Expedient Synthesis of (±) Bipinnatin J

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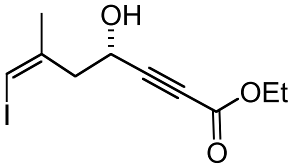
Supporting Information

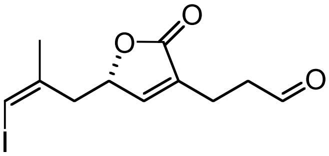
General Experimental Details: All reactions were carried out under an inert N_2 atmosphere in oven-dried glassware. Flash column chromatography was carried out with EcoChrom ICN SiliTech 32-63 D 60 Å silica gel. Reactions and chromatography fractions were monitored with Merck silica gel 60 F_{254} plates and visualized with potassium permanganate and ceric ammonium molybdate. Tetrahydrofuran (THF) and methylene chloride (CH_2Cl_2) were dried by passage through activated alumina columns. Benzene (PhH) and diisopropylamine (*i*-Pr_2NH) were distilled from CaH_2 prior to use. *n*-Butyllithium was titrated with diphenylacetic acid prior to use. All other reagents and solvents were used without further purification from commercial sources. Organic extracts were dried over $MgSO_4$ unless otherwise noted.

Instrumentation: FT-IR spectra were obtained on NaCl plates with an ATI Mattson Gemini spectrometer. Proton and carbon NMR spectra (^1H NMR and ^{13}C NMR) were recorded in deuterated chloroform ($CDCl_3$) on a Bruker DRX-500 spectrometer and calibrated to residual solvent peaks. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet. Melting points were deteremined with an electrothermal apparatus and are uncorrected.



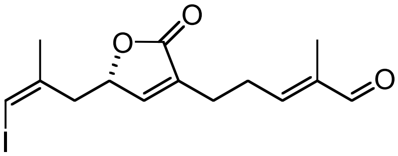
(*Z*)-(*S*)-4-Hydroxy-7-iodo-6-methyl-hept-6-en-2-ynoic acid ethyl ester (11). To a solution of (*Z*)-4-iodo-3-methyl-but-3-en-1-ol (**9**) (3.18 g, 15.0 mmol) in CH_2Cl_2 (75 mL) was added $NaHCO_3$ (6.30 g, 75.0 mmol) followed by Dess-Martin periodinane (6.68 g, 15.8 mmol). After 15 min at rt, a 1:1:1 solution (75 mL) of saturated $Na_2S_2O_3$, saturated $NaHCO_3$, H_2O was added. The resulting biphasic solution was stirred vigorously for 20 min. The layers were separated, and the aqueous was extracted 1 x CH_2Cl_2 (50 mL). The organics were dried, filtered, and concentrated *in vacuo*. To the resulting oil was added 50 mL Et_2O. The mixture was filtered and concentrated *in vacuo*. If additional solids precipitated, the mixture was filtered and concentrated again from Et_2O. The crude aldehyde was taken up in THF (25 mL) and used without further purification. Meanwhile, to a solution of *i*-Pr_2NH (6.31 mL, 45.0 mmol) in THF (45 mL) at −78 °C was added *n*-butyllithium (2.42 M in hexanes, 18.6 mL, 45.0 mmol) dropwise over 5 min. After 20 min at 0 °C, the solution was cooled to −78 °C and ethyl propiolate (4.57 mL, 45.0 mmol) in THF (30 mL) was added via cannula over 15 min. After 1 h, the aldehyde solution at −78 °C was added via cannula to the acetylide solution at −78 °C. After 30 min, a saturated solution of NH_4Cl (30 mL) was added. Then the reaction mixture was allowed to warm to rt. The layers were separated, and the aqueous was extracted 1 x Et_2O (100 mL). The organics were dried, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (16% EtOAc/hexanes) to give 3.07 g (66% for 2 steps) of **11** as a colorless oil.

R_f 0.57, 30% EtOAc/Hexanes. ^1H NMR (500 MHz): δ 6.12 (d, 1 H, J = 1.5 Hz), 4.72 (dt, 1 H, J = 8.5, 6 Hz), 4.25 (q, 2 H, J = 7 Hz), 2.80 (dd, 1 H, J = 13.5, 8.5 Hz), 2.65 (dd, 1 H, J = 13.5, 6 Hz), 2.03 (d, 1 H, J = 6 Hz), 2.00 (d, 3 H, J = 1.5 Hz), 1.32 (t, 3 H, J = 7 Hz). ^{13}C (125 MHz): δ 153.2, 142.4, 86.6, 78.5, 76.9, 62.2, 60.2, 45.4, 24.6, 14.0. IR: 3406, 2981, 1711, 1251. HRMS $(EI)^+$ calcd for $C_{10}H_{13}O_3I$ $(M)^+$ 307.9909, found 307.9907.



3-[(*S*)-5-((*Z*)-3-Iodo-2-methyl-allyl)-2-oxo-2,5-dihydro-furan-3-yl]-propionaldehyde (13). To a solution of **11** (1.98 g, 6.43 mmol) in THF (21 mL) and acetone (10.5 mL) was added allyl alcohol (690 µL, 9.65 mmol), camphorsulfonic acid (373 mg, 1.61 mmol), and $RuCp(MeCN)_3PF_6$ (139 mg, 0.321 mmol) sequentially. After 1.5 h at 50 °C, the reaction mixture was concentrated *in vacuo*. The crude oil was purified by flash column chromatography (40% EtOAc/hexanes) to 1.08 g (52%) of **13** as a light red oil in addition to 154 mg of the regioisomeric product.

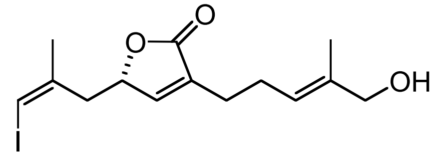
R_f 0.32, 40% EtOAc/Hexanes. ^1H NMR (500 MHz): δ 9.80 (t, 1 H, J = 1 Hz), 7.15 (q, 1 H, J = 1.5 Hz), 6.13 (d, 1 H, J = 1.5 Hz), 5.06 (m, 1 H), 2.79 (m, 2 H), 2.65 (m, 3 H), 2.55 (dd, 1 H, J = 13.5, 7.5 Hz), 1.99 (d, 3 H, J = 1.5 Hz). ^{13}C (125 MHz): δ 200.3, 172.9, 148.7, 142.2, 132.6, 79.5, 78.7, 42.3, 41.1, 24.8, 18.0. IR: 2908, 1752, 1725, 1062. HRMS $(EI)^+$ calcd for $C_{11}H_{13}O_3I$ $(M)^+$ 319.9909, found 319.9905.



(E)-5-[(S)-5-((Z)-3-Iodo-2-methyl-allyl)-2-oxo-2,5-dihydro-furan-3-yl]-2-methyl-pent-2-enal (15). To a solution of **13** (560 mg, 1.75 mmol) in PhH (8.7 mL) was added **14** (1.11 g, 3.50 mmol). After heating at reflux for 12 h, additional **14** (835 mg, 2.62

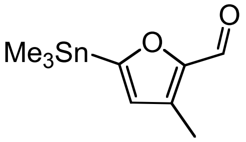
mmol) was added. After heating at reflux for 5 h, the dark solution was cooled to rt. A saturated solution of NH_4Cl (10 mL) and Et_2O (10 mL) were added. The layers were separated, and the aqueous was extracted 1 x Et_2O (15 mL). The organics were dried, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (35-40% EtOAc/hexanes) to give 450 mg (71%) of **15** as a light red oil.

R_f 0.54, 50% EtOAc/Hexanes. ^1H NMR (500 MHz): δ 9.41 (s, 1 H), 7.15 (d, 1 H, $J = 1$ Hz), 6.45 (t, 1 H, $J = 7$ Hz), 6.12 (d, 1 H, $J = 1$ Hz), 5.09 (m, 1 H), 2.66 (m, 3 H), 2.56 (m, 3 H), 1.98 (d, 3 H, $J = 1$ Hz), 1.76 (s, 3 H). ^{13}C (125 MHz): δ 194.9, 172.9, 151.7, 148.2, 142.2, 140.4, 133.1, 79.5, 78.8, 42.3, 26.6, 24.8, 24.2, 9.4. IR: 2945, 2917, 1754, 1682, 1061. HRMS (EI)$^+$ calcd for $C_{14}H_{17}O_3I$ $(M)^+$ 360.0222, found 360.0220.



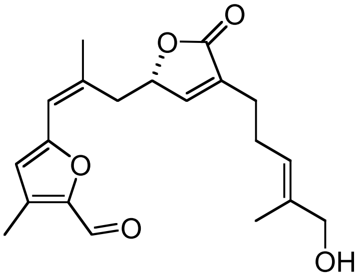
(S)-3-((E)-5-Hydroxy-4-methyl-pent-3-enyl)-5-((Z)-3-iodo-2-methyl-allyl)-5*H*-furan-2-one (16). To a solution of **15** (225 mg, 0.625 mmol) in MeOH (6.2 mL) was added sodium borohydride (26.0 mg, 0.687 mmol). After 20 min, a saturated NH_4Cl solution (5 mL) was added carefully followed by Et_2O (5 mL). The layers were separated, and the aqueous was extracted 1 x Et_2O (10 mL). The organics were dried, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (50% EtOAc/hexanes) to give 224 mg (99%) of **16** as a colorless oil.

R_f 0.30, 50% EtOAc/Hexanes. ^1H NMR (500 MHz): δ 7.10 (d, 1 H, $J = 1.5$ Hz), 6.11 (d, 1 H, $J = 1.5$ Hz), 5.40 (m, 1 H), 5.05 (ddd, 1 H, $J = 7.5, 6.5, 1.5$ Hz), 4.00 (s, 2 H), 2.66 (dd, 1 H, $J = 13.5, 6.5$ Hz), 2.54 (dd, 1 H, $J = 13.5, 6.5$ Hz), 2.35 (m, 4 H), 1.98 (d, 3 H, $J = 1.5$ Hz), 1.66 (s, 3 H), 1.54 (br s, 1 H). ^{13}C (125 MHz): δ 173.4, 147.7, 142.4, 136.3, 134.0, 123.9, 79.4, 78.5, 68.5, 42.4, 25.4, 25.1, 24.8, 13.8. IR: 3356, 2917, 2859, 1749, 1060. HRMS (EI)$^+$ calcd for $C_{14}H_{19}O_3I$ $(M)^+$ 362.0379, found 362.0386.



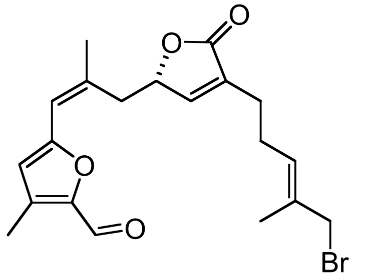
3-Methyl-5-trimethylstannanyl-furan-2-carbaldehyde (19). To a suspension of *N,O*-dimethylhydroxylamine hydrochloride (3.09 g, 31.1 mmol) in THF (155 mL) at −40 °C was added *n*-butyllithium (2.50 M in hexanes, 24.9 mL, 62.2 mmol) over 15 min while keeping the temperature below −40 °C. After 30 min, **17** (2.74 g, 24.9 mmol) in THF (22 mL) was added dropwise over 10 min. After 45 min, *n*-butyllithium (2.50 M in hexanes, 14.9 mL, 37.3 mmol) was added dropwise over 15 min, then stirred at −40 °C for 1 h. A solution of Me_3SnCl (1.0 M in THF, 29.9 mL, 29.9 mmol) was added over 5 min. The solution was allowed to warm to −10 °C over 30 min. A saturated solution of NH_4Cl (150 mL) was added. The layers were separated, and the aqueous was extracted 1 x Et_2O (100 mL). The organics were dried, filtered, and concentrated *in vacuo*. The crude oil was left under high vacuum for 12 h to remove residual Me_3SnCl and then used without further purification as a red/yellow oil, 5.77 g (85%) of **19**.

R_f 0.50, 10% EtOAc/Hexanes. ^1H NMR (500 MHz): δ 9.75 (s, 1 H), 6.55 (s, 1 H), 2.35 (s, 3 H), 0.38 (s, 9 H). ^{13}C (125 MHz): δ 177.3, 170.1, 153.0, 134.7, 126.3, 10.1, −9.2. IR: 2923, 1675, 1580, 768. HRMS (EI)$^+$ calcd for $C_9H_{14}O_2Sn$ (M)$^+$ 274.0016, found 274.0015.



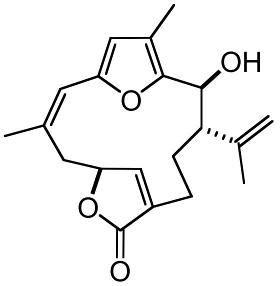
5-{(Z)-3-[(S)-4-((E)-5-Hydroxy-4-methyl-pent-3-enyl)-5-oxo-2,5-dihydro-furan-2-yl]-2-methyl-propenyl}-3-methyl-furan-2-carbaldehyde (20). To a solution of **16** (718 mg, 1.98 mmol) in DMF (13 mL) was added **19** (703 mg, 2.58 mmol) followed by $Pd(PPh_3)_4$ (91.6 mg, 0.0792 mmol), CuI (30.2 mg, 0.159 mmol), and CsF (602 mg, 3.96 mmol). After 20 min at rt, poured onto saturated NH_4Cl (20 mL) and Et_2O (20 mL). The layers were separated, and the aqueous washed extracted 1 x Et_2O (20 mL). The organics were then washed 1 x brine (25 mL). The organics were dried, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (65% EtOAc/hexanes) to give 627 mg (92%) of **20** as a yellow oil.

R_f 0.34, 60% EtOAc/Hexanes. ^1H NMR (500 MHz): δ 9.61 (s, 1 H), 7.33 (br s, 1 H), 6.18 (s, 1 H), 6.17 (s, 1 H), 5.40 (m, 1 H), 5.12 (m, 1 H), 3.99 (s, 2 H), 3.23 (d, 1 H, J = 13 Hz), 2.38 (m, 3 H), 2.36 (s, 3 H), 2.30 (m, 2 H), 2.05 (s, 3 H), 2.04 (s, 1 H), 1.65 (s, 1 H). ^{13}C (125 MHz): δ 175.5, 173.9, 157.0, 149.1, 147.4, 141.9, 136.7, 136.5, 133.4, 123.7, 115.4, 114.0, 81.5, 68.4, 38.2, 26.7, 25.3, 24.8, 13.7, 10.0. IR: 3443, 2923, 2854, 1751, 1658, 1499, 1064. HRMS (EI)$^+$ calcd for $C_{20}H_{24}O_5$ (M)$^+$ 344.1624, found 344.1630.



5-{(Z)-3-[(S)-4-((E)-5-Bromo-4-methyl-pent-3-enyl)-5-oxo-2,5-dihydro-furan-2-yl]-2-methyl-propenyl}-3-methyl-furan-2-carbaldehyde (21). To a solution of **20** (228 mg, 0.662 mmol) in CH_2Cl_2 (13 mL) at −5 °C was added PPh_3 (191 mg, 0.728 mmol) and *N*-bromosuccinimide (130 mg, 0.728 mmol). After 20 min, the solution was poured onto H_2O. The layers were separated, and the aqueous was extracted 1 x CH_2Cl_2. The organics were dried, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (35% EtOAc/hexanes) to give 233 mg (87%) of **21** as a light yellow oil.

R_f 0.49, 40% EtOAc/Hexanes. ^{1}H NMR (500 MHz): δ 9.64 (s, 1 H), 7.25 (br s, 1 H), 6.18 (s, 1 H), 6.17 (s, 1 H), 5.54 (t, 1 H, *J* = 7 Hz), 5.12 (m, 1 H), 3.93 (s, 2 H), 3.17 (d, 1 H, *J* = 13 Hz), 2.55 (m, 1 H), 2.36 (m, 2 H), 2.34 (s, 3 H), 2.29 (m, 2 H), 2.04 (s, 3 H), 1.73 (s, 3 H). ^{13}C (125 MHz): δ 175.6, 173.5, 156.7, 149.0, 147.5, 141.2, 135.9, 133.5, 133.1, 129.3, 115.6, 114.0, 81.2, 41.2, 38.2, 26.7, 26.0, 24.6, 14.7, 10.1. IR: 2924, 2848, 1754, 1663, 1499. HRMS (EI)$^+$ calcd for $C_{20}H_{23}O_4$ (M-Br)$^+$ 327.1596, found 327.1594.



Bipinnatin J (4). To a suspension of $CrCl_2$ (438 mg, 3.56 mmol), $NiCl_2$·DME (196 mg, 0.891 mmol), and 4 Å molecular sieves (1.49 g) in THF (55 mL) was added **19** (121 mg, 0.297 mmol) in THF (5 mL) via syringe pump over 1.5 h. After 12 h at rt, H_2O (20 mL) was added. The biphasic solution was filtered and concentrated to about 30 mL. The layers were separated, and the aqueous was extracted 1 x Et_2O (25 mL). The organics were dried, filtered, and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (30% EtOAc/hexanes) to give 57.9 mg (59%) as a white powder.

R_f 0.33, 30% EtOAc/Hexanes. HRMS (EI)$^+$ calcd for $C_{20}H_{24}O_5$ (M)$^+$ 328.1675, found 328.1674. mp 140-142 °C.

^{1}H NMR isolation	^{1}H NMR current	^{13}C NMR isolation	^{13}C NMR current
6.83 (br s, 1H)	6.84 (br s, 1H)	174.2	174.3
6.09 (br s, 1H)	6.10 (br s, 1H)	152.2	152.3
6.02 (s, 1H)	6.02 (s, 1H)	151.0	151.0
5.14 (br s, 1H)	5.15 (br s, 1H)	149.3	149.2
5.03 (br s, 1H)	5.05 (s, 1H)	142.2	142.1
4.96 (m, 1H)	4.98 (m, 1H)	132.6	132.5
4.49 (br d, 1H, *J* = 10.8 Hz)	4.50 (br d, 1H, *J* = 11 Hz)	128.9	129.0
3.18 (dd, 1H, *J* = 12.0, 11.7 Hz)	3.19 (t, 1H, *J* = 12 Hz)	121.0	121.1
2.71 (dd, 1H, *J* = 12.0, 4.5 Hz)	2.72 (dd, 1H, *J* = 12, 4.5 Hz)	118.4	118.7
2.38 (ddd, 1H, *J* = 14.2, 14.2, 3.0 Hz)	2.40 (dd, 1H, *J* = 14.5, 3.0 Hz)	117.3	117.3
2.35 (dd, 1H, *J* = 10.8, 10.8 Hz)	2.36 (t, 1 H, *J* = 11 Hz)	113.8	113.8
2.07 (m, 1H)	2.07 (m, 1H)	78.6	78.6
2.03 (s, 3H)	2.04 (s, 3H)	65.0	64.9
1.98 (br s, 3H)	1.99 (br s, 3H)	51.1	51.1
1.92 (br s (OH), 1H)	1.89 (br s (OH), 1H)	39.7	39.7
1.78 (br s, 3H)	1.79 (br s, 3H)	30.1	30.0
1.65 (dddd, 1H, *J* = 13.8, 10.8, 3.3, 3.3 Hz)	1.66 (m, 1H)	25.7	25.8
0.88 (ddd, 1H, *J* = 13.8, 13.8, 3.3 Hz)	0.89 (td, 1H, *J* = 13.5, 3.5 Hz)	19.6	19.6
		17.6	17.5
		9.4	9.5

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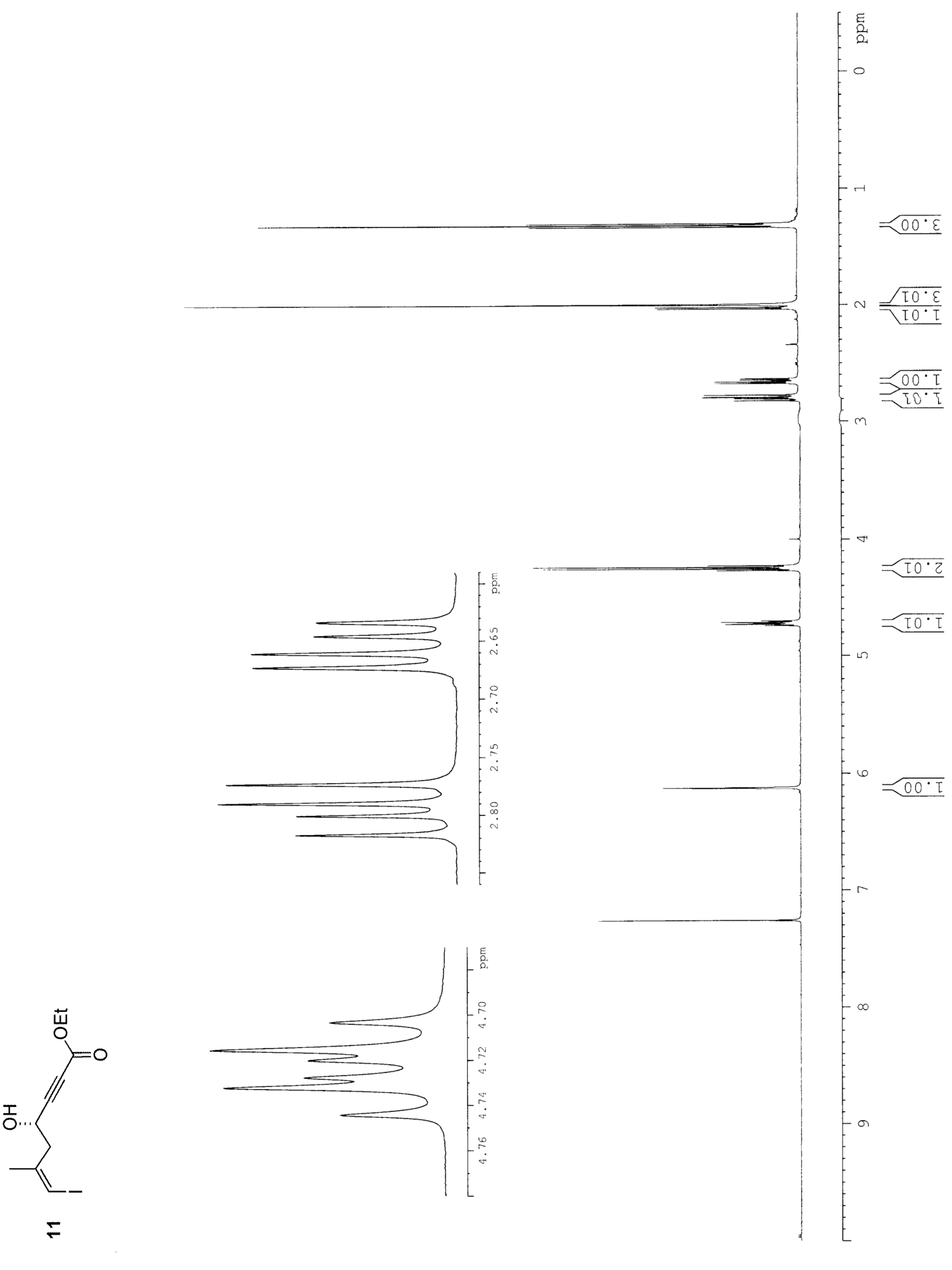
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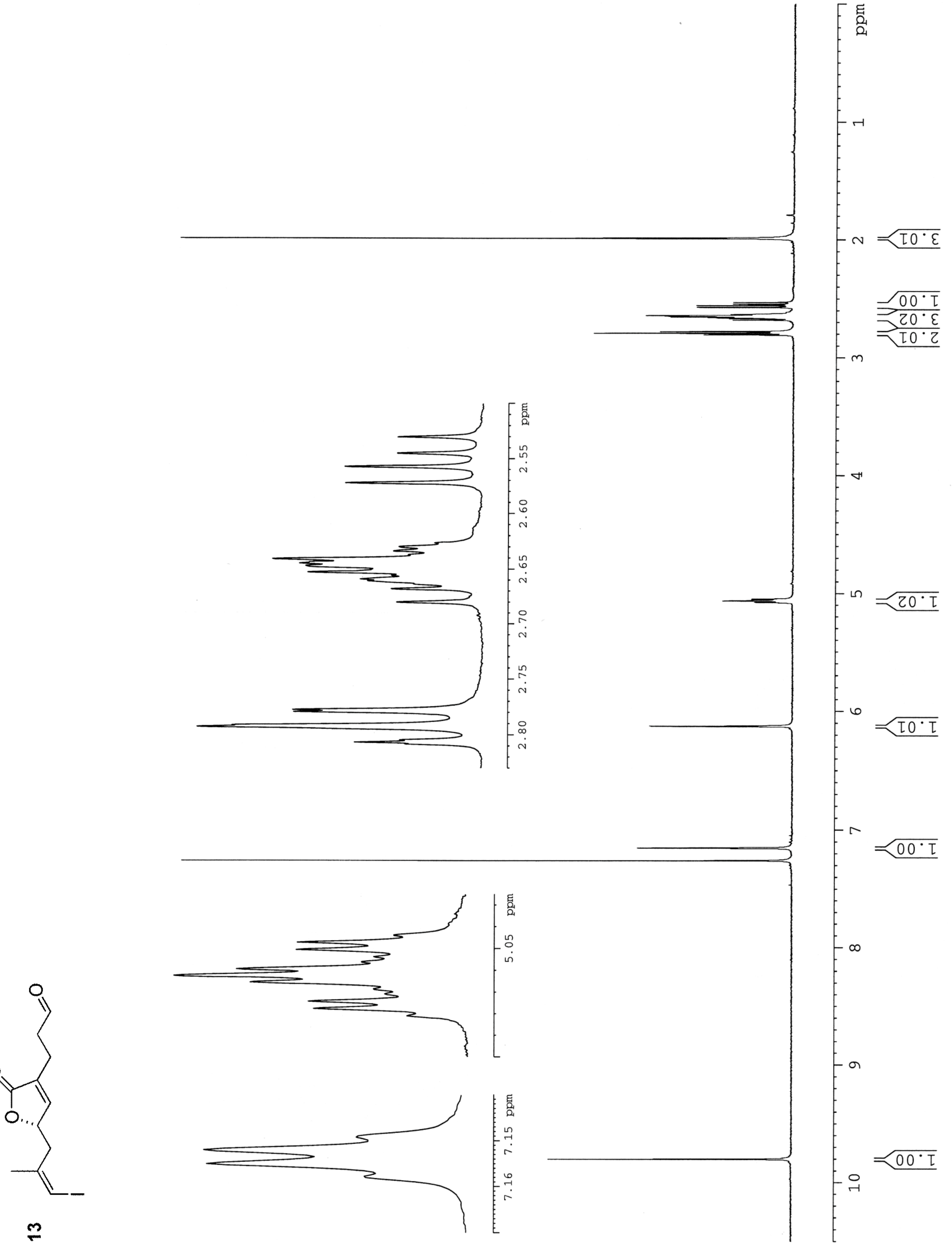

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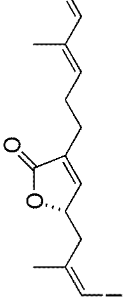

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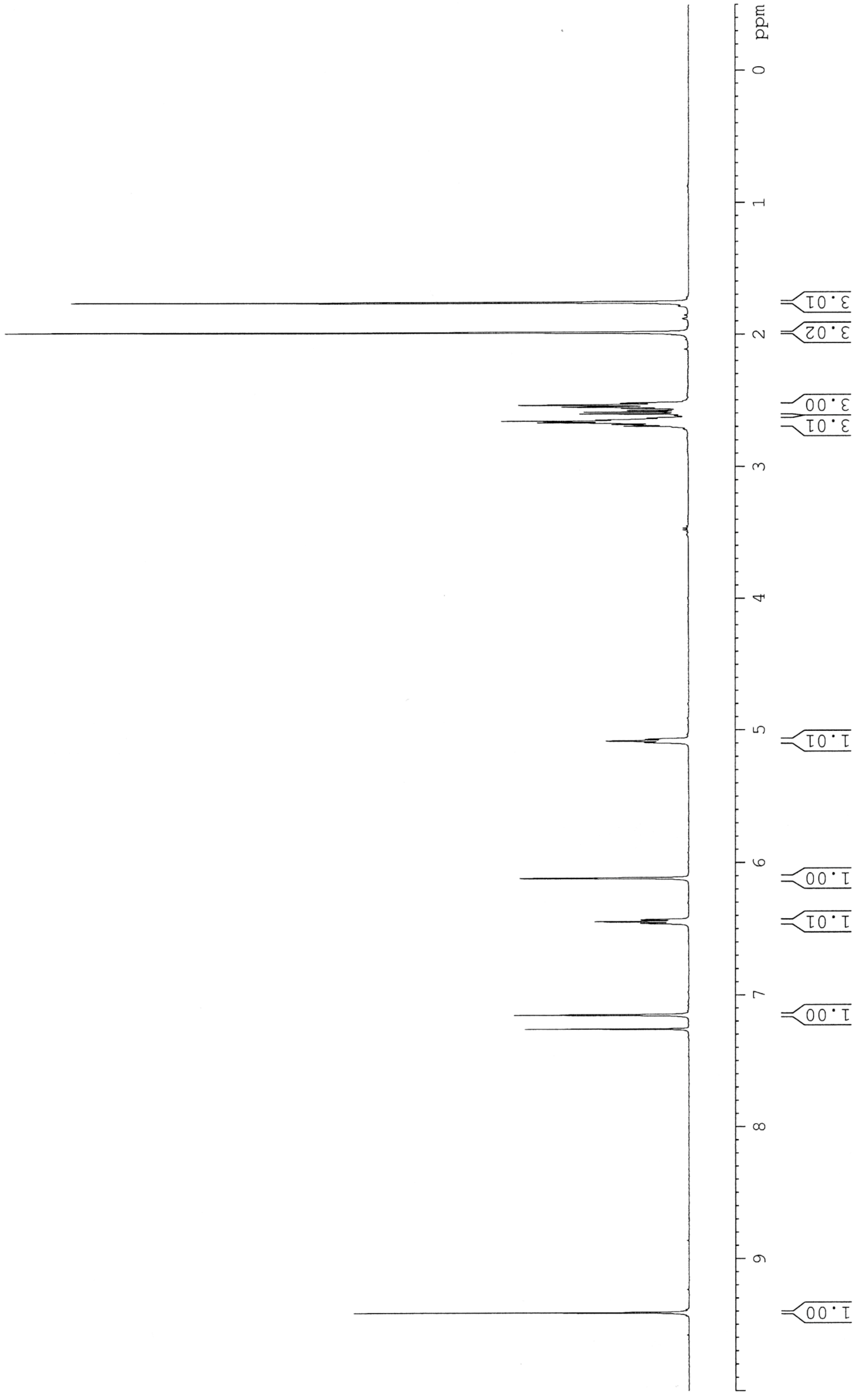

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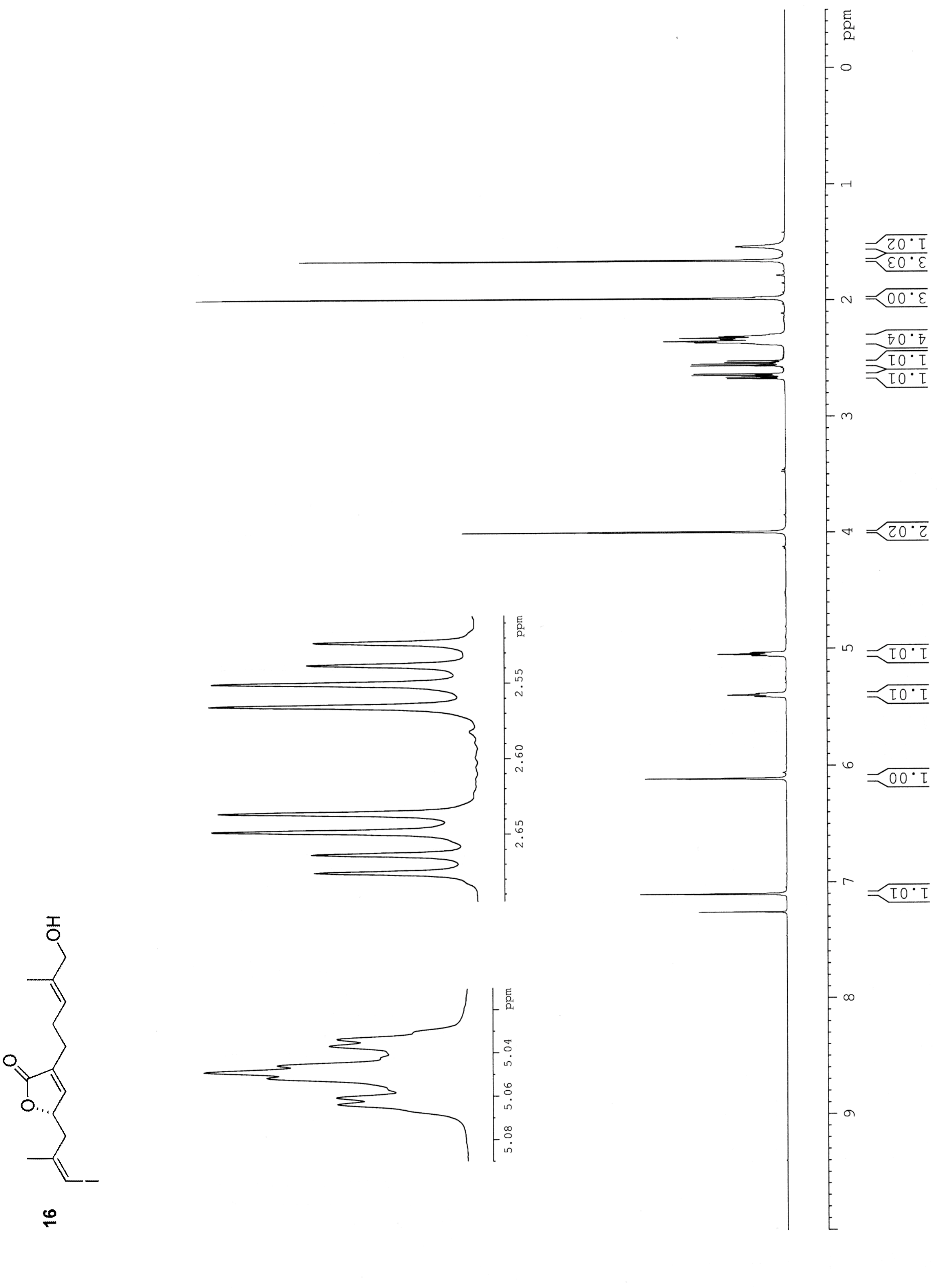
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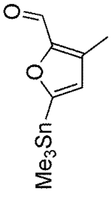

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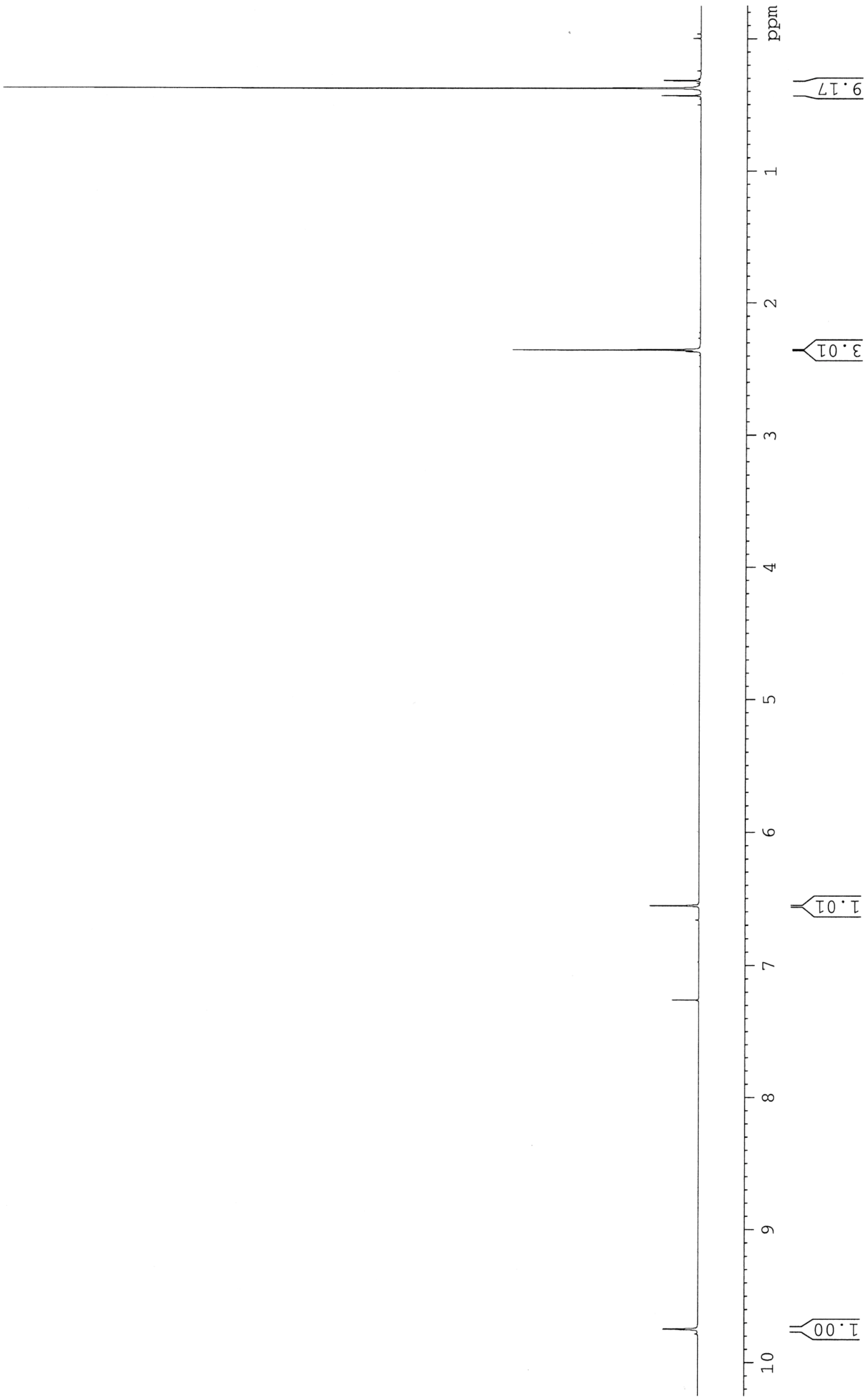

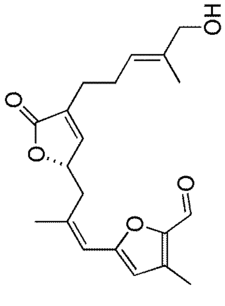

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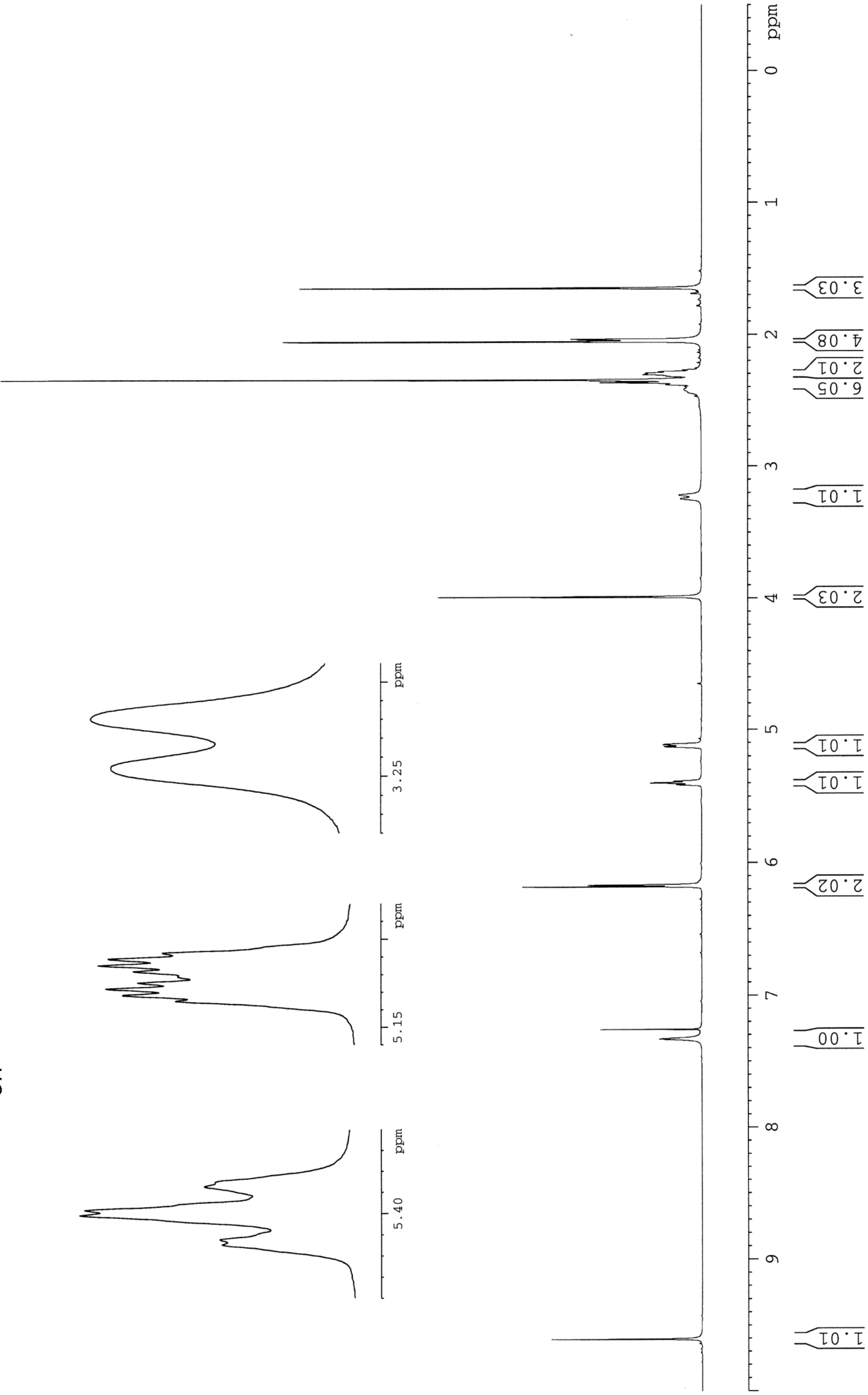

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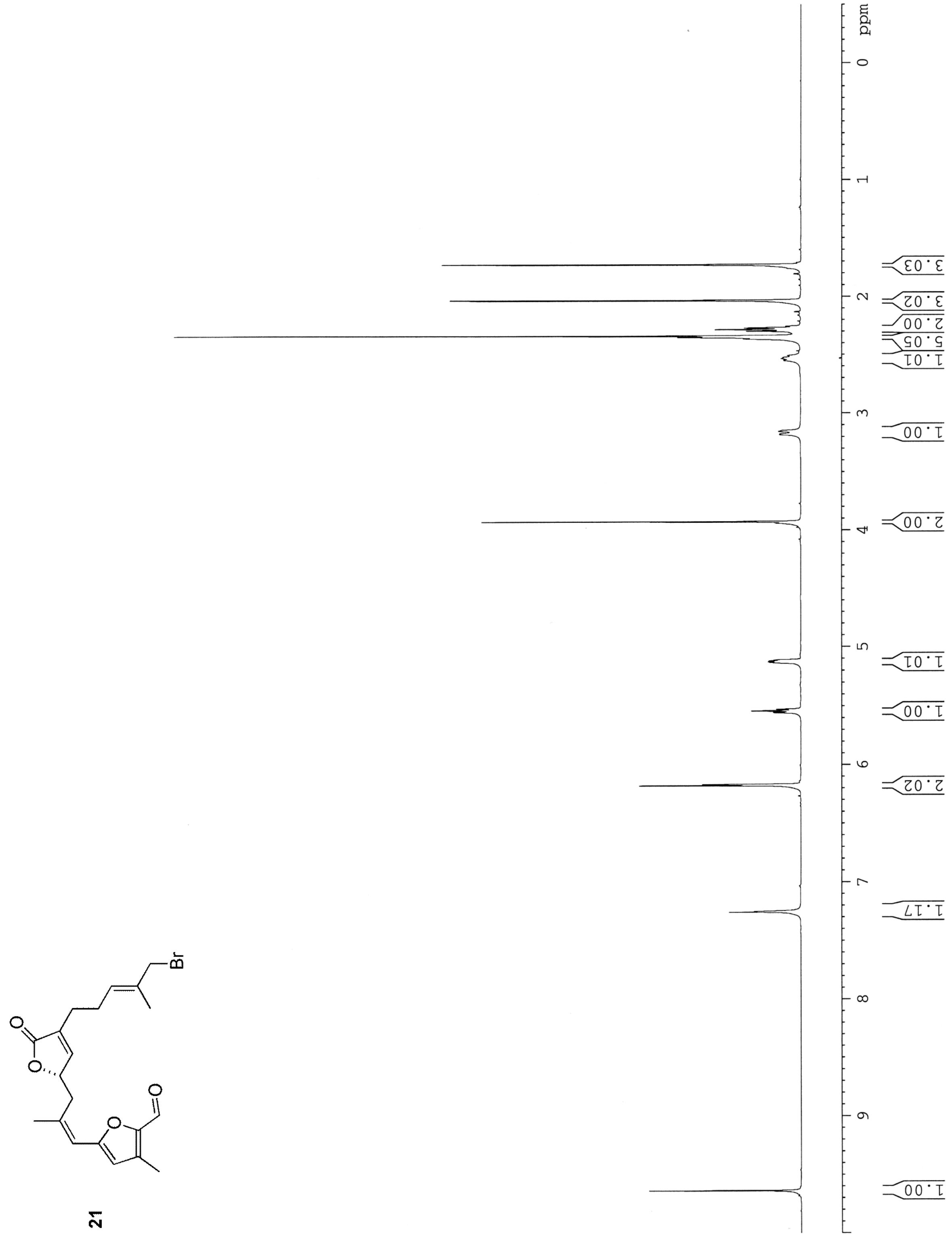
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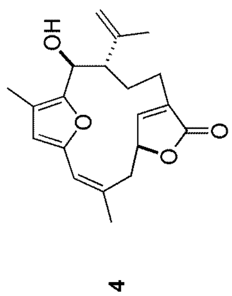
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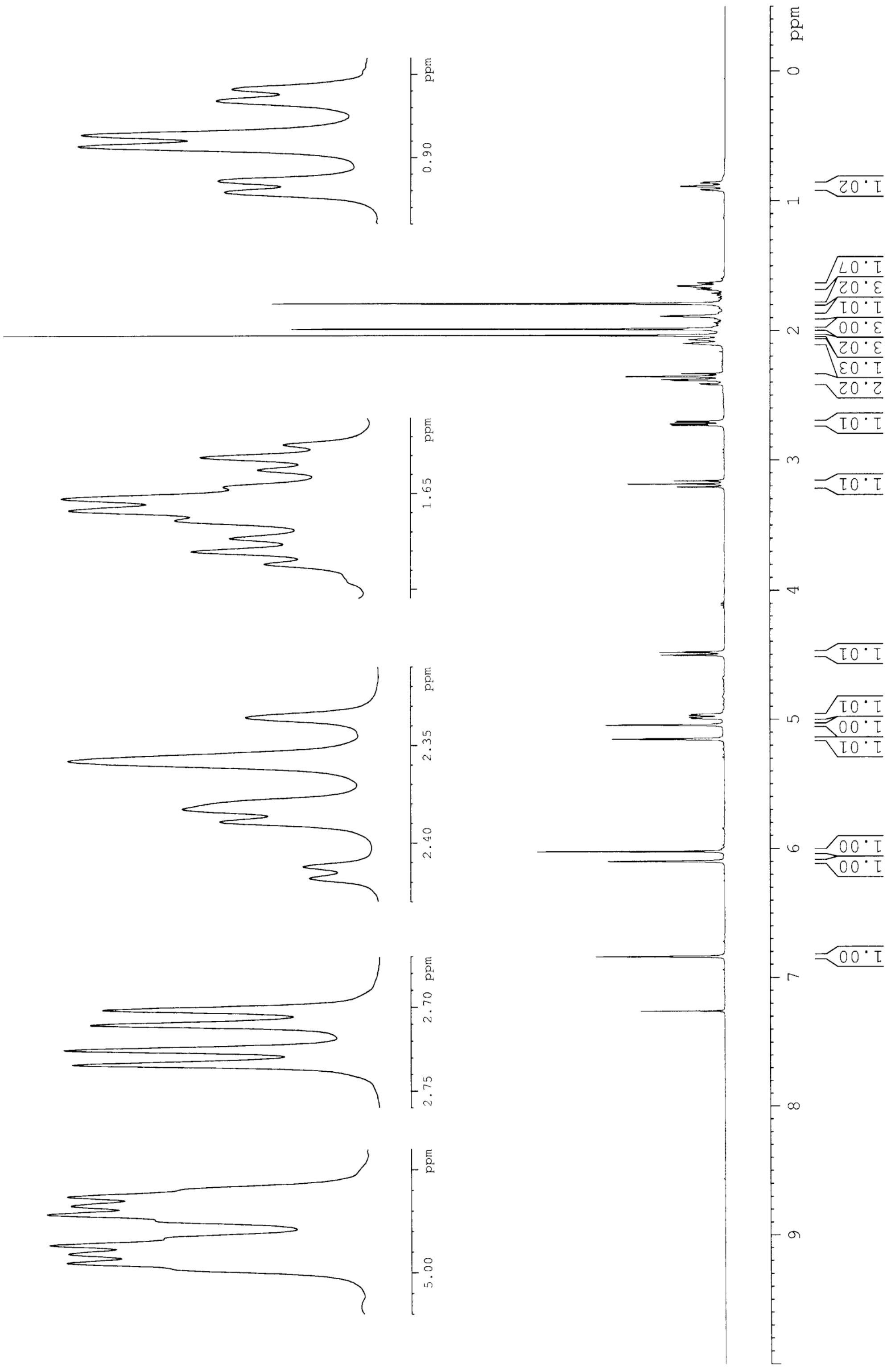
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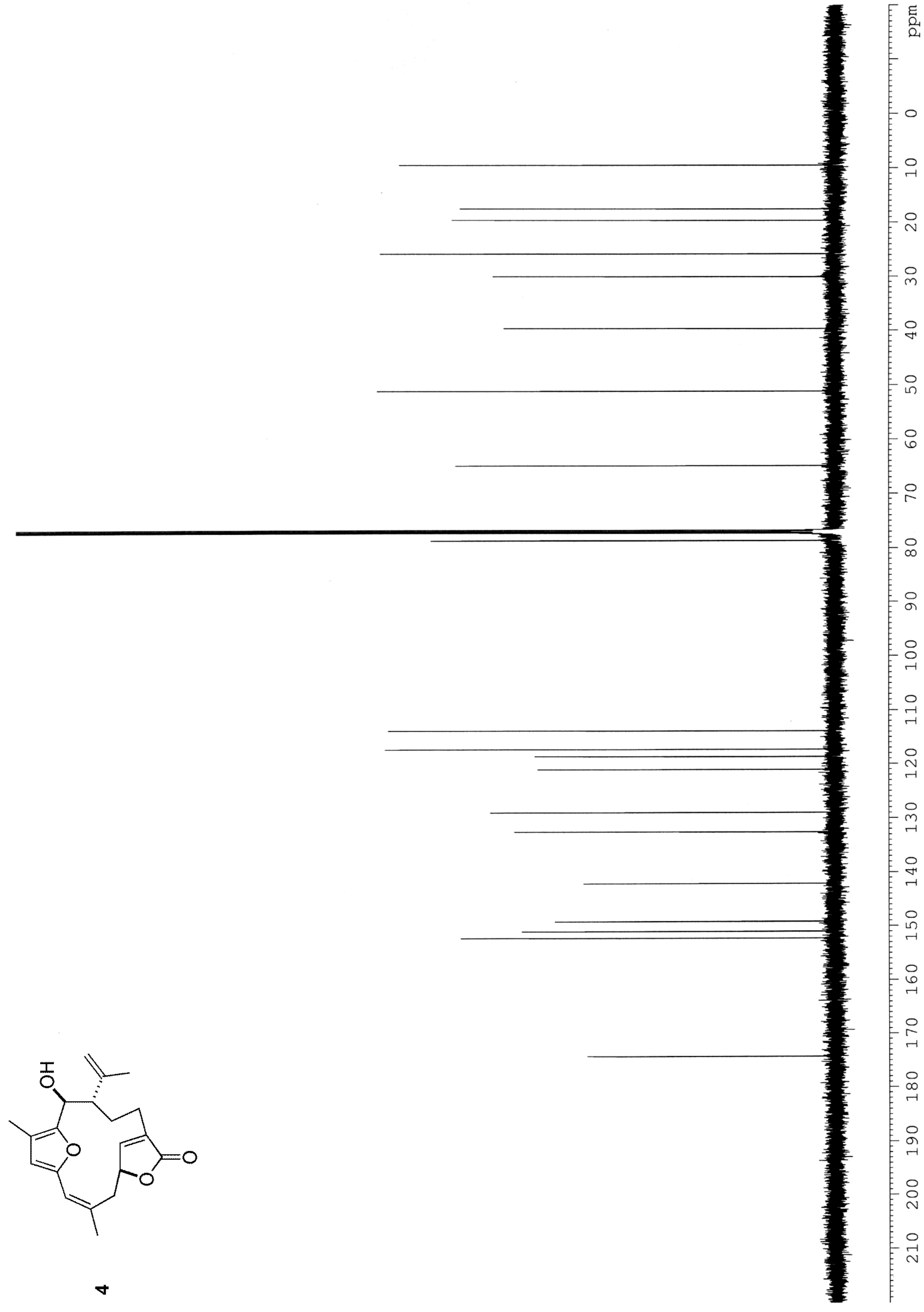
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4