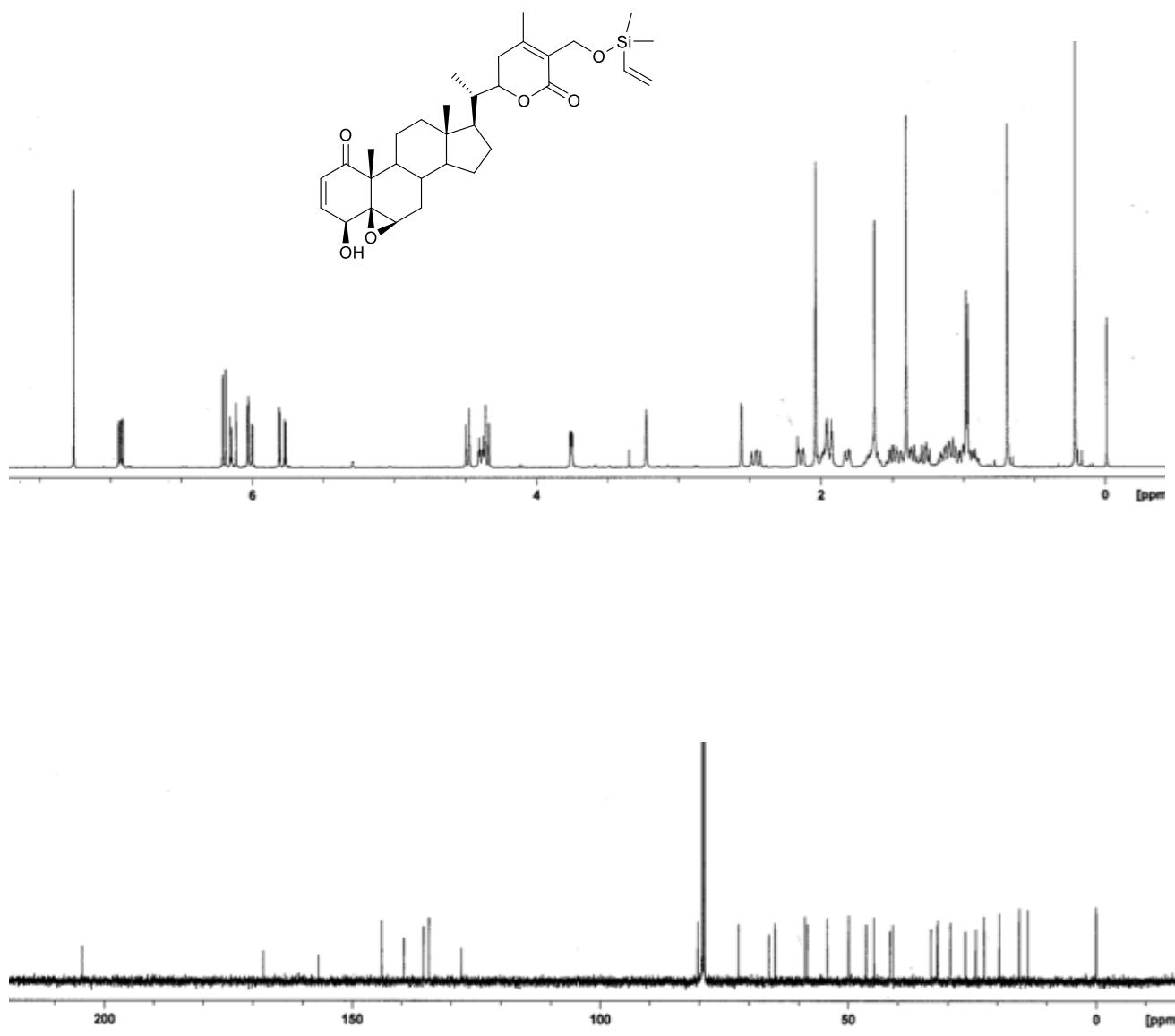
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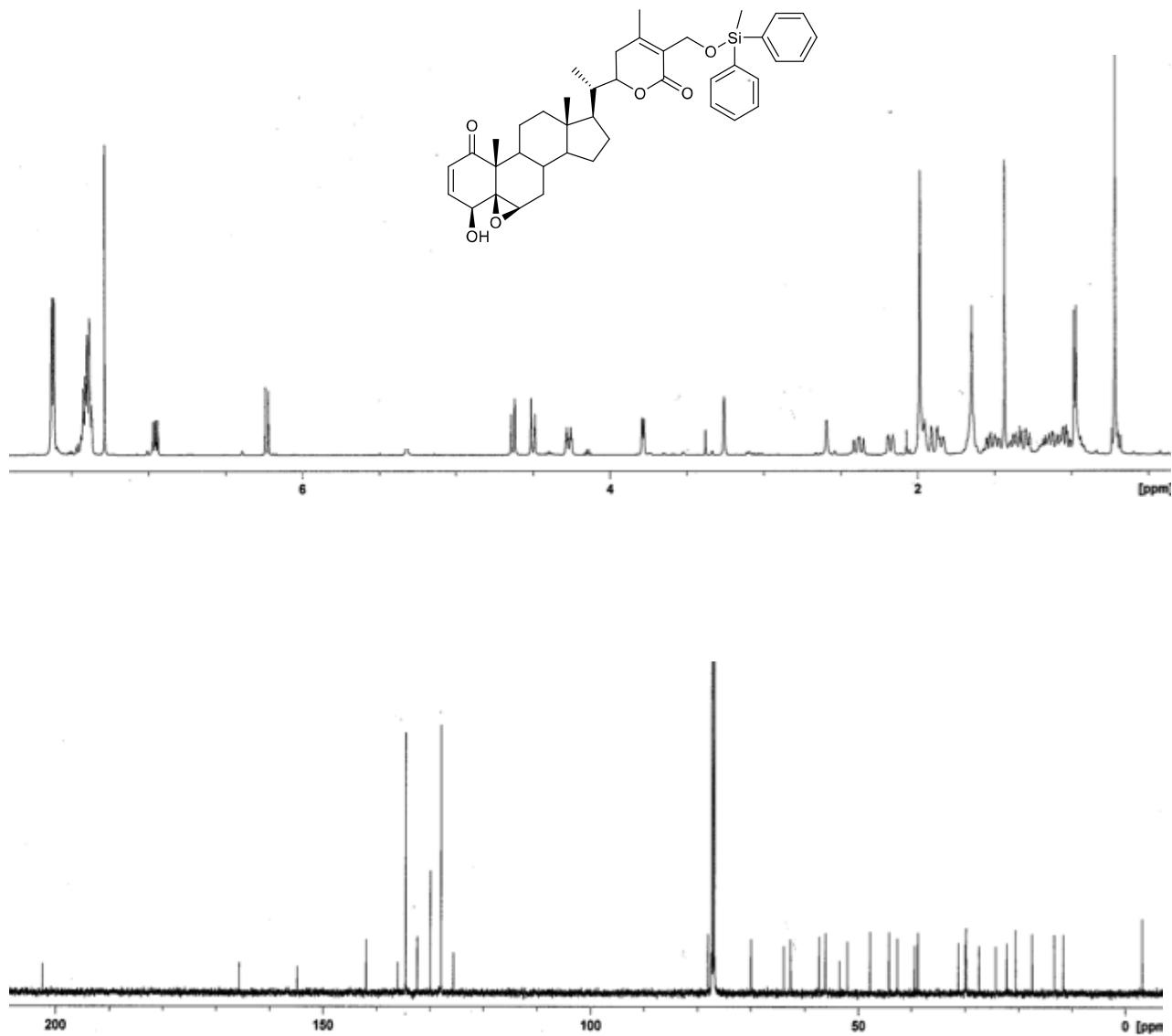
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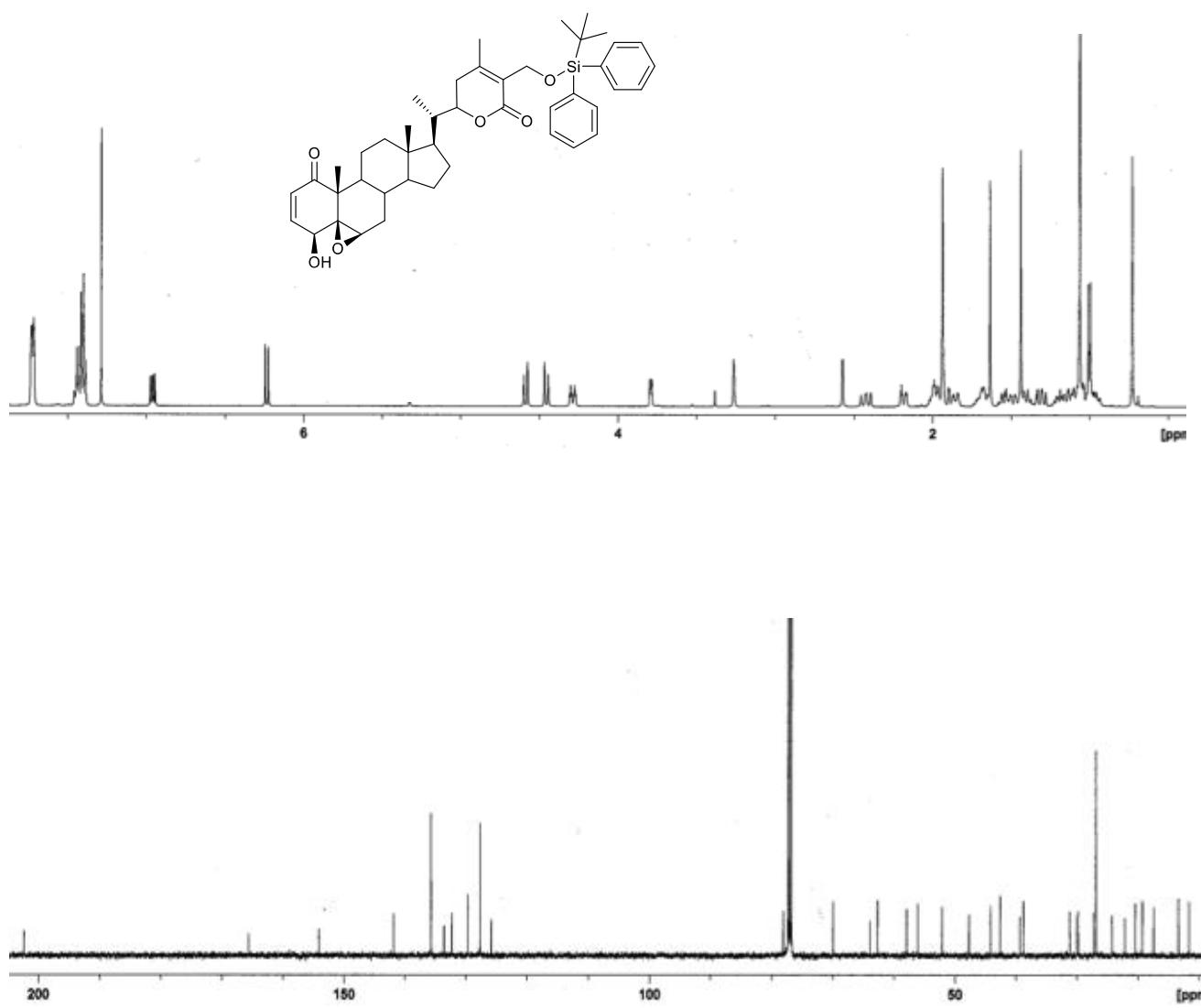
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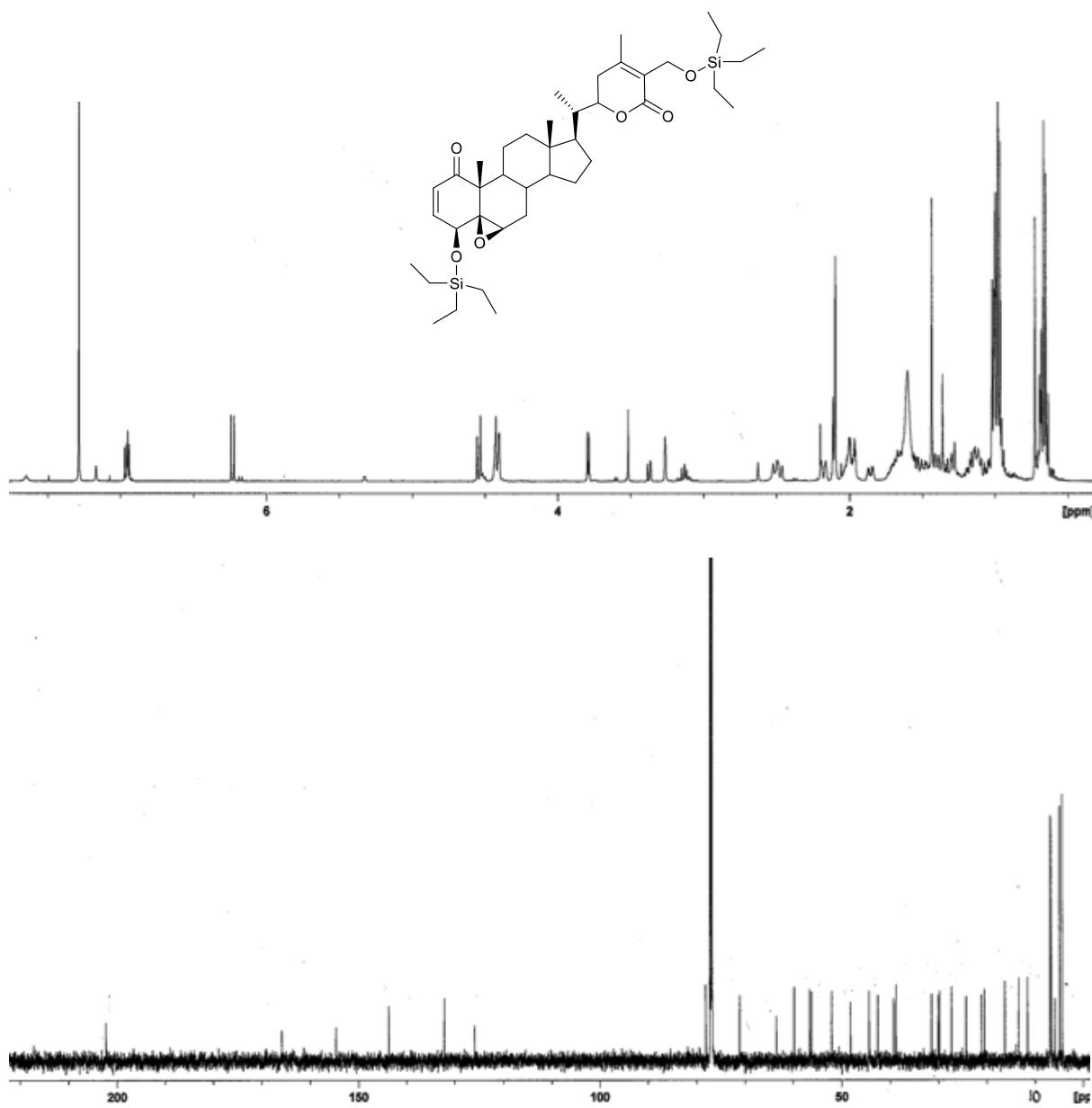
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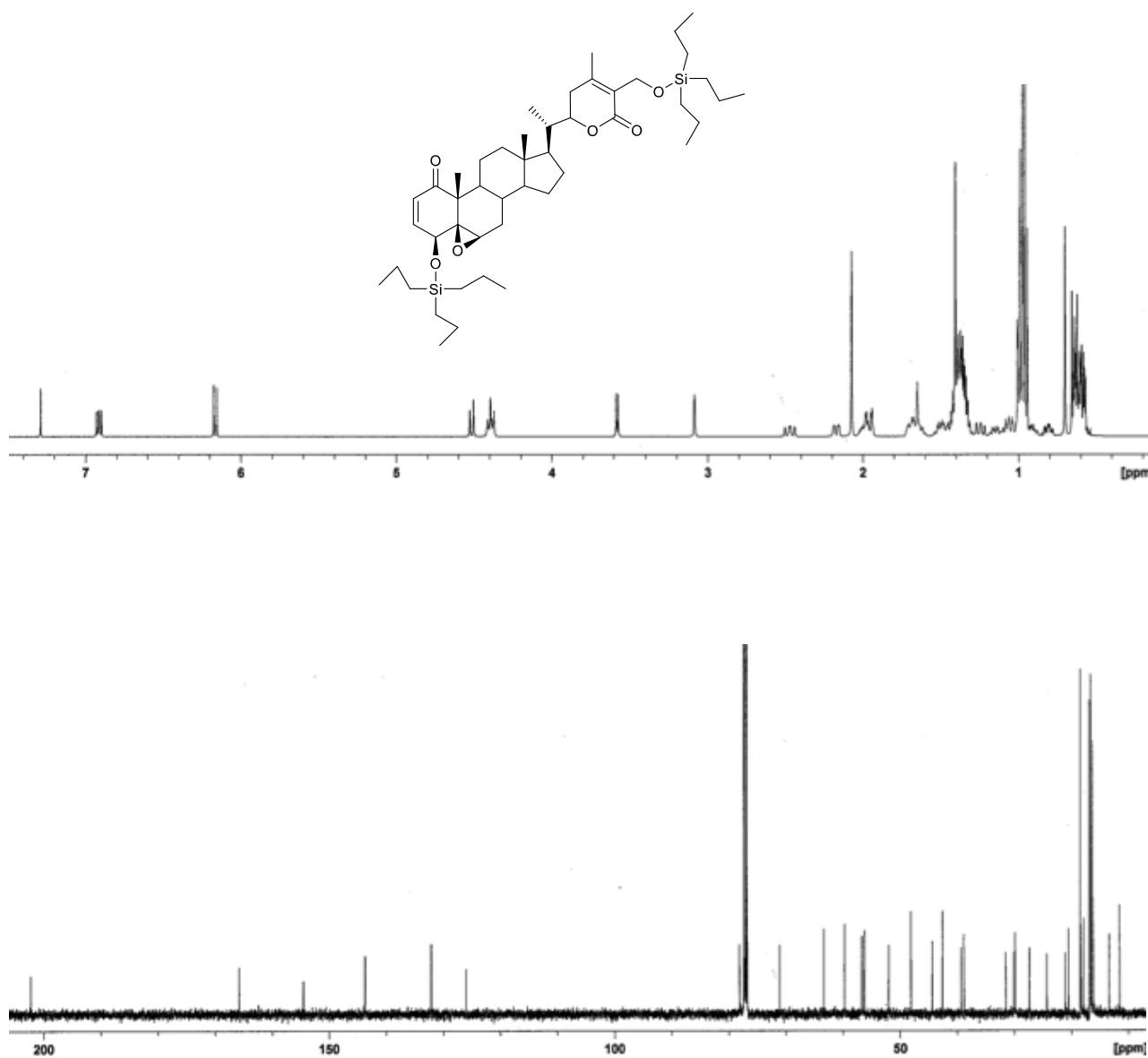
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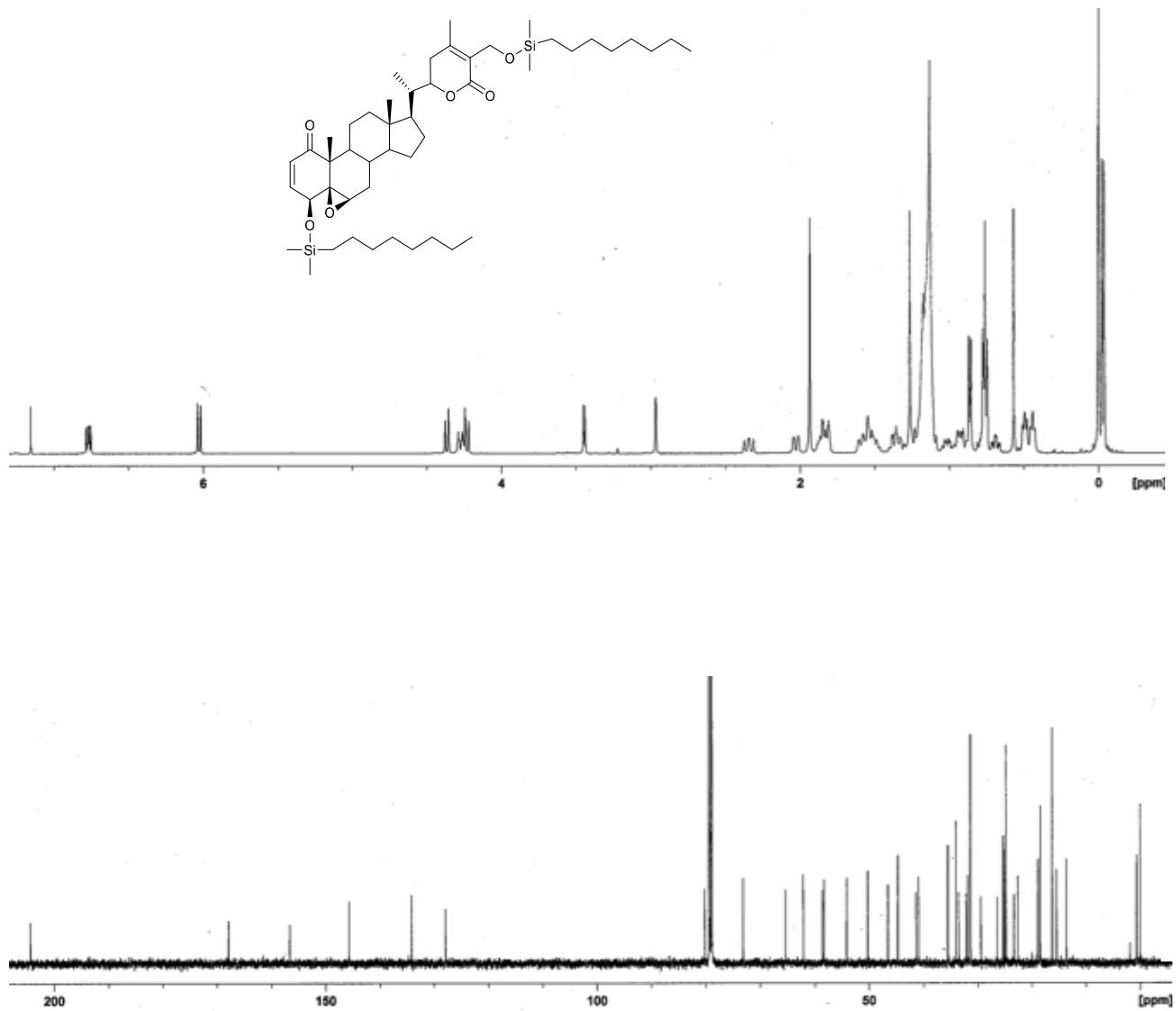
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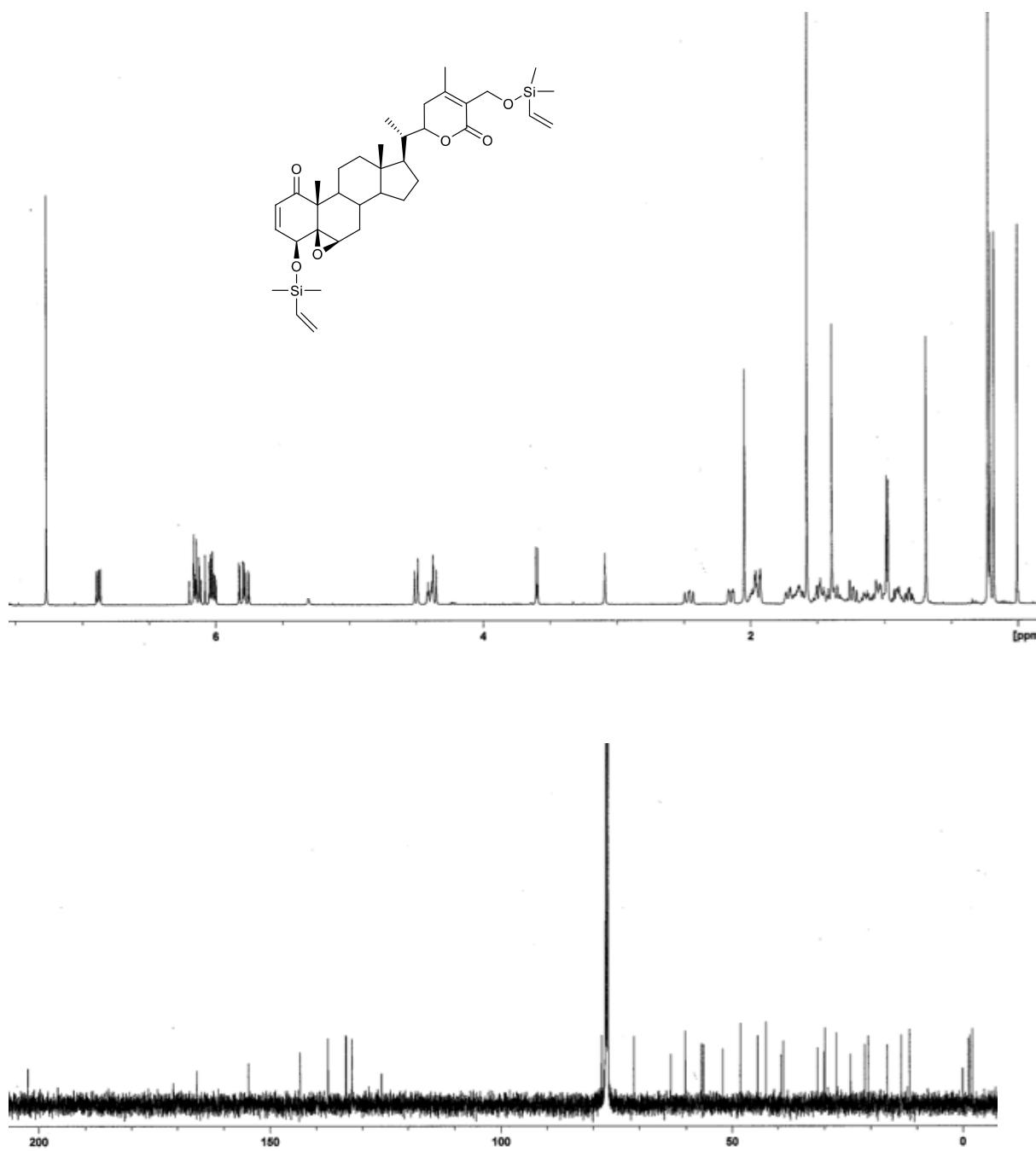
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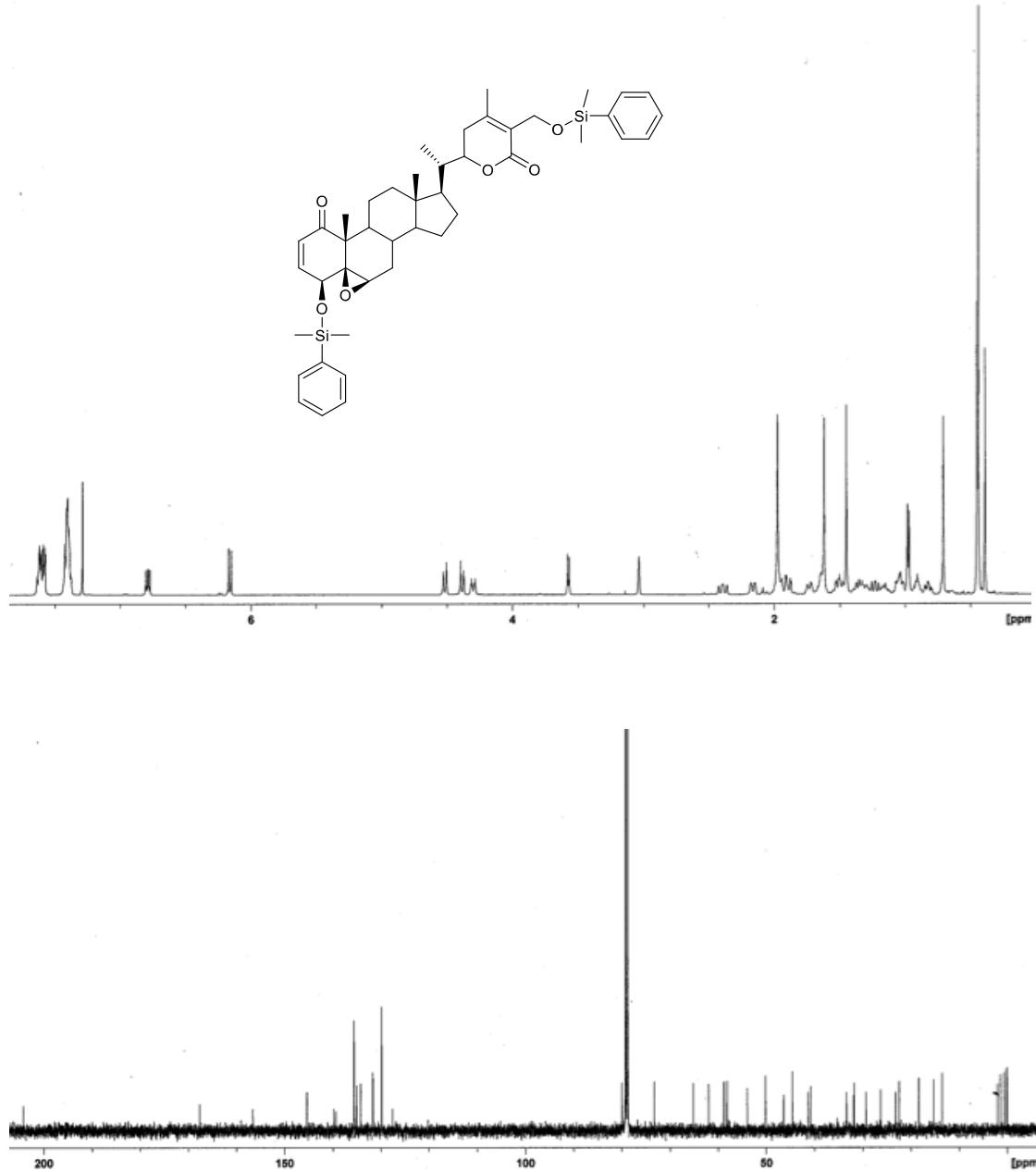
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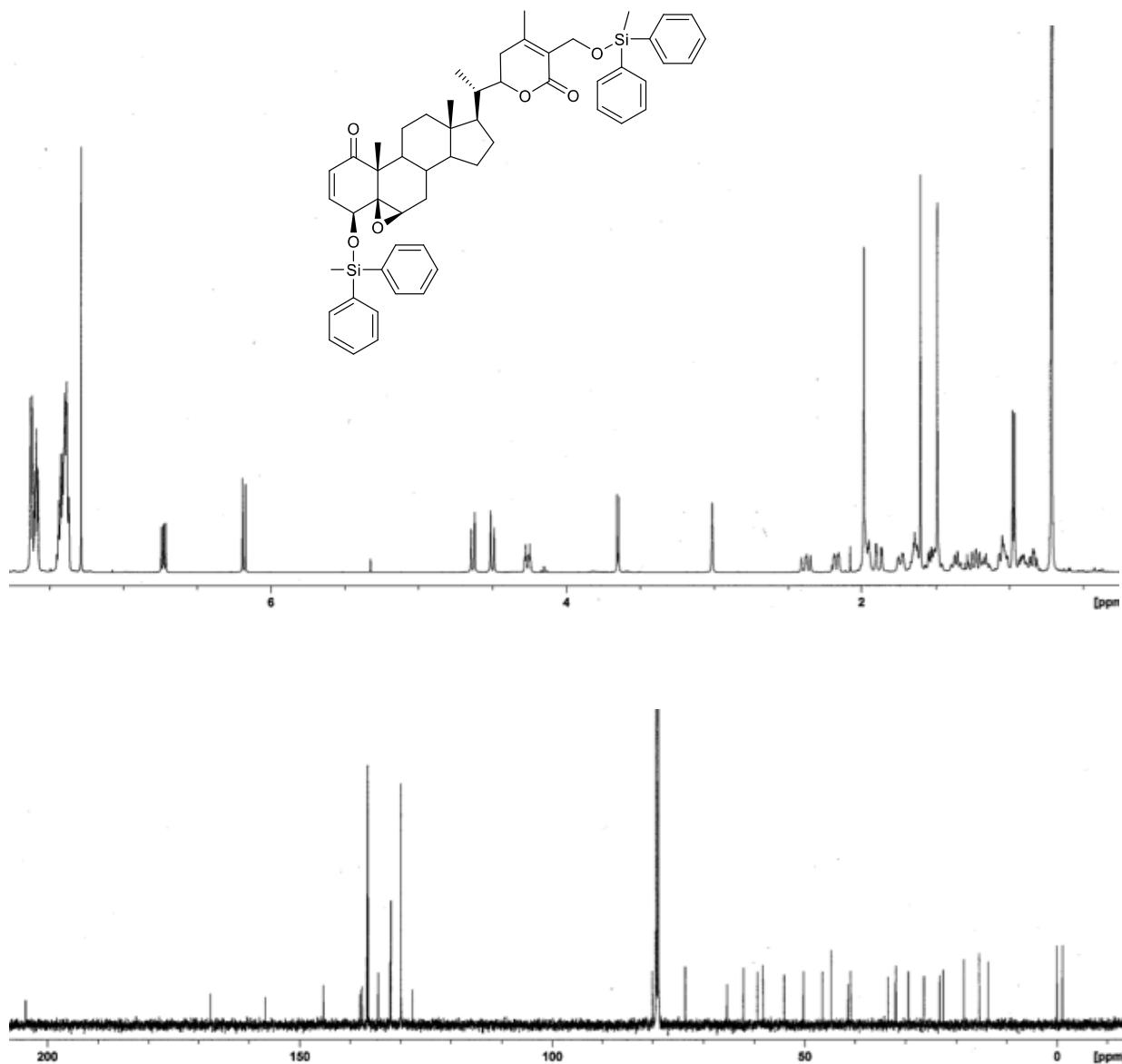
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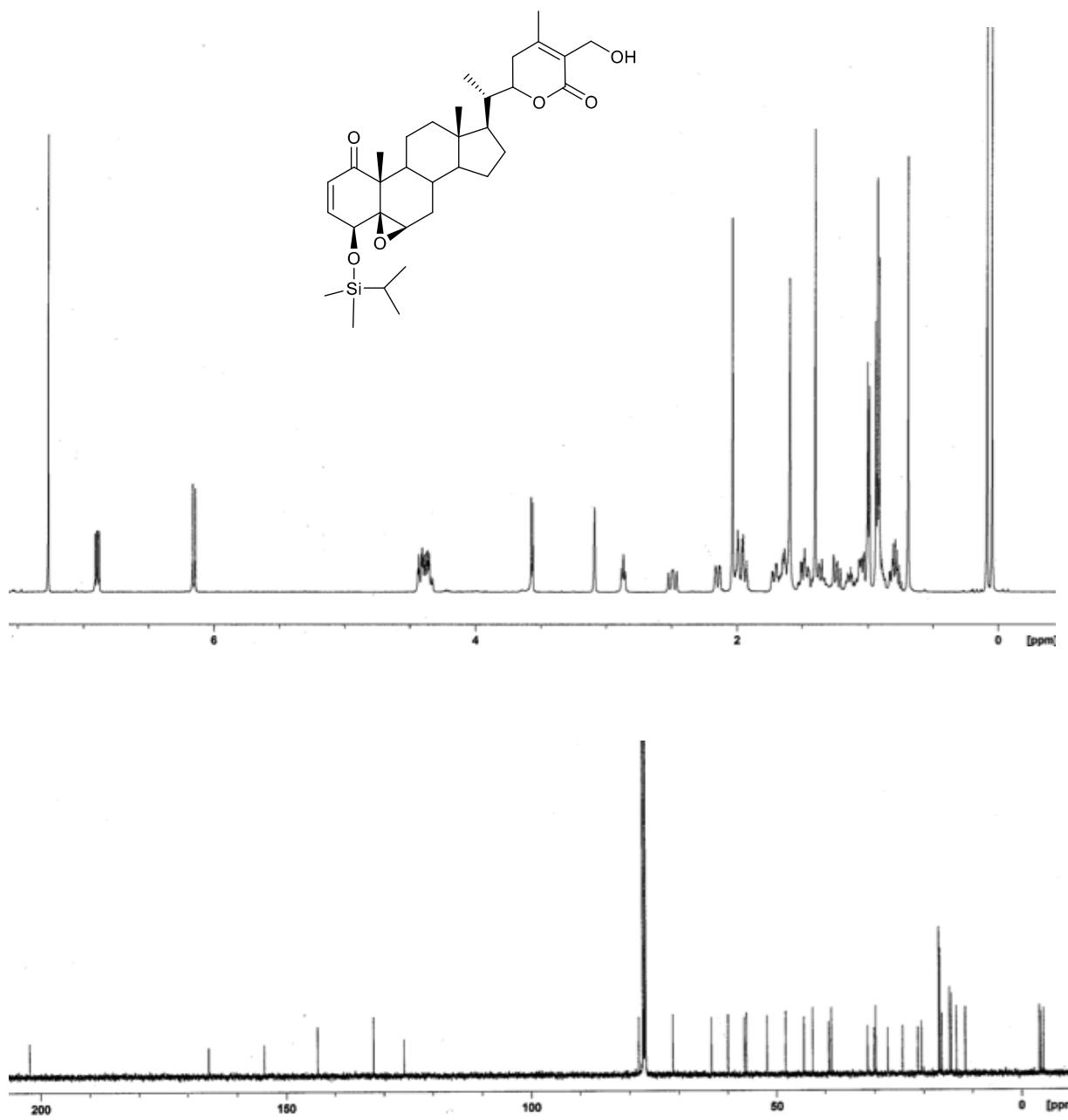
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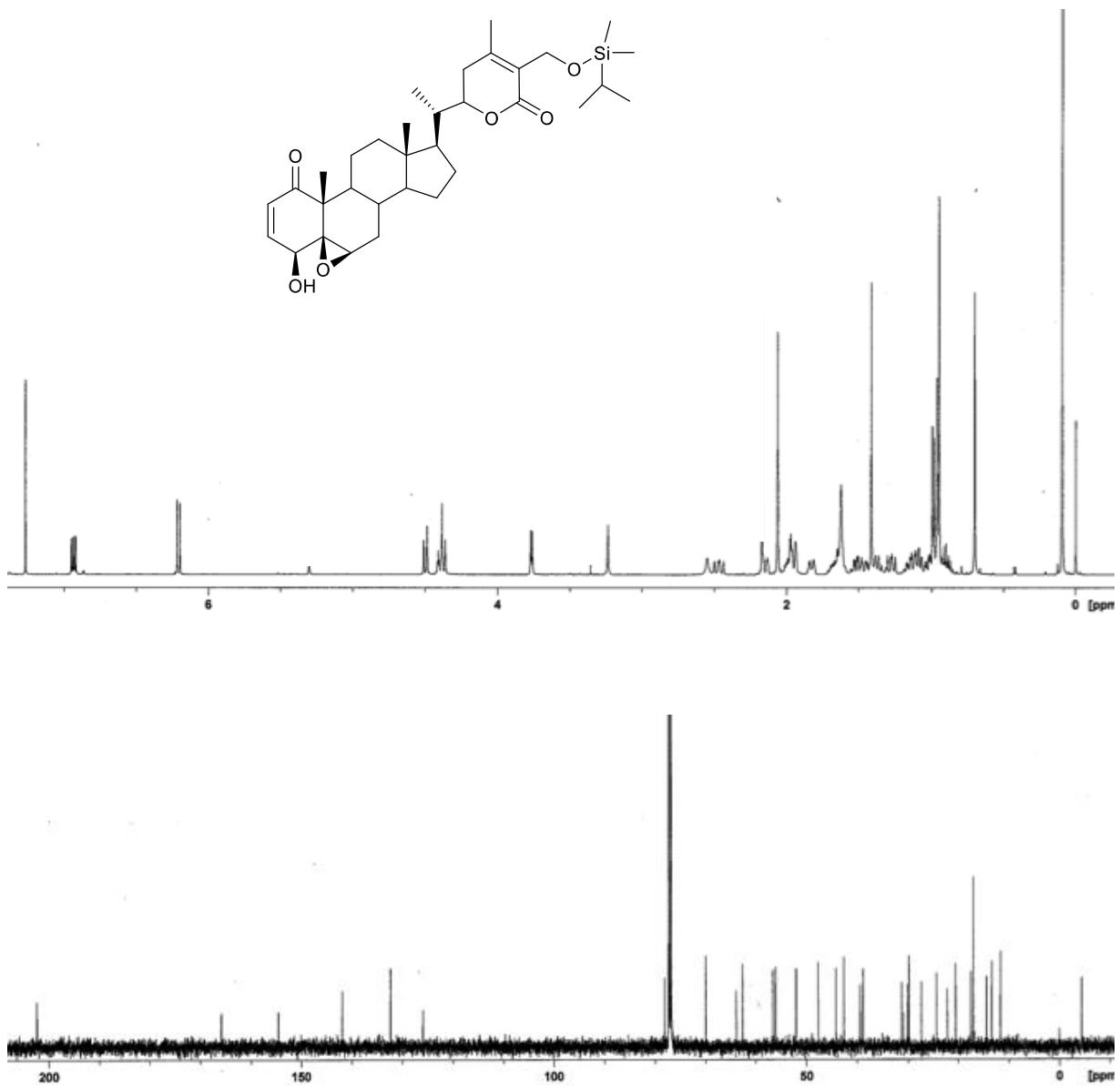
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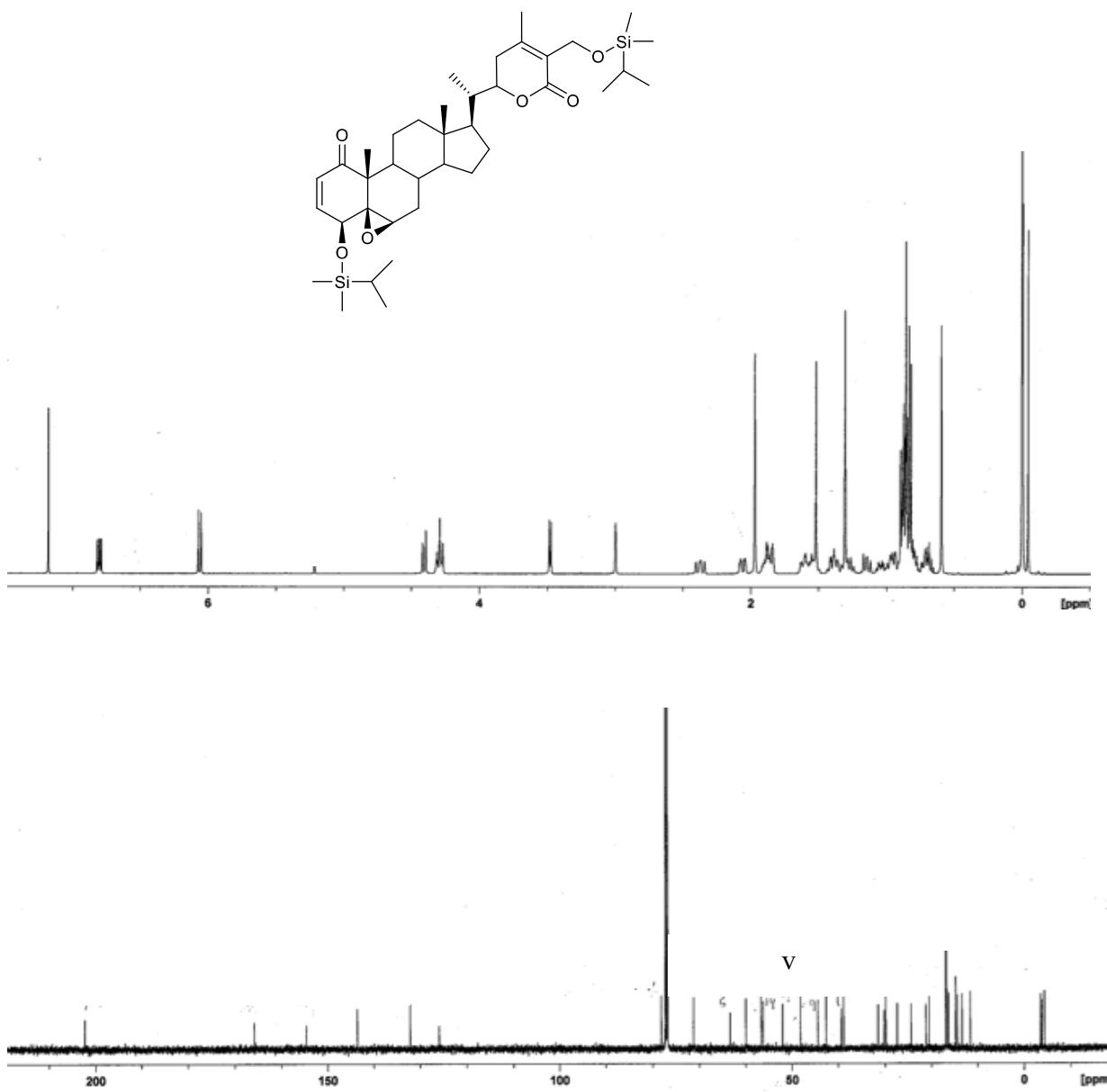
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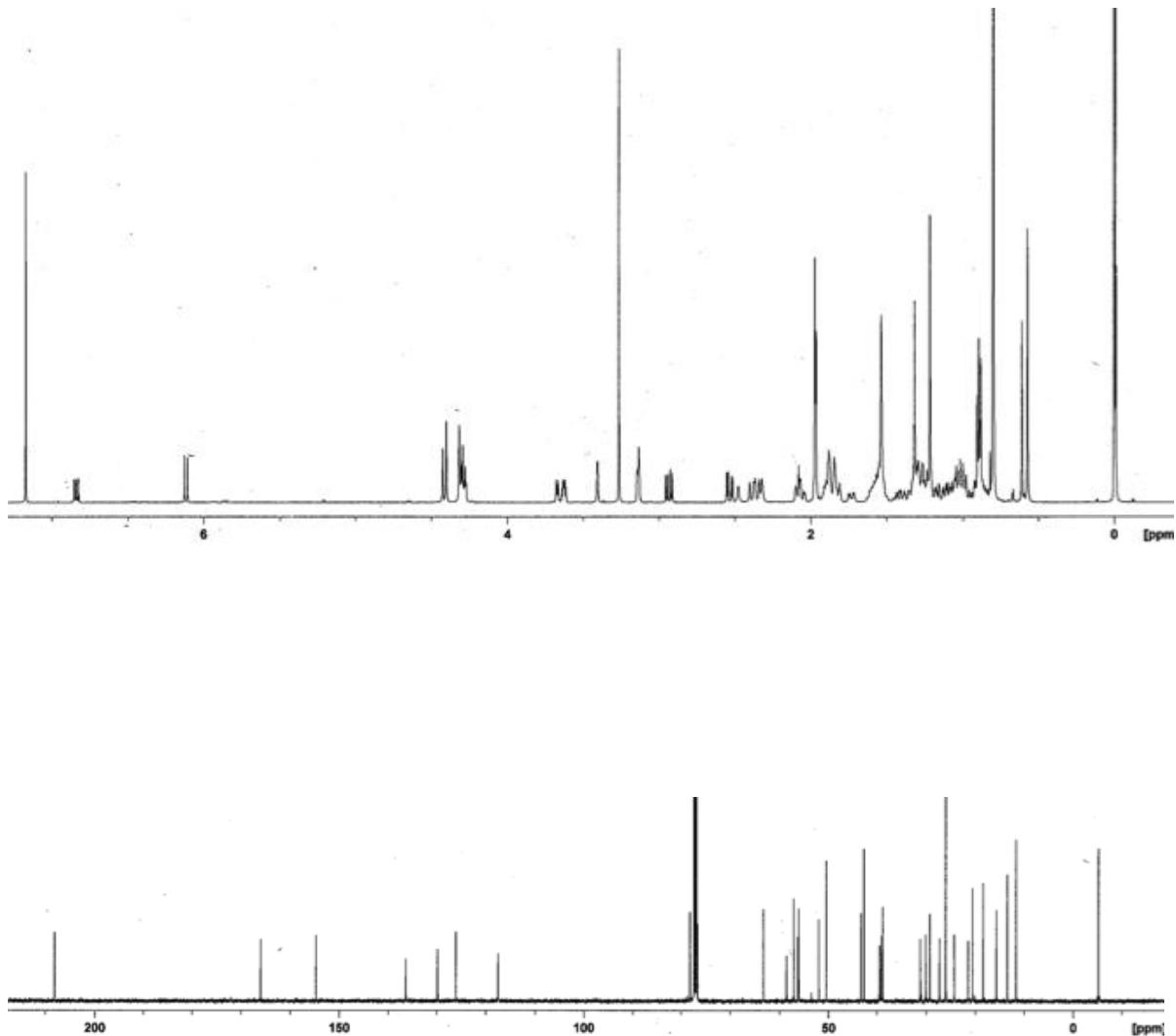
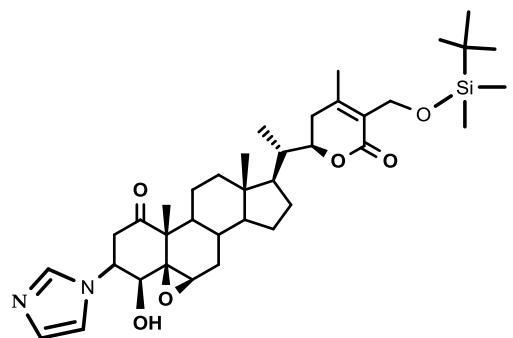
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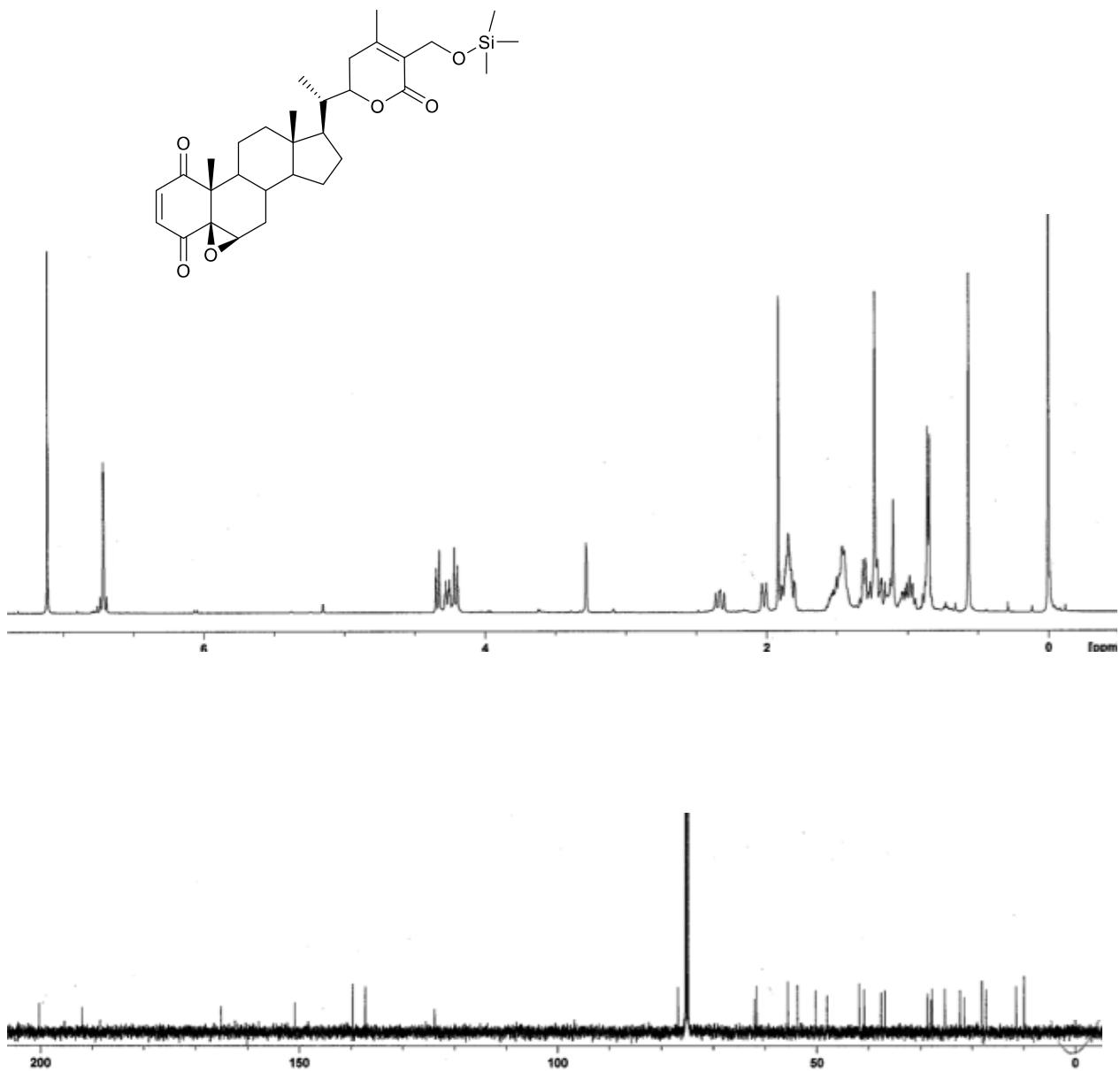
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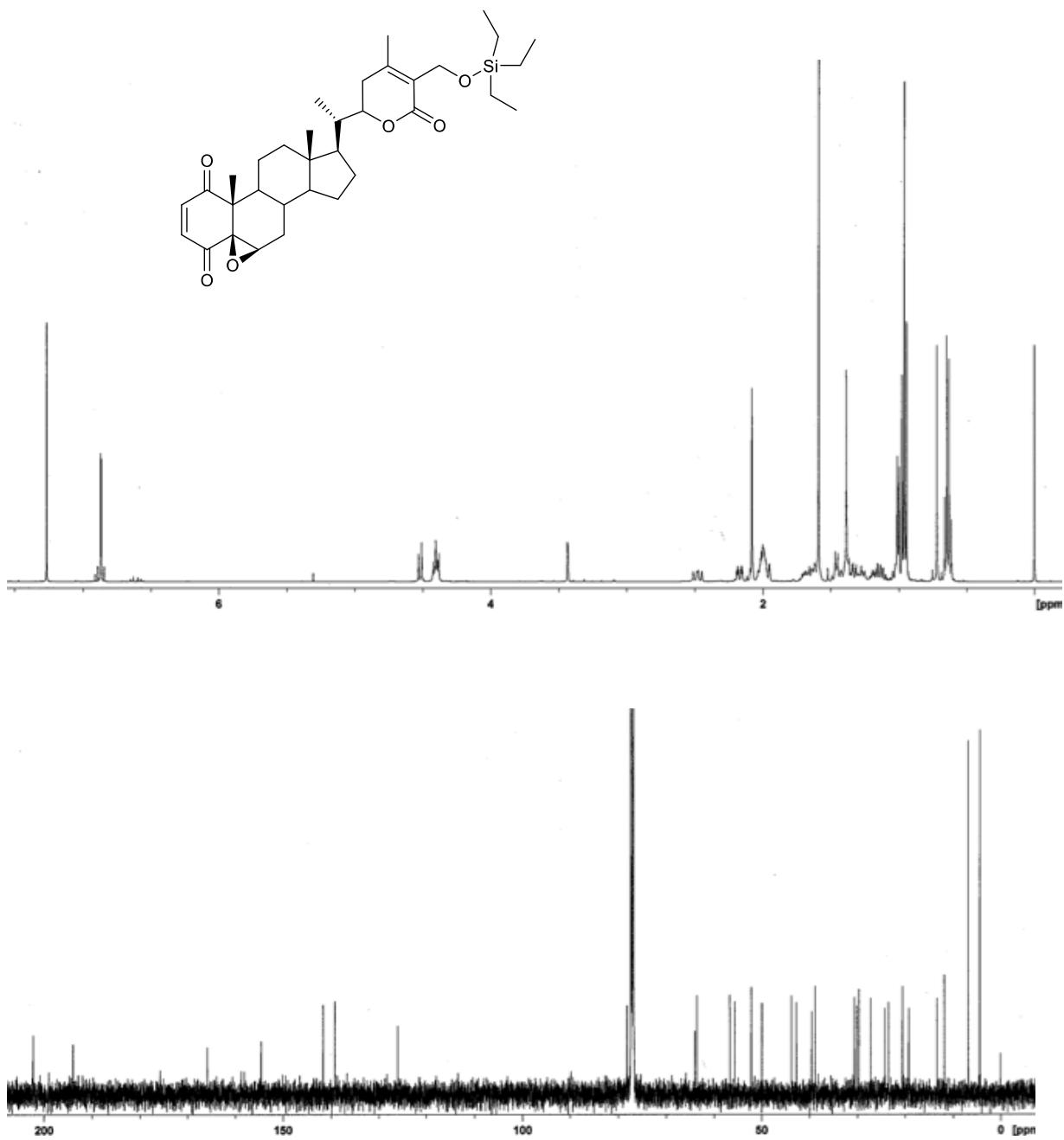
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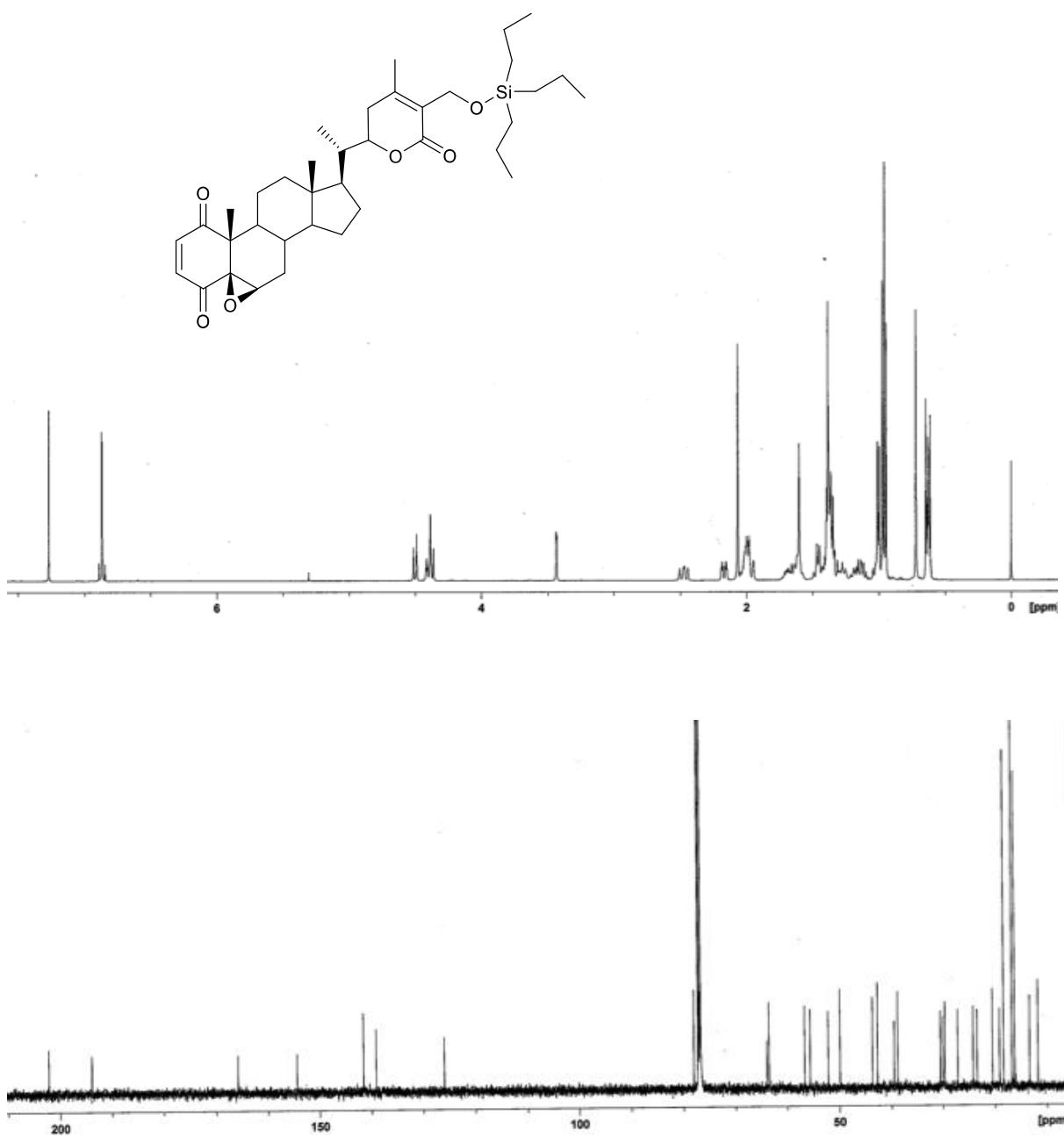
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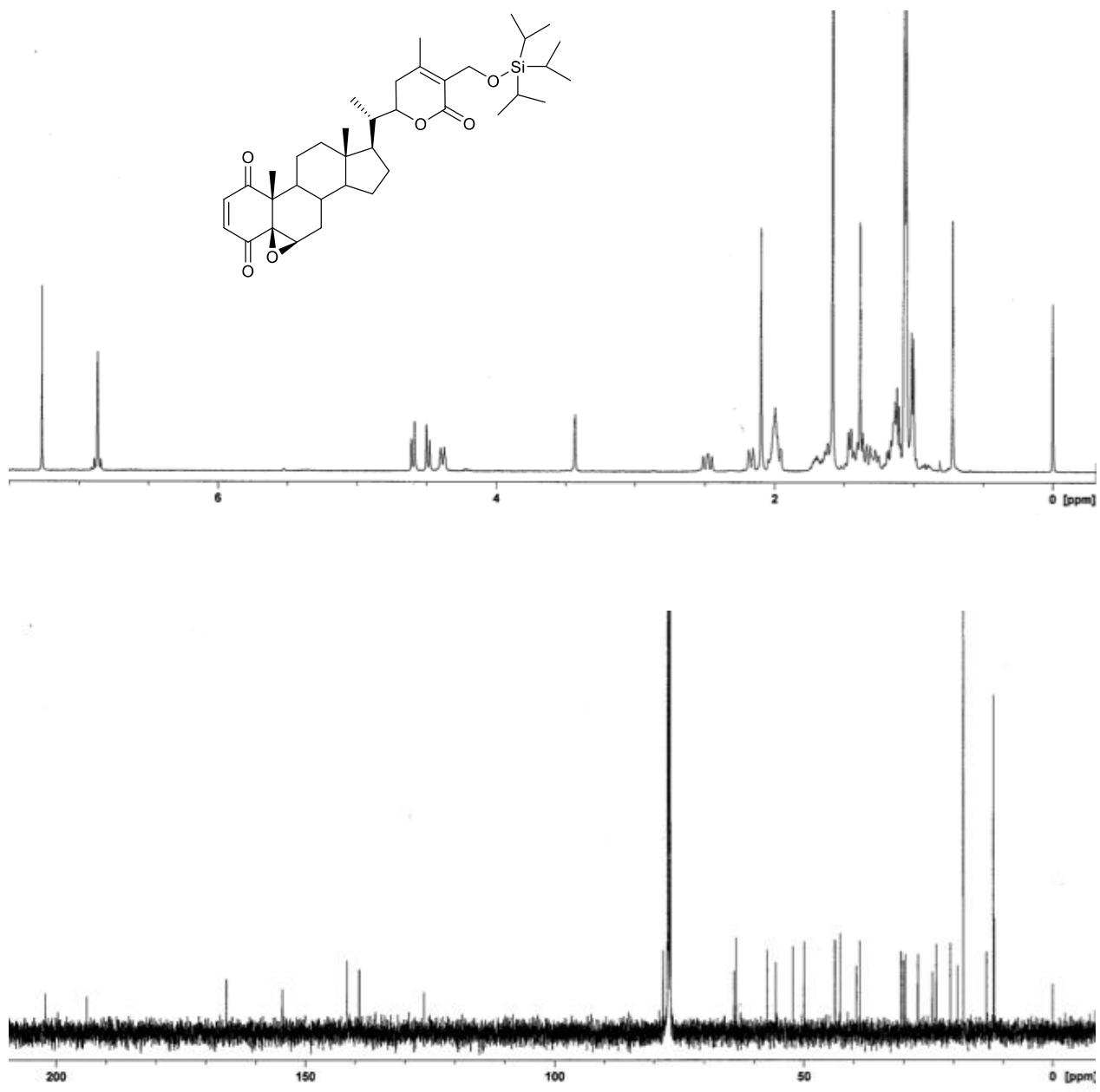
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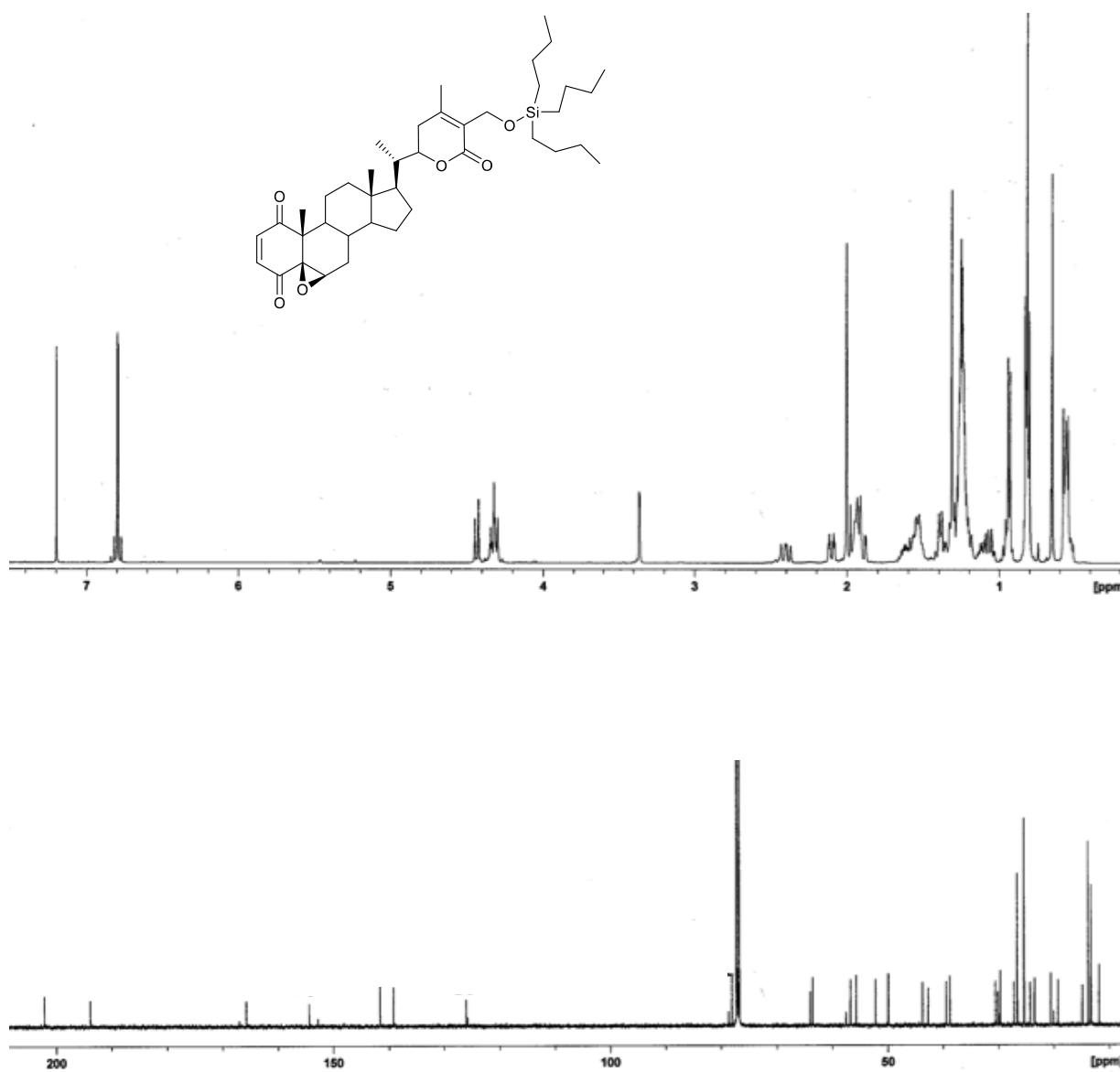
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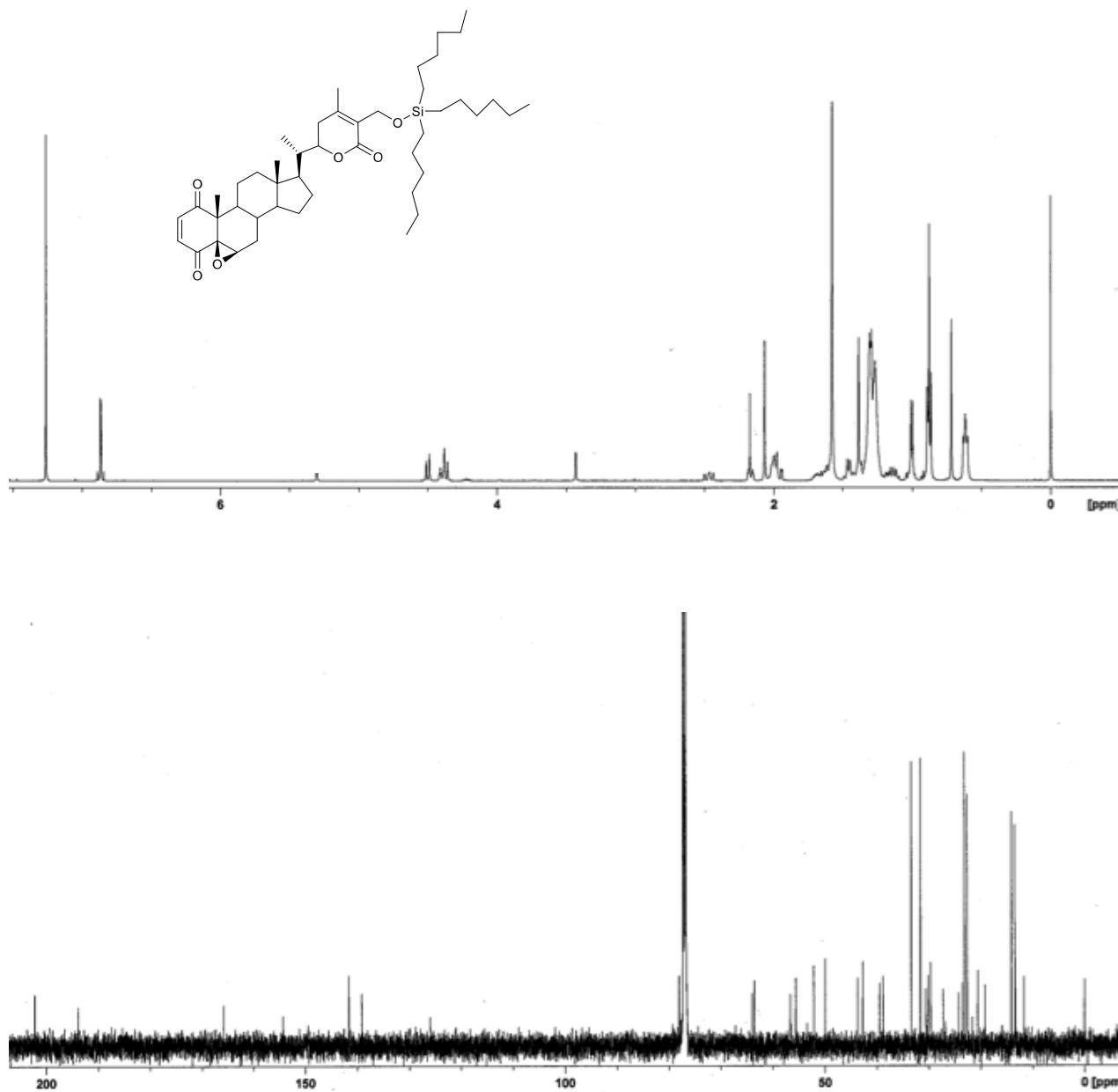
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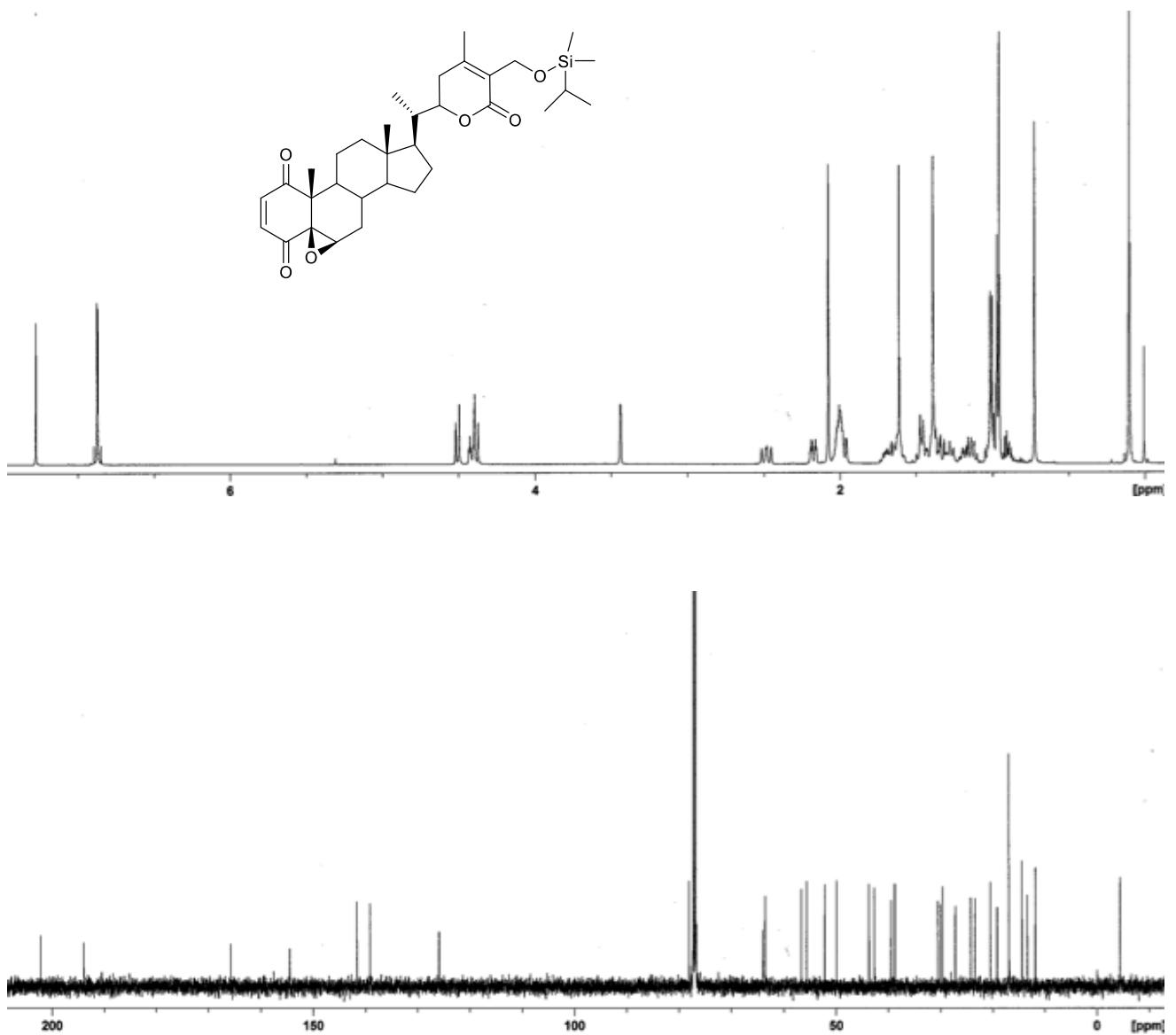
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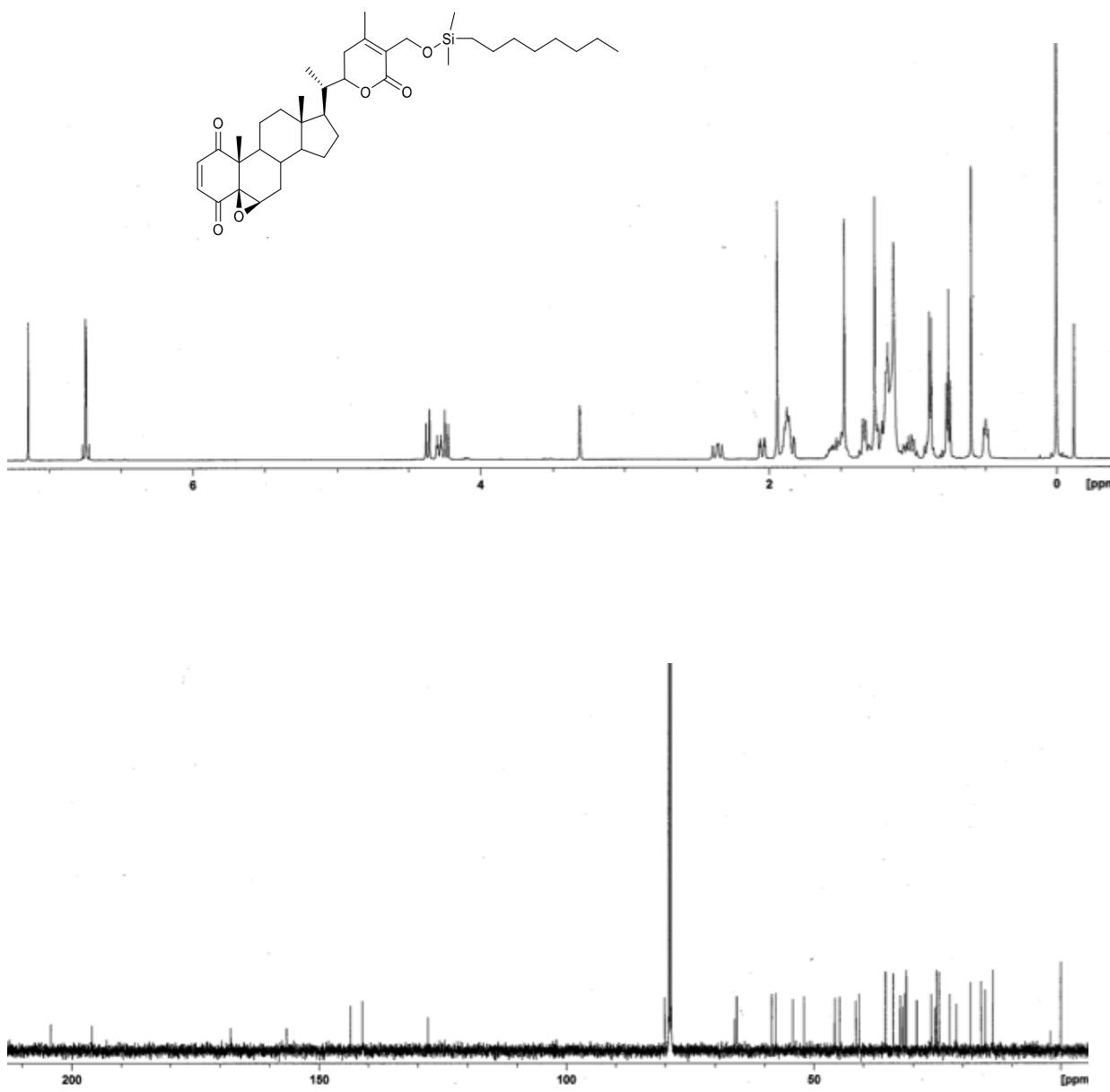
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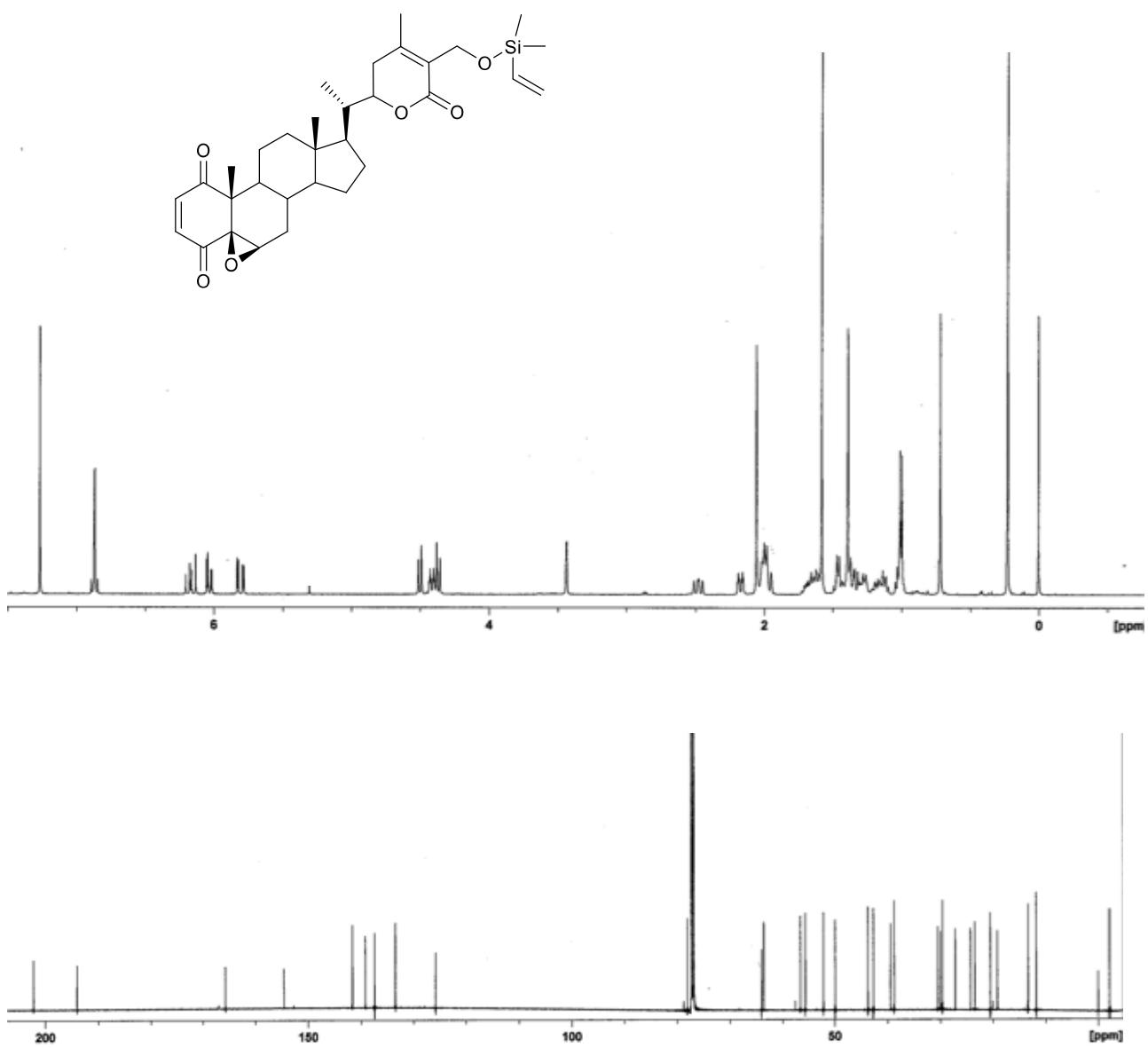
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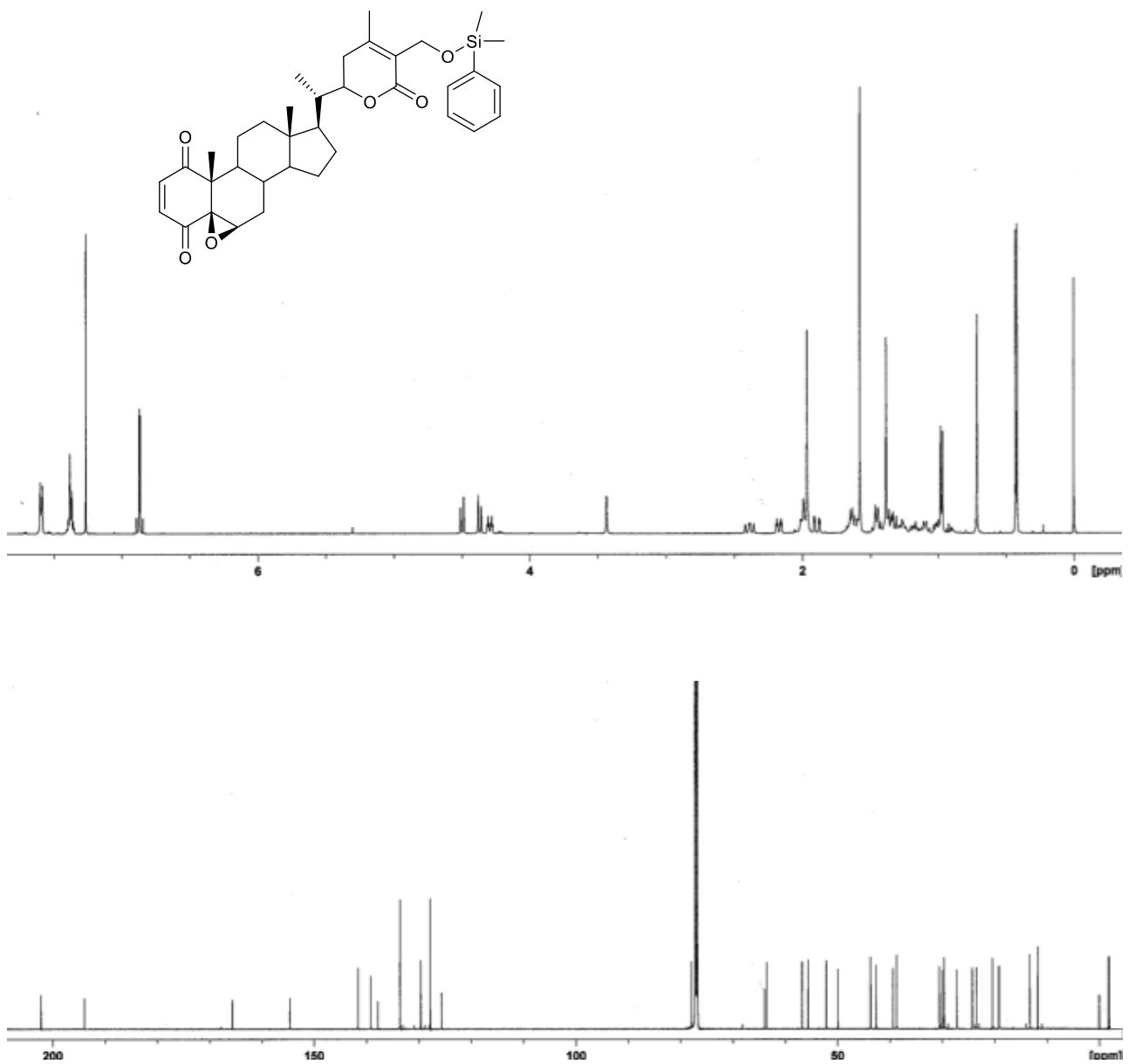
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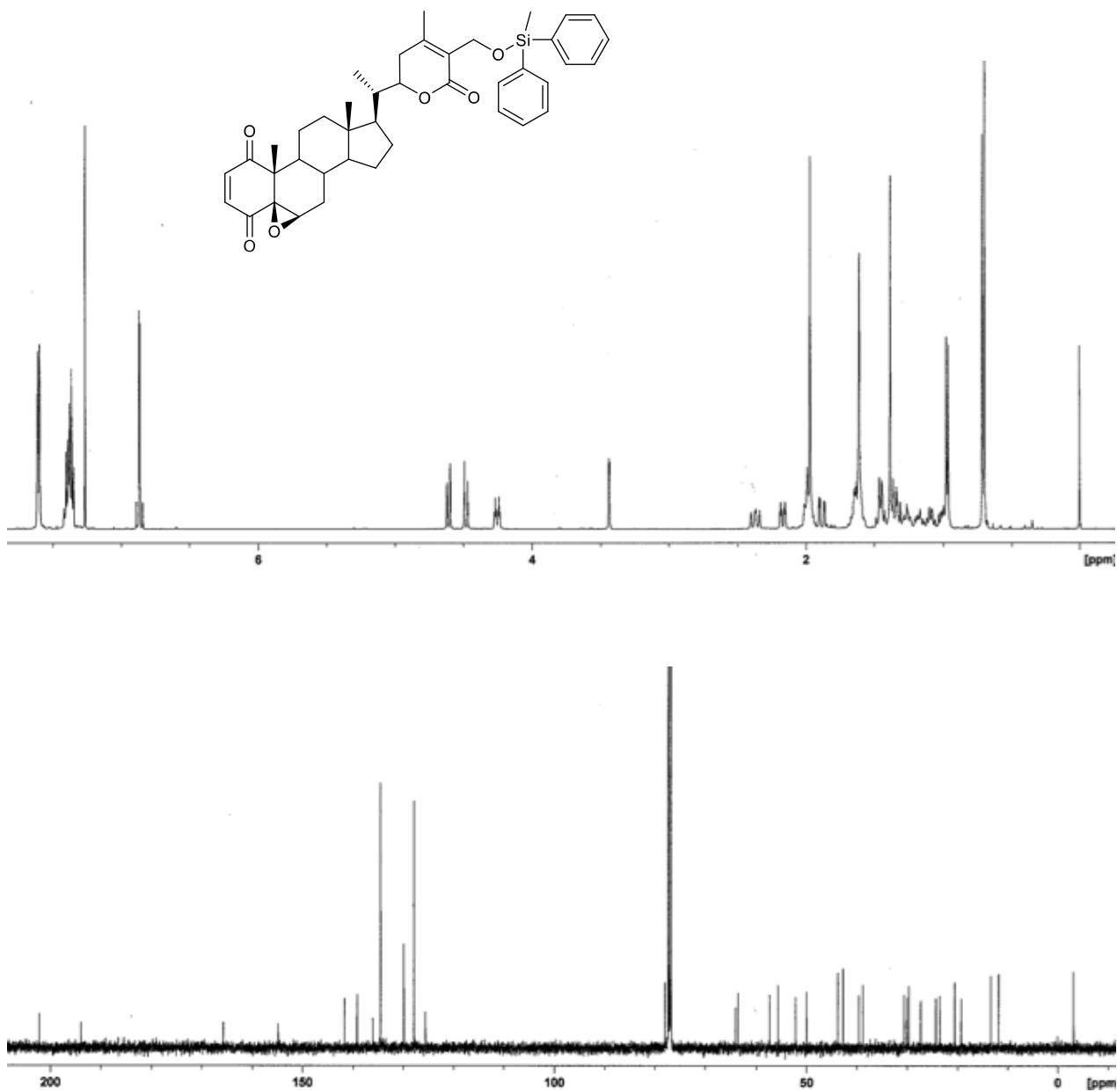
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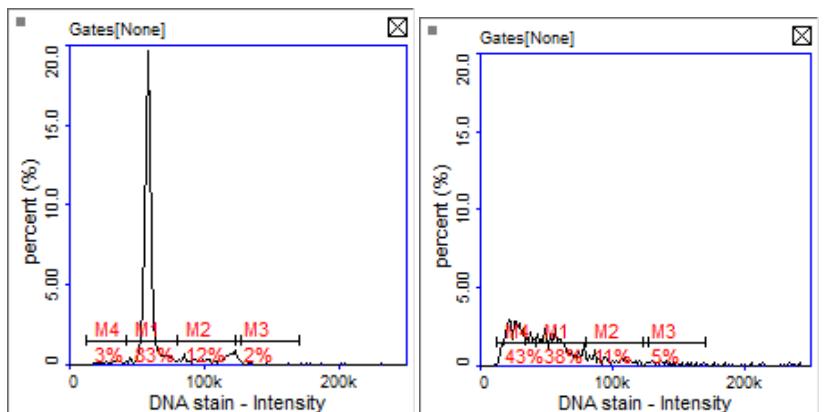
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Table S32. Cytotoxic Activity (IC_{50} , μM)^a of WA-analogues on Human Ovarian Carcinoma Cisplatin-sensible (A2789) and Cisplatin-resistant (A2780-CP70) Cell Lines, and on a non-Carcinoma Cancer Cell Line (ARPE19).

compd	A2780	A2780-CP70	ARPE19	SI ^b A2780	SI ^b A2780-CP70
1	0.0327 ± 0.0002	0.032 ± 0.002	0.037 ± 0.014	1.1	1.2
2	0.153 ± 0.1	0.0128 ± 0.002	0.030 ± 0.01	0.2	2.3
3	0.032 ± 0.002	0.0036 ± 0.0014	0.030 ± 0.0006	0.9	8.3
4	0.030 ± 0.002	0.062 ± 0.02	0.062 ± 0.03	2.1	1.0
5	0.027 ± 0.004	0.022 ± 0.0003	0.260 ± 0.21	9.6	11.8
6	22.43 ± 10.04	11.64 ± 4.04	7.17 ± 3.2	0.3	0.6
7	0.01 ± 0.0007	0.033 ± 0.001	0.032 ± 0.005	3.2	1.0
8	0.027 ± 0.01	0.031 ± 0.002	0.086 ± 0.016	3.2	2.8
9	0.022 ± 0.005	0.028 ± 0.0003	0.070 ± 0.01	3.2	2.53
10	0.046 ± 0.009	0.029 ± 0.006	2.295 ± 0.025	49.9	79.1
11	0.9 ± 0.7	1.28 ± 0.1	20.29 ± 3.8	22.5	15.9
12	19.11 ± 0.73	25.41 ± 4.91	1.06 ± 0.6	0.06	0.04
13	0.0015 ± 0.0005	0.0249 ± 0.01	0.318 ± 0.061	212.0	12.8
14	0.033 ± 0.0005	0.0275 ± 0.005	0.092 ± 0.03	2.8	3.3
15	0.0029 ± 0.001	0.029 ± 0.005	0.309 ± 0.04	106.6	10.7
16	3.58 ± 0.63	12.73 ± 4.89	13.2 ± 5.12	3.7	1.0
17	0.034 ± 0.001	0.023 ± 0.009	0.31 ± 0.2	9.1	13.5
18	0.034 ± 0.0006	0.035 ± 0.0004	6.5 ± 0.15	191.2	185.7
19	1.08 ± 0.63	2.48 ± 0.4	1.85 ± 0.19	1.71	0.8
20	0.02 ± 0.007	0.019 ± 0.01	0.052 ± 0.01	2.6	2.7
21	0.0475 ± 0.019	0.11 ± 0.03	0.0124 ± 0.001	0.3	0.1
22	0.017 ± 0.01	0.147 ± 0.05	1.66 ± 0.09	97.7	11.3
23	0.0073 ± 0.006	< 0.001	0.032 ± 0.002	4.3	> 32
24	0.041 ± 0.005	0.0688 ± 0.008	0.82 ± 0.3	20.0	11.9
25	0.035 ± 0.01	0.02 ± 0.0002	1.87 ± 0.07	53.5	93.5
26	0.069 ± 0.02	0.021 ± 0.006	1.74 ± 0.34	25.2	82.9

27	0.035 ± 0.006	0.035 ± 0.001	0.0375 ± 0.004	1. 1	1.0
28	0.053 ± 0.04	2.46 ± 0.2	0.617 ± 0.5	11.6	0.3
29	25.17 ± 2.4	14.33 ± 5.08	3.22 ± 0.1	0.1	0.2
30	0.043 ± 0.0002	0.034 ± 0.0002	2.14 ± 0.1	49.8	62.9
31	2.19 ± 0.61	2.83 ± 0.45	16.8 ± 2.13	7.7	5.9
32	0.1 ± 0.05	2.75 ± 0.3	2.12 ± 0.43	21.2	0.8
33	0.059 ± 0.01	1.98 ± 0.13	2.305 ± 0.27	39.1	1.2
34	0.035 ± 0.01	0.75 ± 0.028	2.05 ± 0.35	58.6	2.7
CP^c	2.57 ± 0.35	44.92 ± 3.5	4.59 ± 0.92	1.8	0.1

^a IC₅₀ values (μM) of WA analogues were determined as described in the Biological Studies section. Results are expressed as the mean \pm standard deviation of three independent experiments performed in duplicate. ^b SI, Selectivityy Index. ^c Carboplatin used as reference drug.



Control

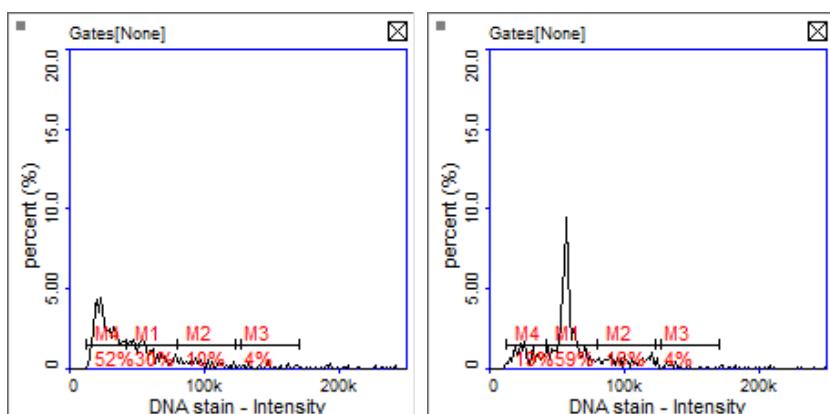
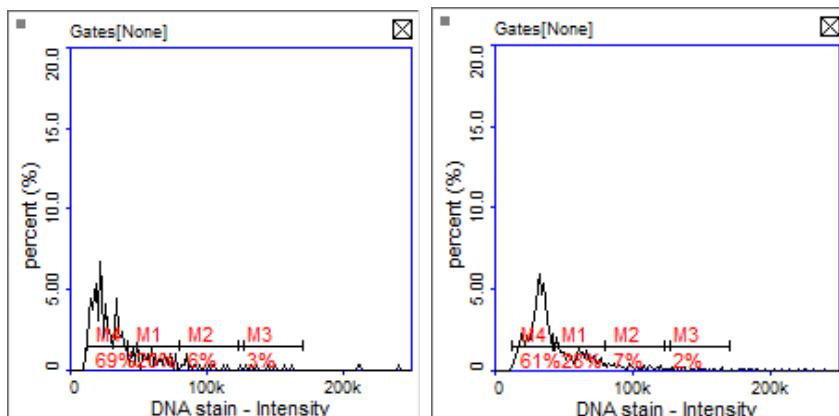
Compound 21 at 5 μ MCompound 21 at 10 μ MCompound 22 at 10 μ MCompound 22 at 30 μ MCompound 22 at 60 μ M

Figure S34. Representative scatter plot indicating the percentage of cells in G0/G1 (M1), S (M2), and G2 (M3) and Sub-G1 (M4) phases in human ovarian carcinoma cells (A2789) after 48 h exposure times with different concentrations of analogues **21** and **22**.

Table S35. *In silico* ADME^a profile of WA (**1**) and selected WA-analogues^b

Compound	#stars	QPlogBB	QPPCaco	QPPMDCK	QPlogKhsa	QPlogPo/w	QPlogKp	QPlogS	# metab	Percent Human Oral	PSA	SASA	mol MW	#rotor	donor HB	accpt HB	volume
1	0	-1.31	258.20	114.48	0.33	3.05	-3.84	-5.00	4.00	87.95	96.36	718.23	470.61	5	1.0	9.40	1,396.69
2	1	-1.07	1,060.23	526.99	1.19	5.96	-2.27	-7.59	4	90.07	85.36	906.77	584.87	9	1.0	9.55	1,803.47
3	8	-1.56	789.50	383.18	1.65	7.26	-2.23	-9.56	4	95.39	85.36	1,043.95	626.95	12	1.0	9.55	2,026.33
4	4	-0.95	1,314.93	665.07	1.51	6.77	-2.08	-8.12	4	96.49	85.36	936.66	626.95	9	1.0	9.55	1,919.20
5	9	-1.57	1,068.80	531.60	1.91	8.26	-1.68	-9.87	4	100.00	85.36	1,087.83	669.03	15	1.0	9.55	2,167.12
7	8	-1.43	1,102.50	549.74	1.71	7.59	-1.86	-9.57	4	100.00	85.36	1,053.52	640.97	13	1.0	9.55	2,062.13
8	1	-1.11	759.53	367.48	1.02	5.29	-2.64	-7.34	4	83.57	85.36	874.31	554.80	7	1.0	9.55	1,709.06
9	5	-1.12	973.14	480.36	1.74	7.50	-1.28	-9.36	4	100.00	85.36	996.53	666.93	8	1.0	9.55	1,991.17
10	7	-1.11	1,041.78	517.09	2.10	8.40	-1.29	-9.75	4	100.00	85.36	1,027.42	709.01	9	1.0	9.55	2,135.68
11	8	-1.11	1,856.78	965.71	2.20	9.11	-1.47	-10.16	4	100.00	74.36	1,087.63	699.13	13	0.0	8.70	2,223.86
13	11	-1.90	1,583.05	812.79	3.36	12.44	-0.82	-14.50	4	100.00	74.36	1,385.46	811.34	21	0.0	8.70	2,741.08
14	7	-0.84	1,978.20	1,034.15	1.74	7.81	-1.55	-9.45	4	100.00	74.36	1,016.22	638.99	9	0.0	8.70	2,008.46
15	9	-0.89	2,018.60	1,057.00	2.53	9.91	-0.57	-11.93	4	100.00	74.36	1,147.05	739.11	9	0.0	8.70	2,280.15
17	1	-1.25	550.18	259.34	1.14	5.75	-3.08	-7.38	4	83.76	85.36	885.42	570.84	7	0.0	8.55	1,757.66
18	1	-1.16	678.13	325.10	1.16	5.55	-2.85	-7.57	4	84.18	85.36	887.39	570.84	7	1.0	9.55	1,761.12
20	1	-1.26	600.43	285.03	1.10	5.57	-2.82	-7.84	5	83.39	103.18	949.88	638.92	7	1.0	11.55	1,903.72
21	1	-1.10	764.50	370.08	1.28	5.87	-2.74	-7.85	4	87.01	85.36	903.19	584.87	7	1.0	9.55	1,805.47
22	1	-0.87	996.05	492.60	0.89	5.46	-2.62	-6.71	3	86.68	82.20	877.56	582.85	6	0.0	9.85	1,778.77
23	0	-1.27	243.69	107.54	-0.13	2.52	-3.98	-3.97	3	84.41	93.20	711.72	468.59	4	0.0	9.70	1,383.64
24	1	-1.03	709.27	341.27	0.60	4.62	-2.98	-6.52	3	92.06	82.20	858.88	540.77	5	0.0	9.85	1,665.00
25	0	-1.16	711.66	342.51	0.83	5.39	-2.74	-6.49	3	83.64	82.20	882.91	582.85	8	0.0	9.85	1,785.65
26	3	-1.36	839.29	409.36	1.22	6.62	-2.31	-7.85	3	92.10	82.20	980.52	624.93	11	0.0	9.85	1,965.33
27	1	-0.96	1,032.26	511.98	1.12	6.16	-2.44	-6.92	3	91.02	82.20	905.83	624.93	8	0.0	9.85	1,885.36
28	6	-1.42	1,052.90	523.06	1.41	7.40	-1.84	-8.05	3	100.00	82.20	1,016.62	667.01	14	0.0	9.85	2,075.02
30	1	-0.98	866.68	423.82	0.81	5.25	-2.71	-6.83	3	84.32	82.20	883.63	568.82	6	0.0	9.85	1,751.01
32	0	-0.93	899.71	441.31	0.63	4.87	-2.59	-6.19	3	95.36	82.20	850.14	552.78	6	0.0	9.85	1,686.72
33	1	-1.12	721.91	347.85	1.03	5.89	-2.24	-7.66	3	86.66	82.20	927.60	602.84	6	0.0	9.85	1,826.32
34	4	-1.16	792.00	384.49	1.46	7.15	-1.55	-8.76	3	94.75	82.20	993.97	664.91	7	0.0	9.85	1,988.49
Range/recommended values	0-5	-3.0 to 1.2	< 25 poor; >500 great	< 25 poor; >500 great	-1.5 to 1.5	-2.0 to 6.5	-8.0 to -1.0	-6.5 to 0.5	1 to 8	>80% is high; <25% is poor	7.0-to-200.0	300.0 to 1,000.0	130.0 to 725.0	0 to 15	0 to 6.0	2.0 to 20.0	500.0 to 2,000.0

^a #star (number of property values that fall outside the 95% range of similar values for known drugs), QPlogBB (predicted brain/blood partition coefficient), QPPCaco2 (predicted human epithelial colorectal adenocarcinoma cell lines permeability in nm/s), QPPMDCK (predicted Madin-Darby Canine Kidney permeability in nm/s), QPlogKhsa (prediction of binding to human serum albumin), QPlogPo/w (predicted octanol/water partition coefficient), QPlogKp (skin permeability), QPlogS (predicted aqueous solubility), #metab (number of likely metabolic reactions), PSA (Van der Waals surface area polar nitrogen and oxygen atoms and carbonyl atoms), SASA (total solvent accessible surface area), MW (molecular weight), number of non-trivial, non-hindered rotatable bonds). ^b WA-analogues exhibiting IC₅₀ values ≤ 1 μM on A2780 and/or A2789-CP70 cell lines.