Supplementary data

Synthesis and biological evaluation of caulibugulones A-E

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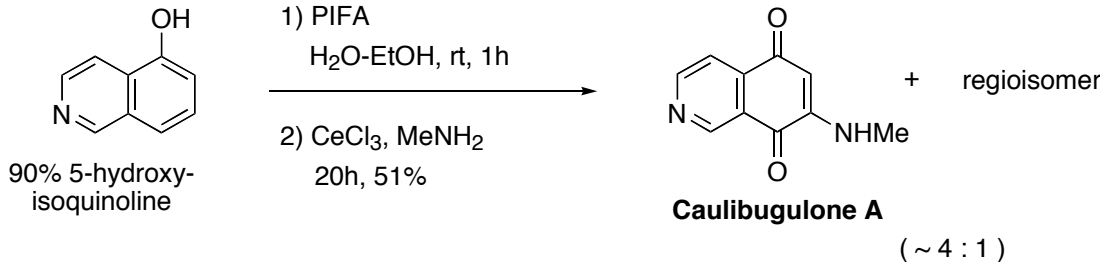
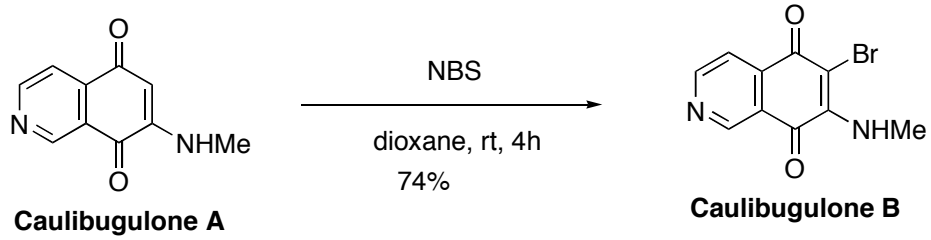
General Methods. CH_2Cl_2 was dried by distillation over CaH_2. Unless otherwise stated, all commercially available materials were used without purification. IR spectra were recorded neat by adding a drop of a solution of the sample onto the surface of a NaCl cell, followed by drying in air. NMR spectra were obtained at 300MHz/75MHz ($^1H/^{13}C$ NMR). High and low resolution masses were determined by introduction with a direct insertion probe into a VG- 70-70 HF spectrometer operating in the electron ionization (EI) mode.



Caulibugulone A (1). To a solution of 5-hydroxyisoquinoline (90%, 0.80 g, 5.0 mmol) in EtOH/H_2O (20 mL/2 mL) was added PIFA (4.28 g, 12.0 mmol) at room temperature. The

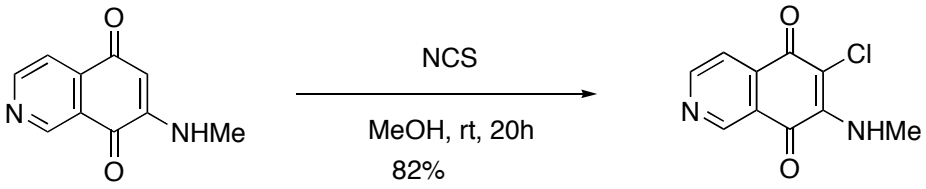
reaction mixture was stirred for 1 h, treated with $CeCl_3$ (2.4 g, 10 mmol) and methylamine (2.0 M in MeOH, 20 mL, 40 mmol) at room temperature, stirred for 20 h and concentrated under reduced pressure. The crude residue was diluted with EtOAc (250 mL) and washed with brine (100 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (Hexanes/EtOAc = 1:1) to give a mixture of caulibugulone A and its regioisomer (0.48 g, 51%, ~4:1 ratio by ^1H NMR). Further separation by chromatography on SiO_2 (CH_2Cl_2/MeOH = 200:1 → 100:1) gave **1** as a red solid: Mp. 228-230 °C (dec.); IR (neat) 3263, 1685, 1598, 1501, 1419, 1173, 1075, 830 cm^{-1}; ^1H NMR ($CDCl_3/CD_3OD$ = 1:1) δ 9.14 (s, 1 H), 8.92 (d, 1 H, *J* = 4.5 Hz), 7.91 (d, 1 H, *J* = 4.5 Hz), 5.76 (s, 1 H), 2.92 (s, 3 H); ^{13}C NMR ($CDCl_3/CD_3OD$ = 1:1) δ 181.4 (2C), 156.1, 150.7, 147.8, 140.7, 125.6, 120.0, 100.6, 29.3; MS (EI) *m/z* (relative intensity) 188 (M^+, 100), 173 (30), 159 (14), 131 (20), 105 (21), 82 (64); HRMS (EI) *m/z* calcd for $C_{10}H_8N_2O_2$ 188.0586, found 188.0583.



Caulibugulone A **Caulibugulone B**

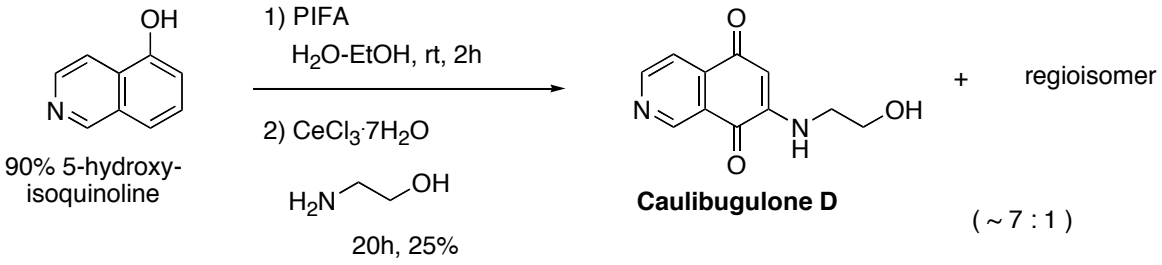
Caulibugulone B (2). To a solution of **1** (30 mg, 0.16 mmol) in dioxane (4 mL) was added NBS (29 mg, 0.16 mmol) in dioxane (1 mL) at room temperature. The reaction mixture was stirred for 4 h and concentrated under reduced pressure. The crude residue was directly purified by chromatography on SiO_2 (CH_2Cl_2 → CH_2Cl_2/MeOH = 50:1) to give **2** (32 mg, 74%) as a dark red solid: Mp. 182-184 °C (dec.); IR (neat) 3278, 1690,

1583, 1542, 1419, 1291 cm^{-1}; ^1H NMR (pyridine-d_5) 9.36 (s, 1 H), 9.00 (d, 1 H, *J* = 5.0 Hz), 8.20 (bs, 1 H, -N*H*), 7.98 (d, 1 H, *J* = 4.9 Hz), 3.39 (d, 3 H, *J* = 5.7 Hz); ^{13}C NMR (pyridine-d_5) 180.1 (2C), 156.1, 148.4 (2C), 138.2, 119.2, 33.0 (2 carbons are buried in solvent peaks); MS (EI) *m/z* (relative intensity) 266 (M^+, 100), 187 (49), 160 (39), 82 (23); HRMS (EI) *m/z* calcd for $C_{10}H_7BrN_2O_2$ 265.9691, found 265.9695.

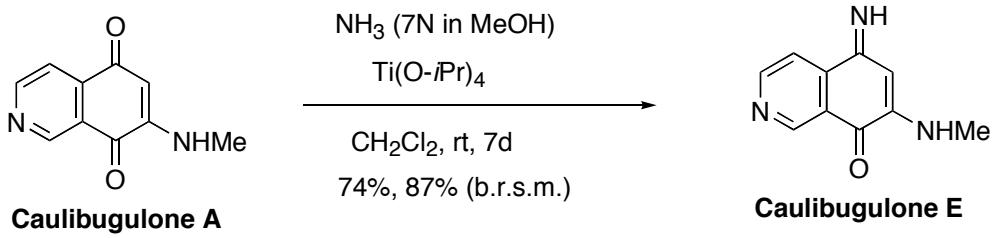


Caulibugulone A **Caulibugulone C**

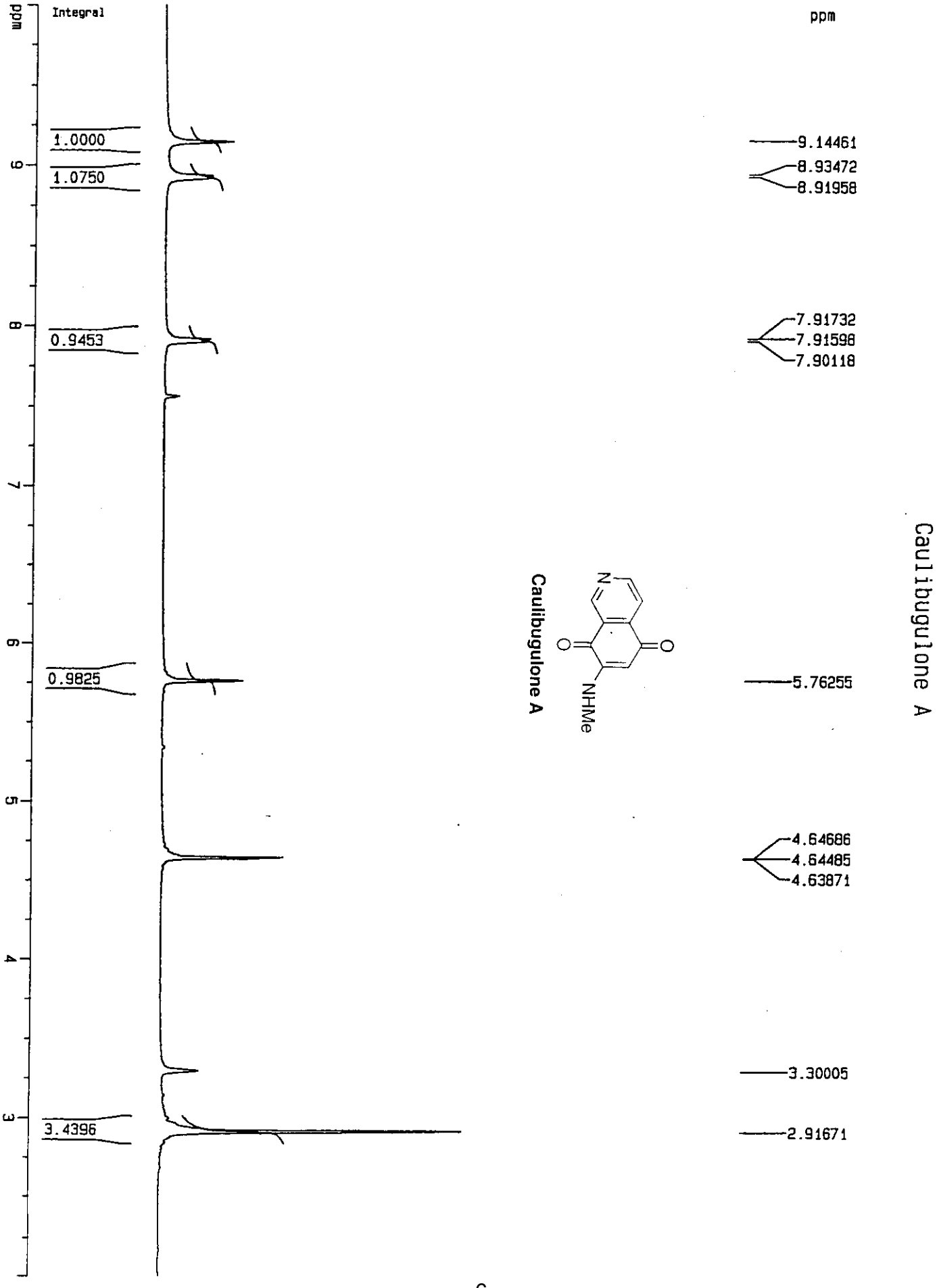
Caulibugulone C (3). To a solution of **1** (9.4 mg, 0.050 mmol) in MeOH (5 mL) was added NCS (6.7 mg, 0.050 mmol) at room temperature. The reaction mixture was stirred for 20 h and concentrated under reduced pressure. The crude residue was directly purified by chromatography on SiO_2 (Hexanes/EtOAc = 1:1) to give **3** (9.1 mg, 82%) as a dark red solid: Mp. 219-221 °C (dec.); IR (neat) 3274, 1689, 1588, 1563, 1417, 1316 cm^{-1}; ^1H NMR (pyridine-d_5) 9.35 (s, 1 H), 9.01 (d, 1 H, *J* = 5.0 Hz), 8.35 (bs, 1 H, -N*H*), 7.98 (d, 1 H, *J* = 5.0 Hz), 3.38 (d, 3 H, *J* = 5.6 Hz); ^{13}C NMR (pyridine-d_5) 180.5 (2C), 156.3, 148.4 (2C), 146.6, 138.6, 119.2, 32.5 (1 carbon is buried in solvent peaks); MS (EI) *m/z* (relative intensity) 222 (M^+, 100), 187 (51), 160 (35), 131 (25); HRMS (EI) *m/z* calcd for $C_{10}H_7ClN_2O_2$ 222.0196, found 222. 0194.



Caulibugulone D (4). To a solution of 5-hydroxyisoquinoline (90%, 200 mg, 1.25 mmol) in EtOH/H_2O (10 mL/1 mL) was added PIFA (1.07 g, 2.50 mmol) at room temperature. The reaction mixture was stirred for 2 h, treated with $CeCl_3 \bullet 7H_2O$ (930 mg, 2.50 mmol) and ethanolamine (0.60 mL, 10 mmol) at room temperature, stirred for 20 h, diluted with EtOAc (100 mL) and washed with brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO_2 (EtOAc → CH_2Cl_2/MeOH = 50:1 → 10:1) to give a mixture of caulibugulone D and its regioisomer (68 mg, 25%, ~7:1 ratio by ^{1}H NMR). Further separation by chromatography on SiO_2 (CH_2Cl_2/MeOH = 100:1) gave **4** as a dark orange solid: Mp. 189-191 °C (dec.); IR (neat) 3335, 3168, 2921, 2846, 1680, 1633, 1593, 1562, 1301, 1059 cm^{-1}; ^{1}H NMR ($CDCl_3$/CD_3OD = 1:1) δ 9.17 (s, 1 H), 8.94 (bd, 1 H, $J \approx 4.2$ Hz), 7.92 (d, 1 H, $J = 5.0$ Hz), 5.86 (s, 1 H), 3.78 (t, 2 H, $J = 5.4$ Hz), 3.35 (t, 2 H, $J = 5.4$ Hz); ^{13}C NMR ($CDCl_3$/CD_3OD = 1:1) δ 181.0, 180.5, 155.4, 149.2, 147.2, 140.0, 125.0, 119.3, 100.5, 59.0, 44.7; MS (EI) *m/z* (relative intensity) 218 (M^+, 22), 200 (23), 187 (100); HRMS (EI) *m/z* calcd for $C_{11}H_{10}N_2O_3$ 218.0691, found 218.0691.



Caulibugulone E (5). To a solution of **1** (230 mg, 1.22 mmol) in CH_2Cl_2 (25 mL) was added Ti(O-*i*Pr)$_4$ (1.7 mL, 6.1 mmol) and ammonia (7N in MeOH, 3.6 mL, 25 mmol) at room temperature. The reaction mixture was stirred for 7 d and directly purified by chromatography on SiO_2 (CH_2Cl_2/MeOH = 50:1 → 10:1) to give caulibugulone A (34 mg, 15%) and **5** (170 mg, 74%) as an orange solid: Mp. 228-230 °C (dec.); IR (neat) 3351, 3210, 1618, 1571, 1545, 1519, 1413, 1365, 1280, 1069 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 11.1 (bs, 1 H, =N*H*) 9.06 (s, 1 H), 8.89 (d, 1 H, *J* = 4.9 Hz), 8.00 (d, 1 H, *J* = 4.9 Hz), 6.80 (bs, 1 H, -N*H*), 5.78 (s, 1 H), 3.00 (d, 3 H, *J* = 5.3 Hz); ^{13}C NMR (DMSO-d_6) δ 179.5, 158.3, 153.5, 153.2, 147.1, 137.3, 123.8, 118.6, 98.4, 29.5; MS (EI) *m/z* (relative intensity) 187 (M^+, 100), 158 (29), 130 (57), 103 (28), 76 (29); HRMS (EI) *m/z* calcd for $C_{10}H_9N_3O$ 187.0746, found 187.0744.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7.90118
5.76255
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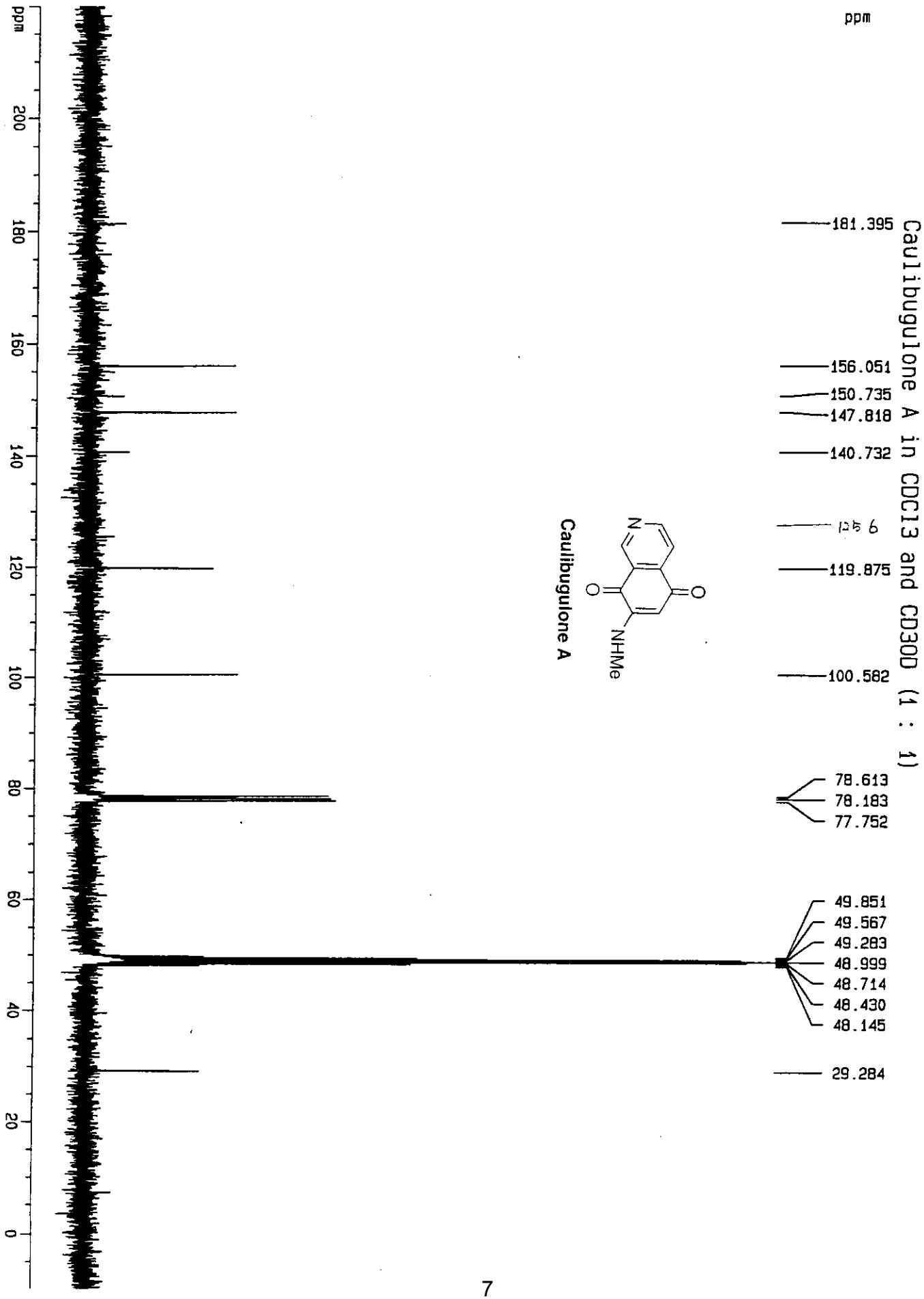
Caulibugulone A
N
O
O
NHMe
Caulibugulone A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78.183
77.752
49.851
49.567
49.283
48.999
48.714
48.430
48.145
29.284
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NHMe
O
O
N
ppm
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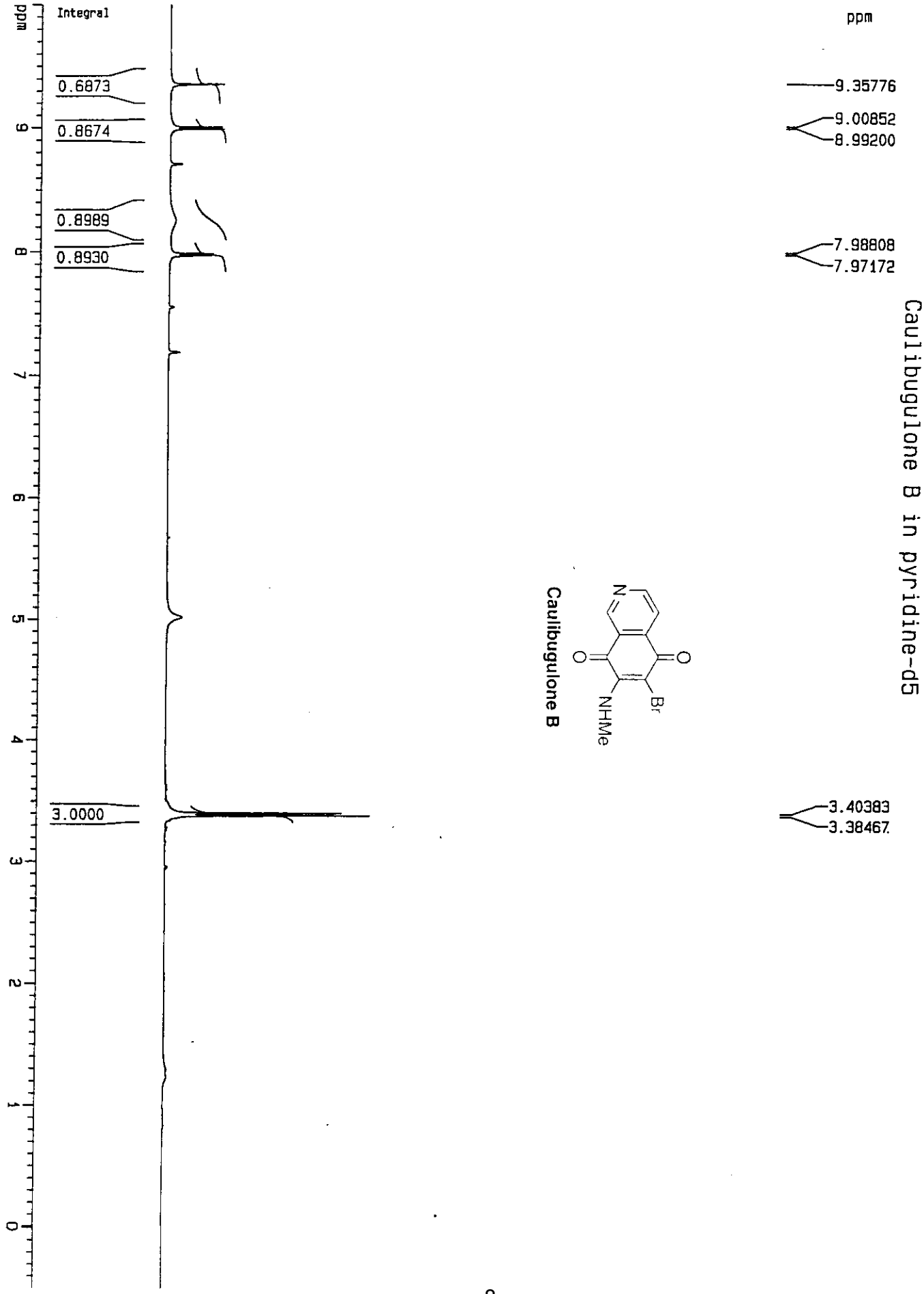
160
140
120
100
80
60
40
20
0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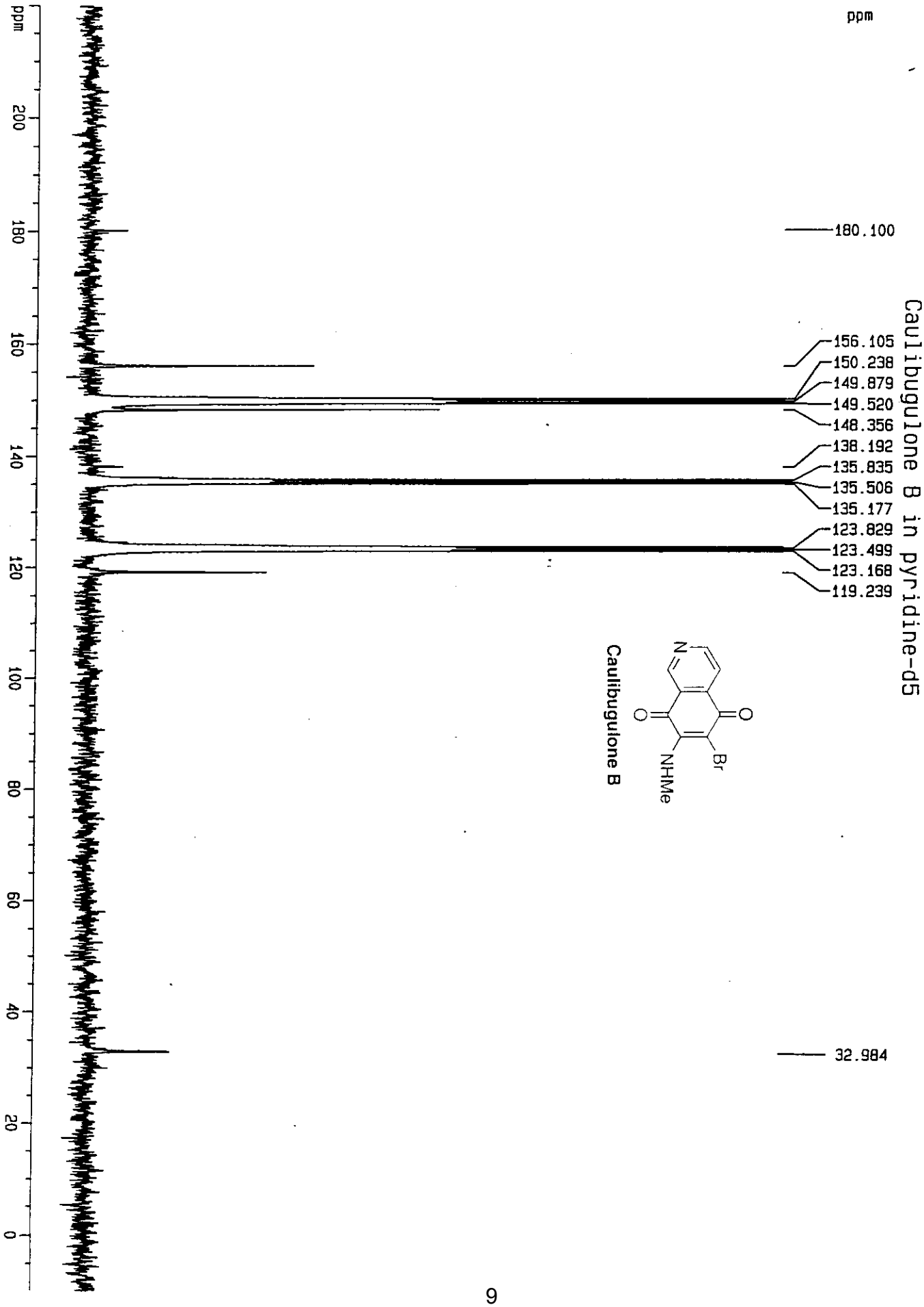
Br
NHMe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180
160
140
120
100
80
60
40
20
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ppm
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148.356
138.192
135.835
135.506
135.177
123.829
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119.239
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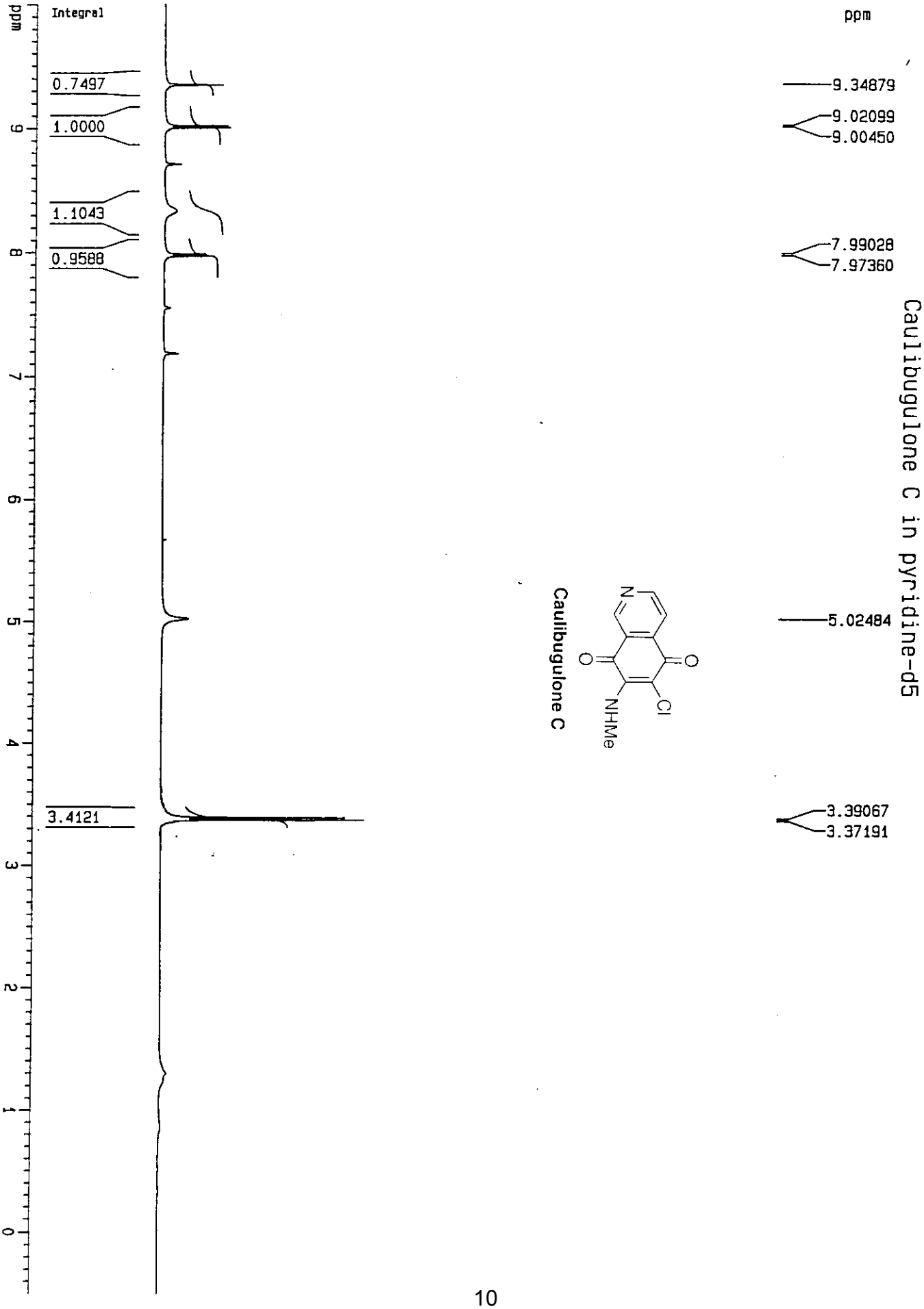
Caulibugulone B in pyridine-d5
Caulibugulone B
N
O
O
Br
NHMe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7.97360
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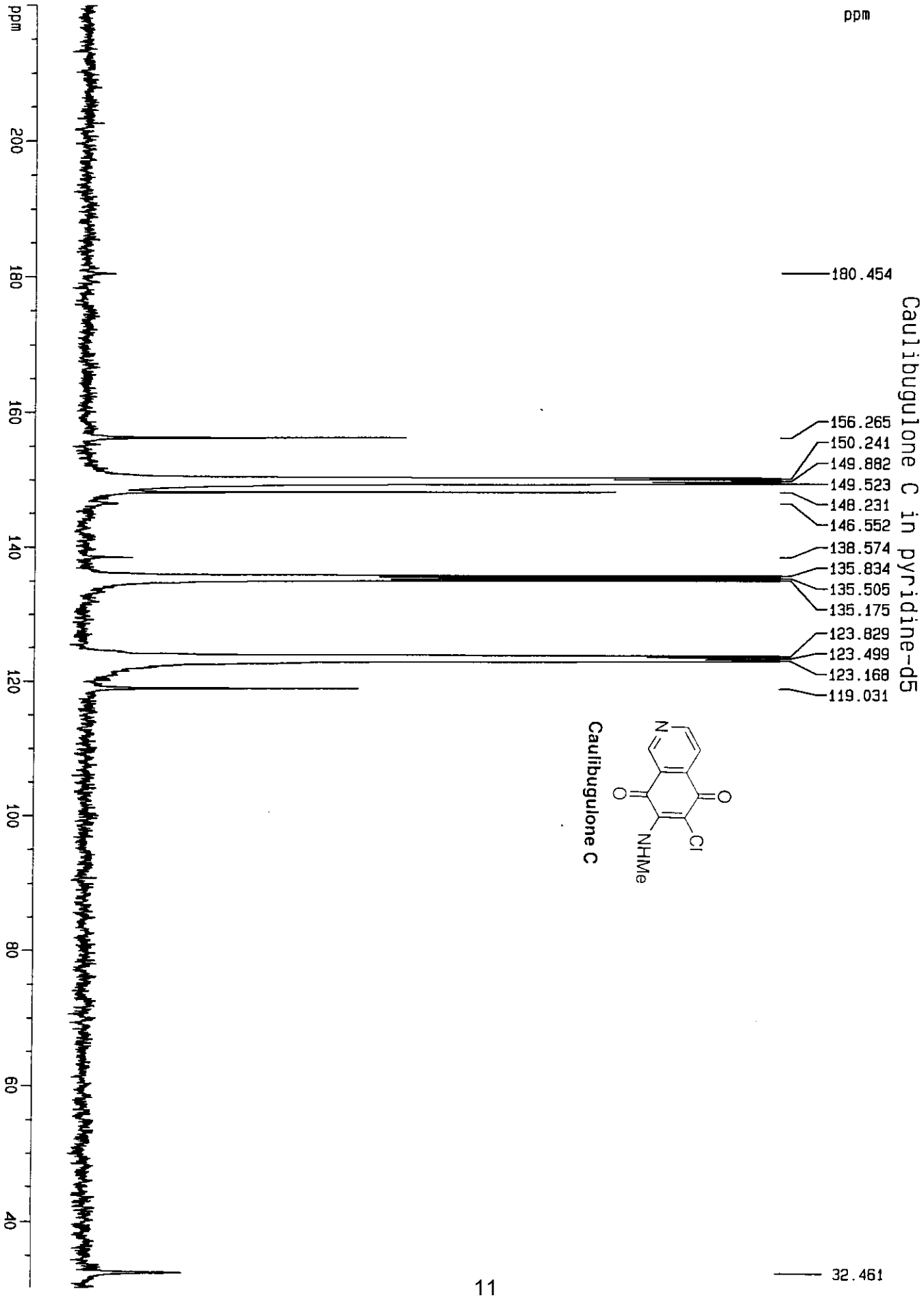
Caulibugulone C in pyridine-d5
Caulibugulone C
N
O
O
Cl
NHMe


ppm
200
180
160
140
120
100
80
60
40
ppm
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146.552
138.574
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135.175
123.829
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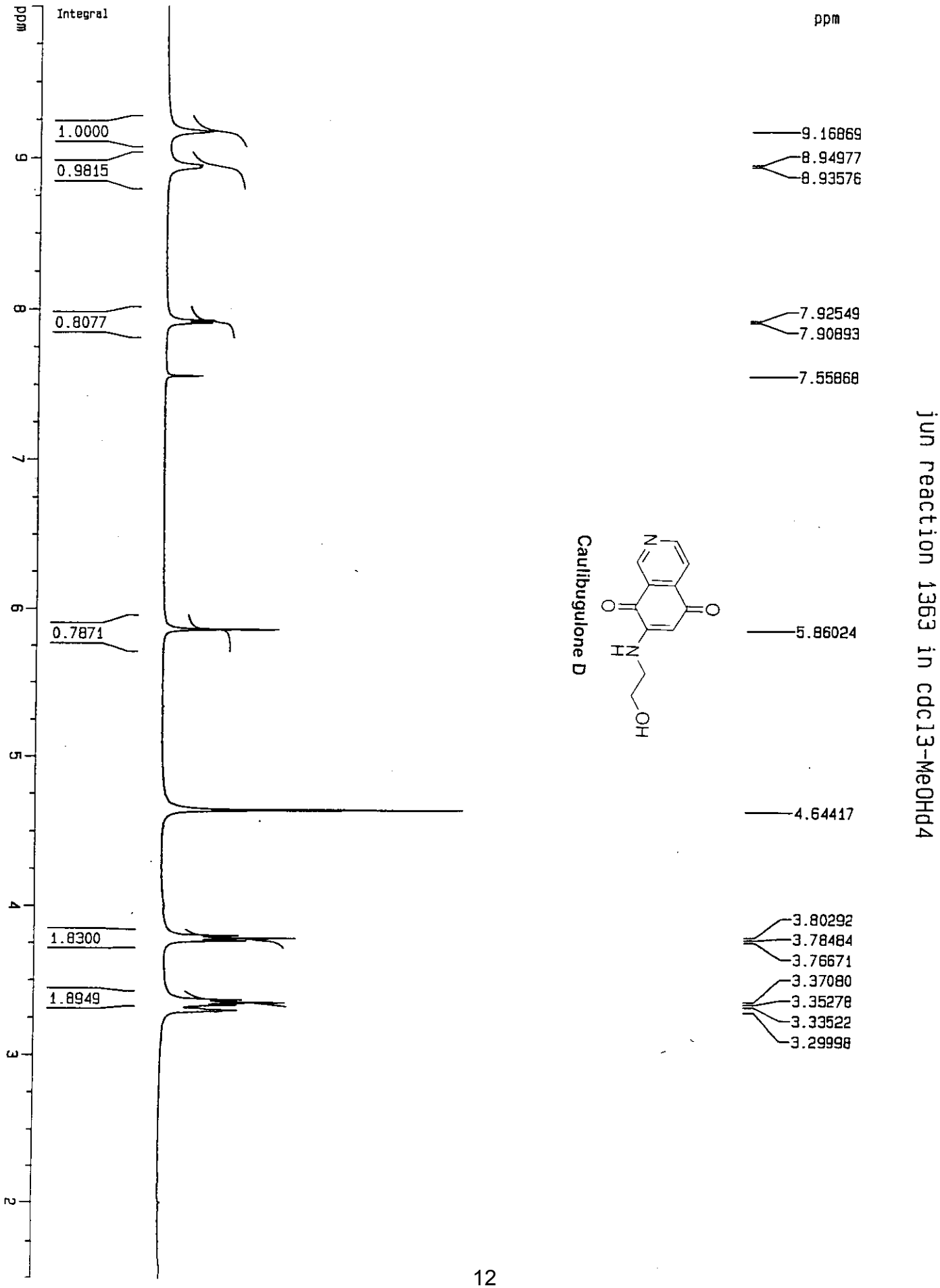
Caulibugulone C in pyridine-d5
N
O
O
Cl
NHMe
Caulibugulone C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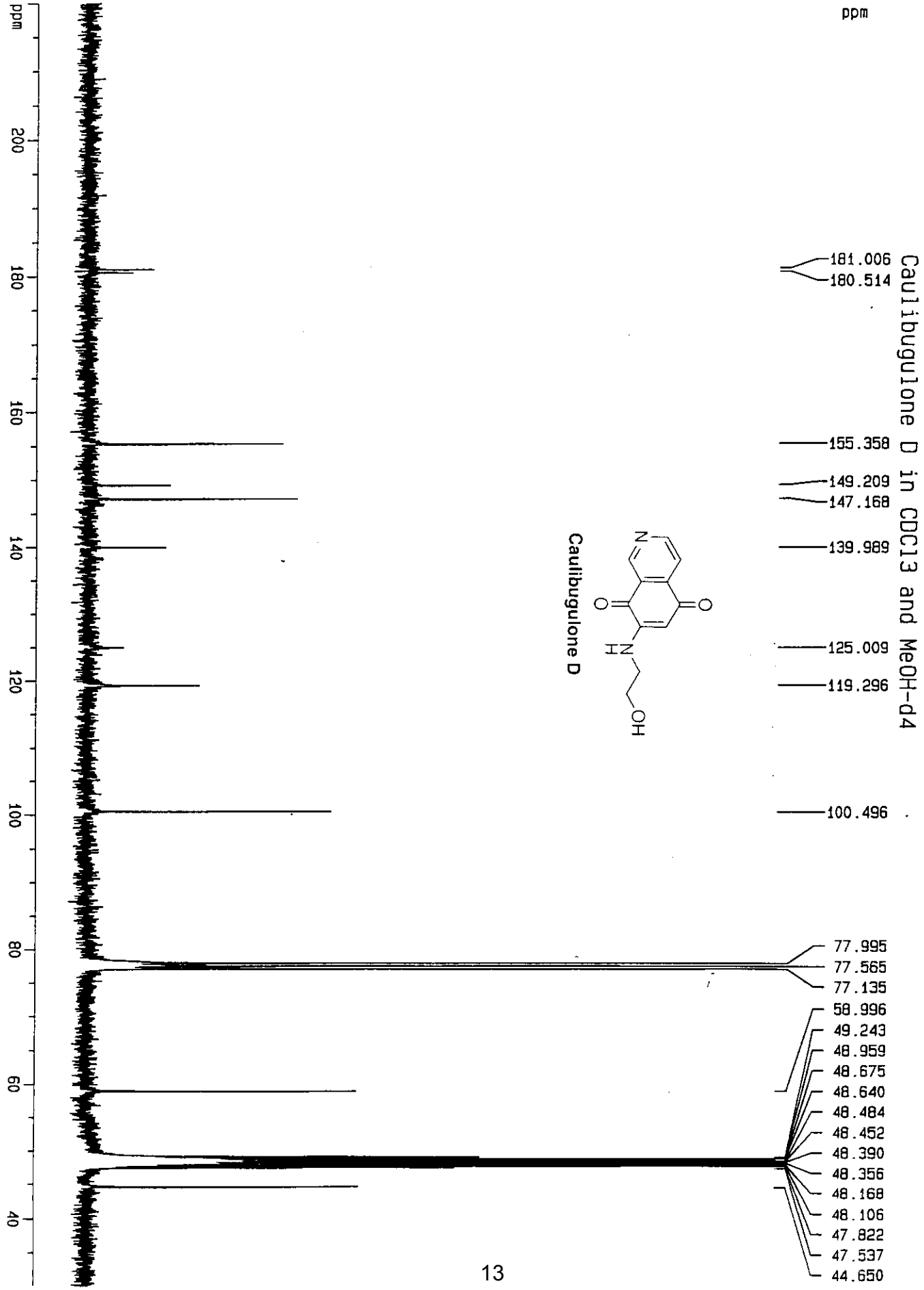
Caulibugulone D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147.168
139.989
125.009
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100.496
77.995
77.565
77.135
58.996
49.243
48.959
48.675
48.640
48.484
48.452
48.390
48.356
48.168
48.106
47.822
47.537
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60
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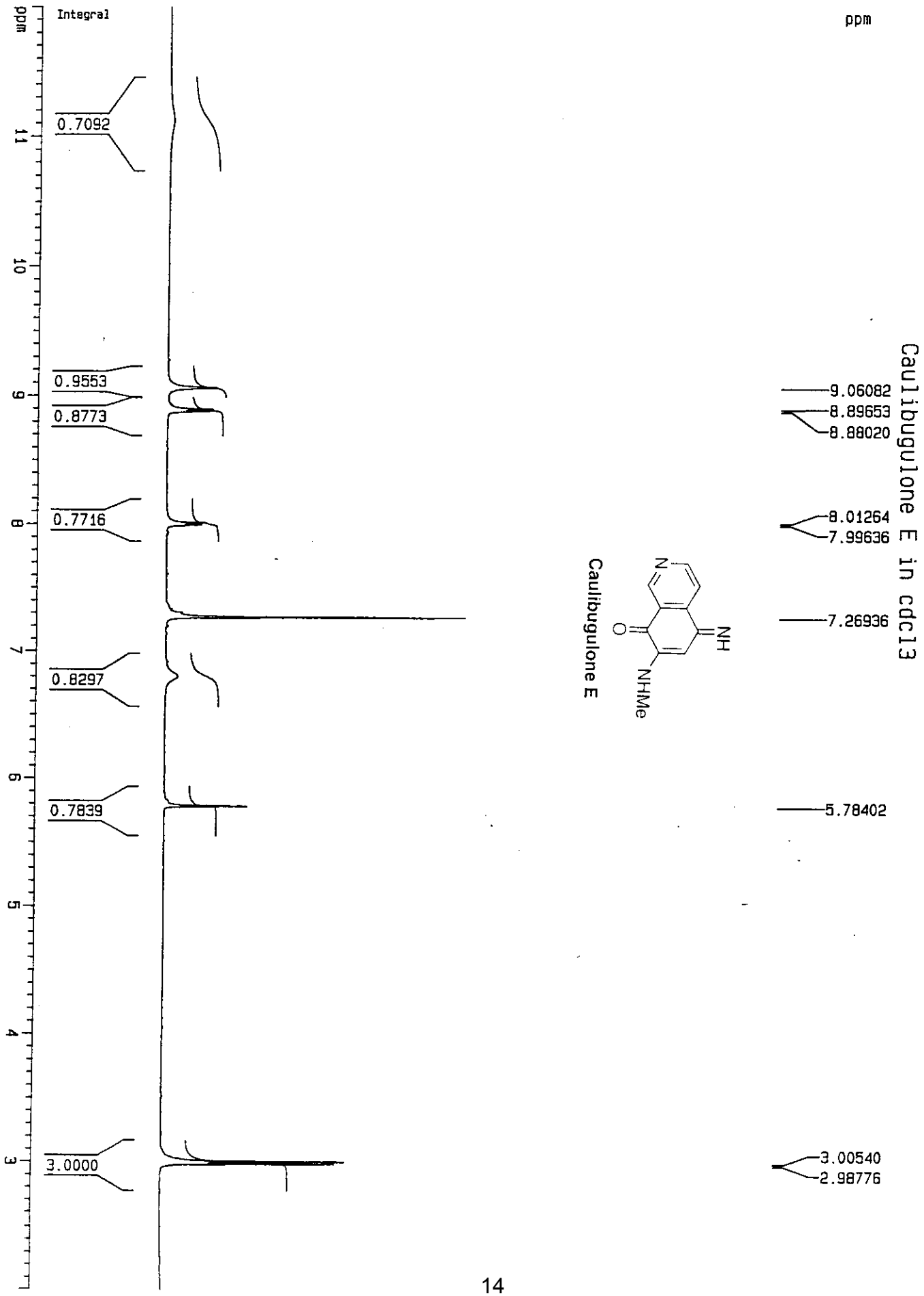
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7.99636
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3.00540
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Caulibugulone E in cdcl3
Caulibugulone E
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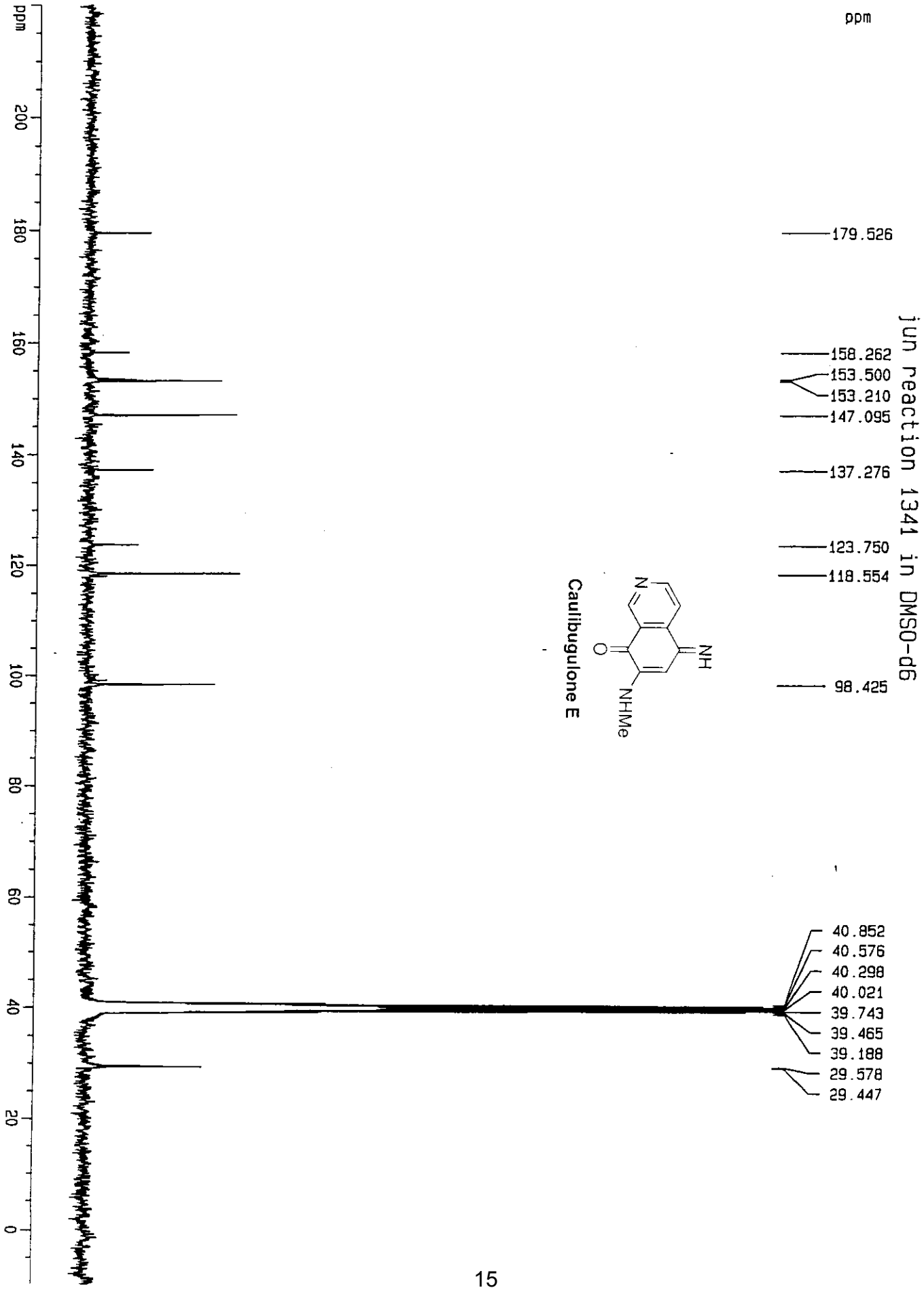
NHMe
O
N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40.021
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39.188
29.578
29.447
jun reaction 1341 in DMSO-d6
Caulibugulone E
N
NH
O
NHMe