

Supplementary data

Synthesis and biological evaluation of caulibugulones A-E

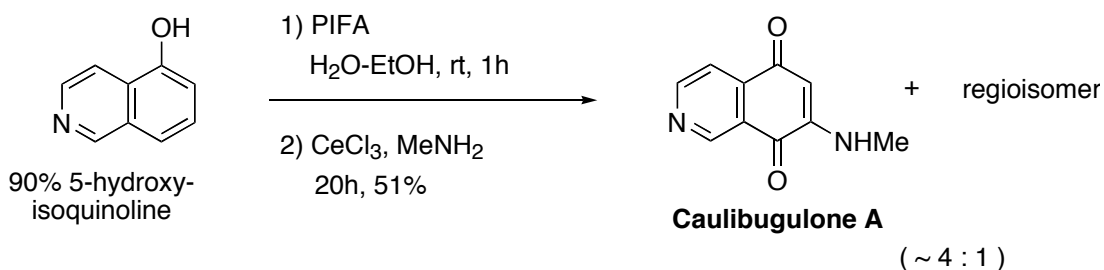
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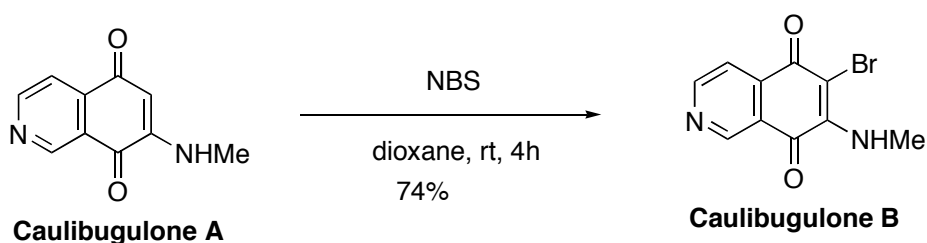
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General Methods. CH₂Cl₂ was dried by distillation over CaH₂. Unless otherwise stated, all commercially available materials were used without purification. IR spectra were recorded neat by adding a drop of a solution of the sample onto the surface of a NaCl cell, followed by drying in air. NMR spectra were obtained at 300MHz/75MHz (¹H/¹³C 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.



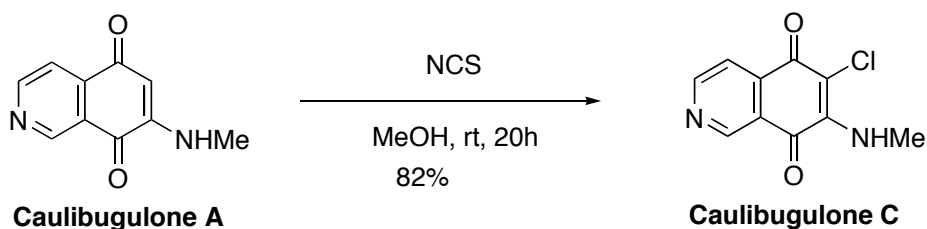
Caulibugulone A (1). To a solution of 5-hydroxyisoquinoline (90%, 0.80 g, 5.0 mmol) in EtOH/H₂O (20 mL/2 mL) was added PIFA (4.28 g, 12.0 mmol) at room temperature. The

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 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ = 200:1 \square 100:1) gave **1** as a red solid: Mp. 228-230 $^\circ\text{C}$ (dec.); IR (neat) 3263, 1685, 1598, 1501, 1419, 1173, 1075, 830 cm^{-1} ; ^1H NMR ($\text{CDCl}_3/\text{CD}_3\text{OD}$ = 1:1) \square 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 ($\text{CDCl}_3/\text{CD}_3\text{OD}$ = 1:1) \square 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 $\text{C}_{10}\text{H}_8\text{N}_2\text{O}_2$ 188.0586, found 188.0583.

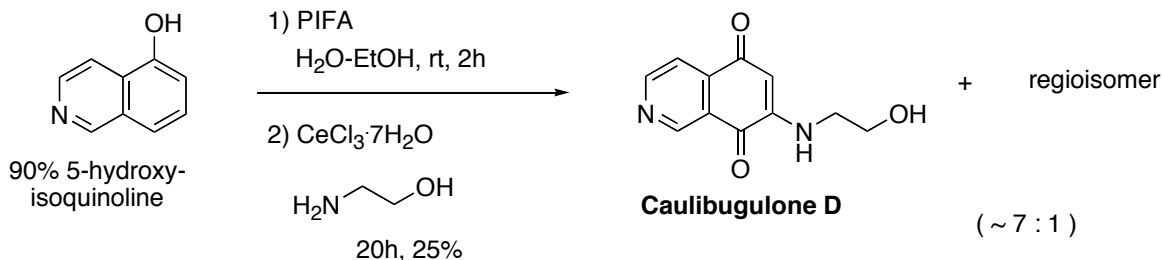


Caulibugulone B (2). To a solution of **1** (30 mg, 0.16 mmol) in dioxane (4 mL) was added NBS (29 mg, 0.16 mmol) in dioxane (1 mL) at room temperature. The reaction mixture was stirred for 4 h and concentrated under reduced pressure. The crude residue was directly purified by chromatography on SiO_2 (CH_2Cl_2 \square $\text{CH}_2\text{Cl}_2/\text{MeOH}$ = 50:1) to give **2** (32 mg, 74%) as a dark red solid: Mp. 182-184 $^\circ\text{C}$ (dec.); IR (neat) 3278, 1690,

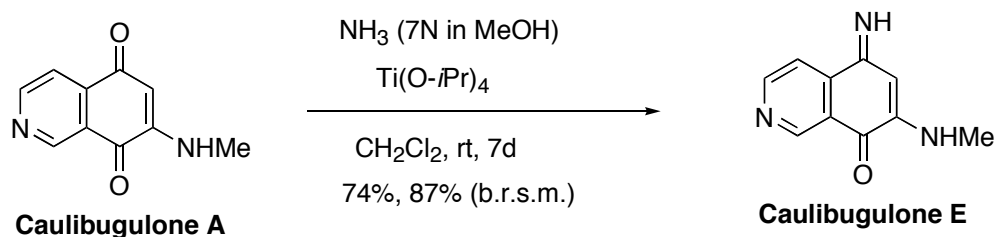
1583, 1542, 1419, 1291 cm^{-1} ; ^1H NMR (pyridine- d_5) \square 9.36 (s, 1 H), 9.00 (d, 1 H, $J = 5.0$ Hz), 8.20 (bs, 1 H, -NH), 7.98 (d, 1 H, $J = 4.9$ Hz), 3.39 (d, 3 H, $J = 5.7$ Hz); ^{13}C NMR (pyridine- d_5) \square 180.1 (2C), 156.1, 148.4 (2C), 138.2, 119.2, 33.0 (2 carbons are buried in solvent peaks); MS (EI) m/z (relative intensity) 266 (M^+ , 100), 187 (49), 160 (39), 82 (23); HRMS (EI) m/z calcd for $\text{C}_{10}\text{H}_7\text{BrN}_2\text{O}_2$ 265.9691, found 265.9695.



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 $^{\circ}\text{C}$ (dec.); IR (neat) 3274, 1689, 1588, 1563, 1417, 1316 cm^{-1} ; ^1H NMR (pyridine- d_5) \square 9.35 (s, 1 H), 9.01 (d, 1 H, $J = 5.0$ Hz), 8.35 (bs, 1 H, -NH), 7.98 (d, 1 H, $J = 5.0$ Hz), 3.38 (d, 3 H, $J = 5.6$ Hz); ^{13}C NMR (pyridine- d_5) \square 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 $\text{C}_{10}\text{H}_7\text{ClN}_2\text{O}_2$ 222.0196, found 222.0194.

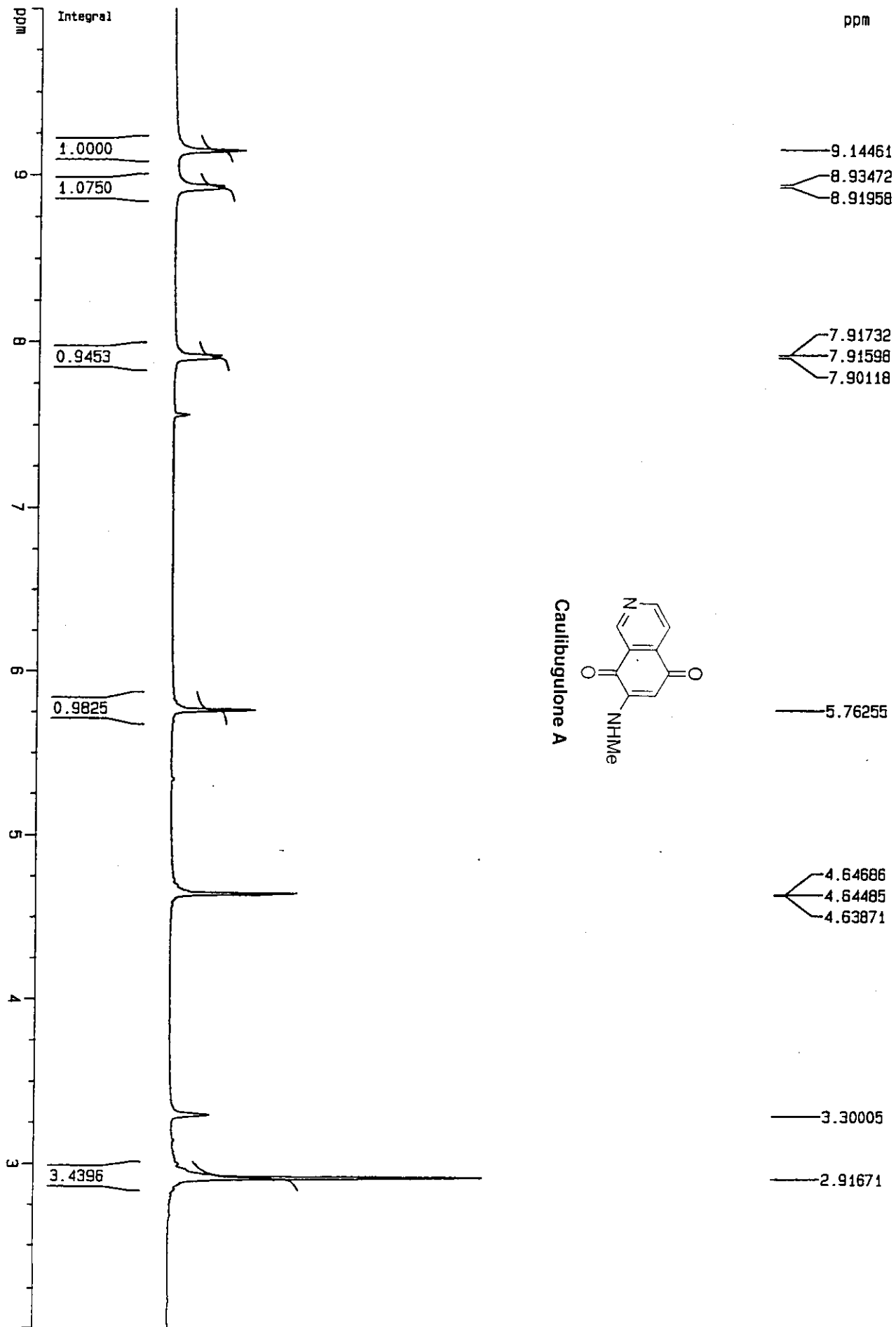
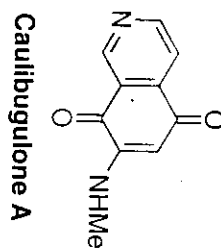


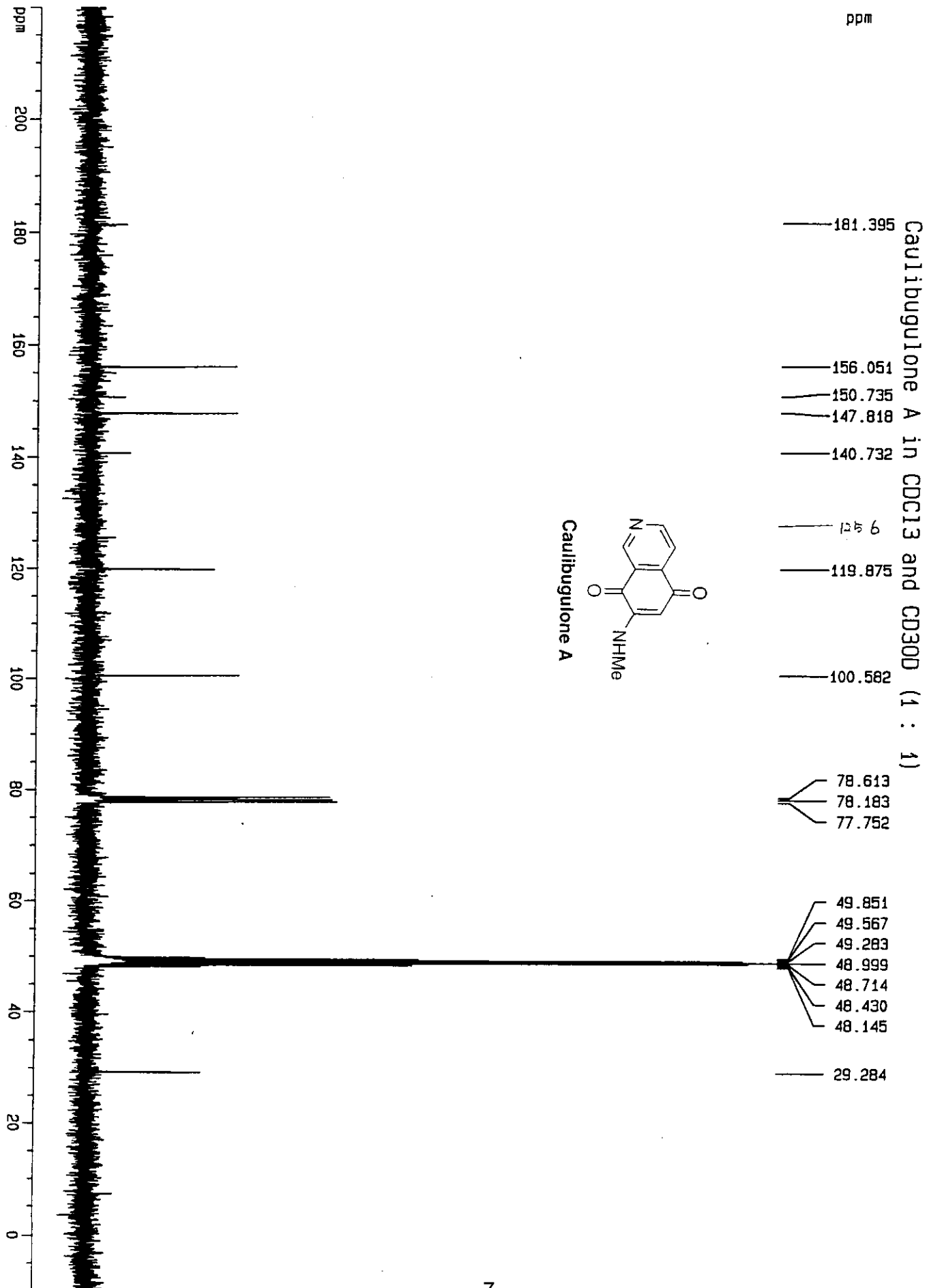
Caulibugulone D (4). To a solution of 5-hydroxyisoquinoline (90%, 200 mg, 1.25 mmol) in EtOH/H₂O (10 mL/1 mL) was added PIFA (1.07 g, 2.50 mmol) at room temperature. The reaction mixture was stirred for 2 h, treated with CeCl₃·7H₂O (930 mg, 2.50 mmol) and ethanolamine (0.60 mL, 10 mmol) at room temperature, stirred for 20 h, diluted with EtOAc (100 mL) and washed with brine (50 mL). The organic layer was dried (MgSO₄) and concentrated under reduced pressure. The crude residue was purified by chromatography on SiO₂ (EtOAc □ CH₂Cl₂/MeOH = 50:1 □ 10:1) to give a mixture of caulibugulone D and its regioisomer (68 mg, 25%, ~7:1 ratio by ¹H NMR). Further separation by chromatography on SiO₂ (CH₂Cl₂/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; ¹H NMR (CDCl₃/CD₃OD = 1:1) □ 9.17 (s, 1 H), 8.94 (bd, 1 H, *J* ≈ 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); ¹³C NMR (CDCl₃/CD₃OD = 1:1) □ 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 C₁₁H₁₀N₂O₃ 218.0691, found 218.0691.



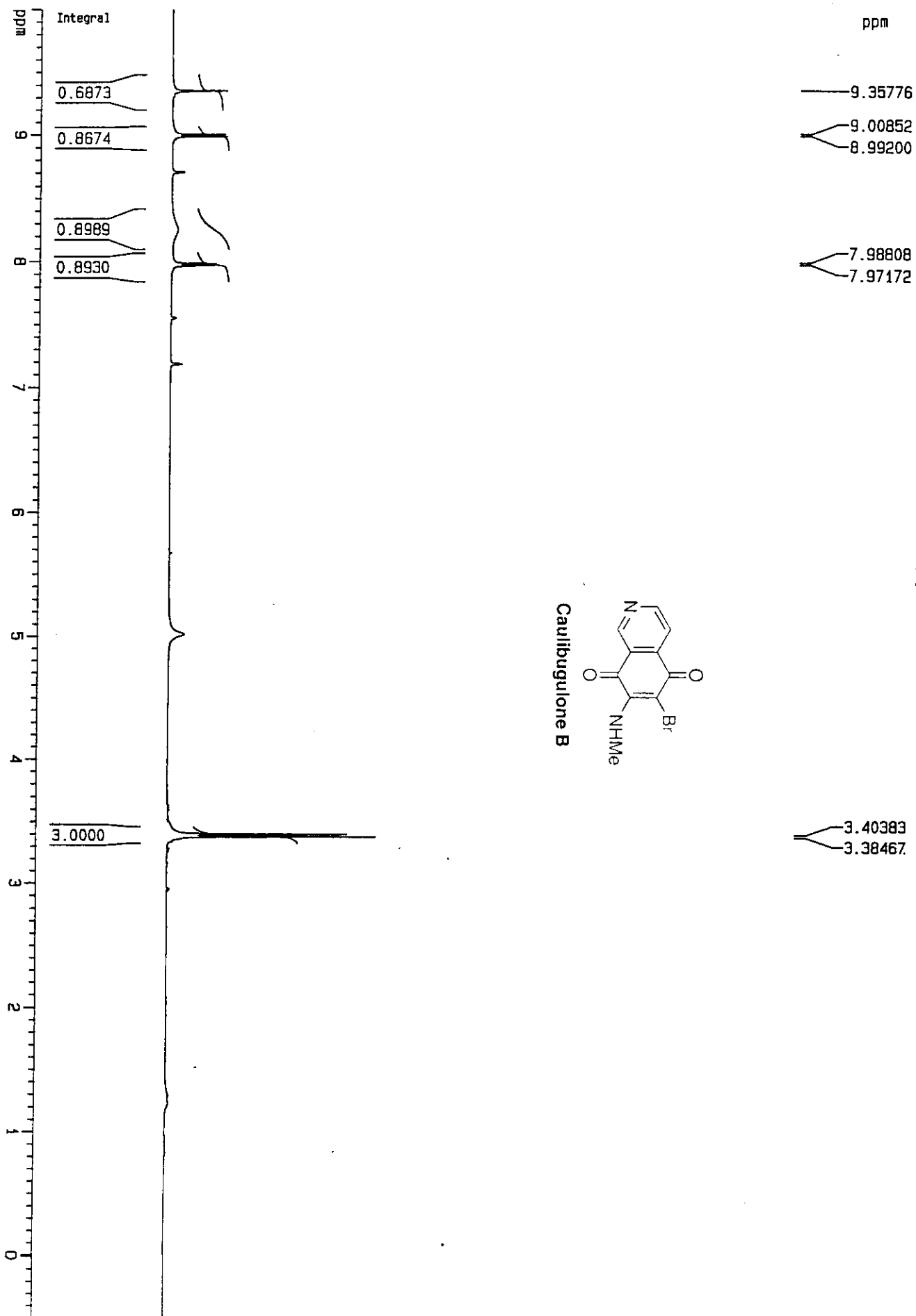
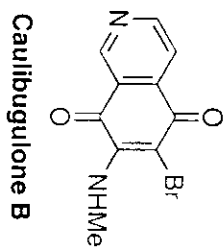
Caulibugulone E (5). To a solution of **1** (230 mg, 1.22 mmol) in CH_2Cl_2 (25 mL) was added $\text{Ti}(\text{O-}i\text{Pr})_4$ (1.7 mL, 6.1 mmol) and ammonia (7N in MeOH, 3.6 mL, 25 mmol) at room temperature. The reaction mixture was stirred for 7 d and directly purified by chromatography on SiO_2 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 50:1 \square 10:1$) 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} ; ^1H NMR (CDCl_3) \square 11.1 (bs, 1 H, =NH) 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, -NH), 5.78 (s, 1 H), 3.00 (d, 3 H, $J = 5.3$ Hz); ^{13}C NMR (DMSO-d_6) \square 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 $\text{C}_{10}\text{H}_9\text{N}_3\text{O}$ 187.0746, found 187.0744.

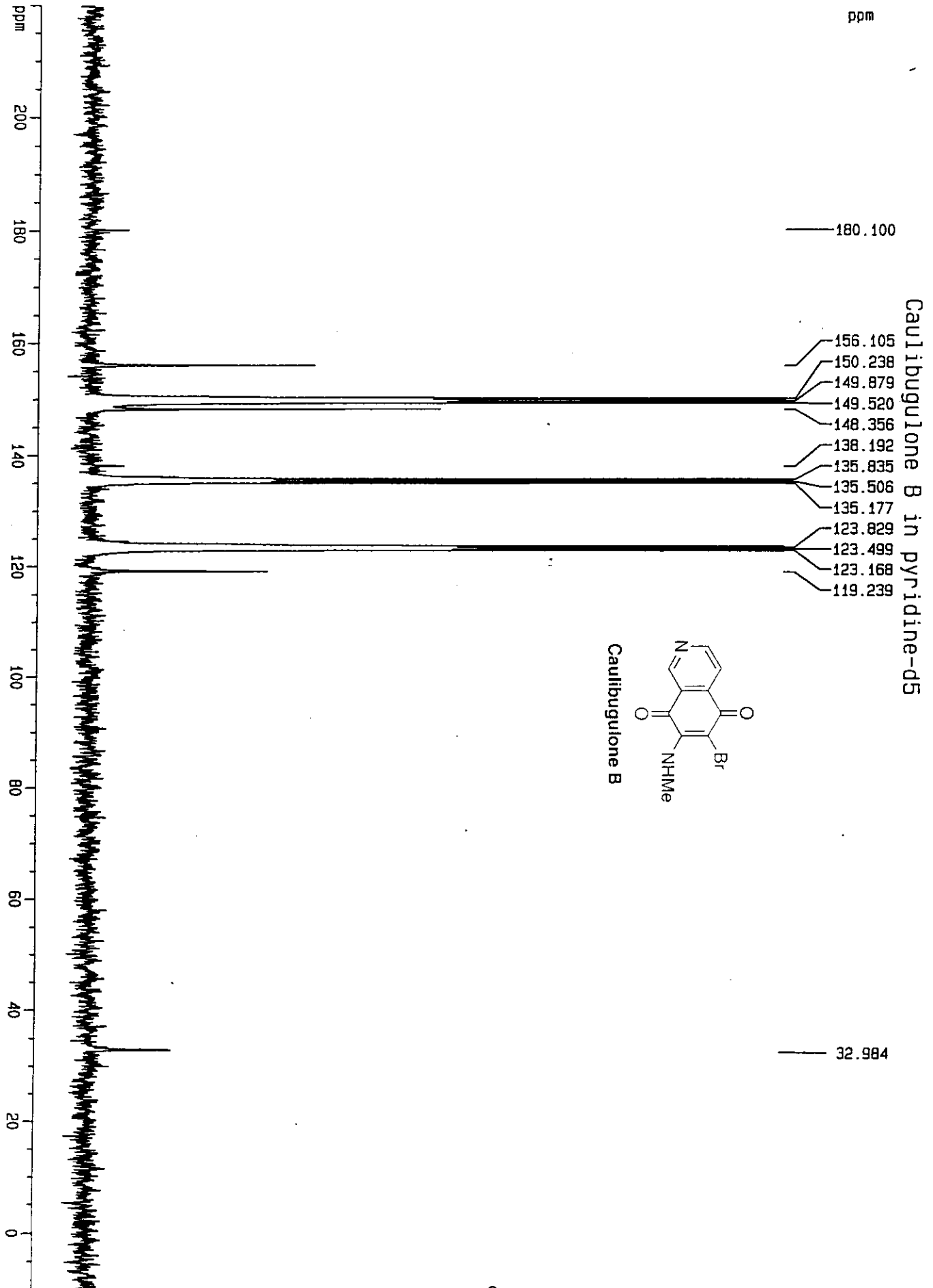
Caulibuglione A

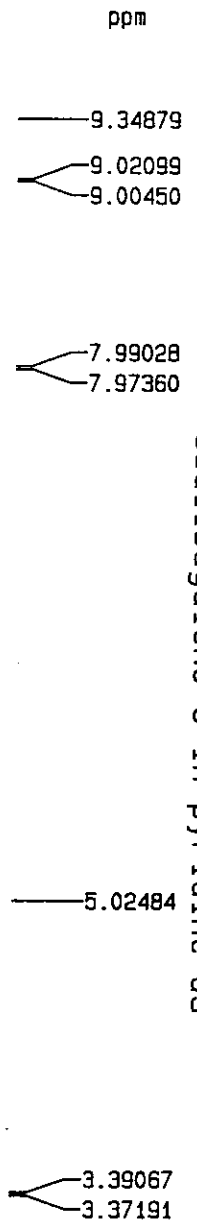
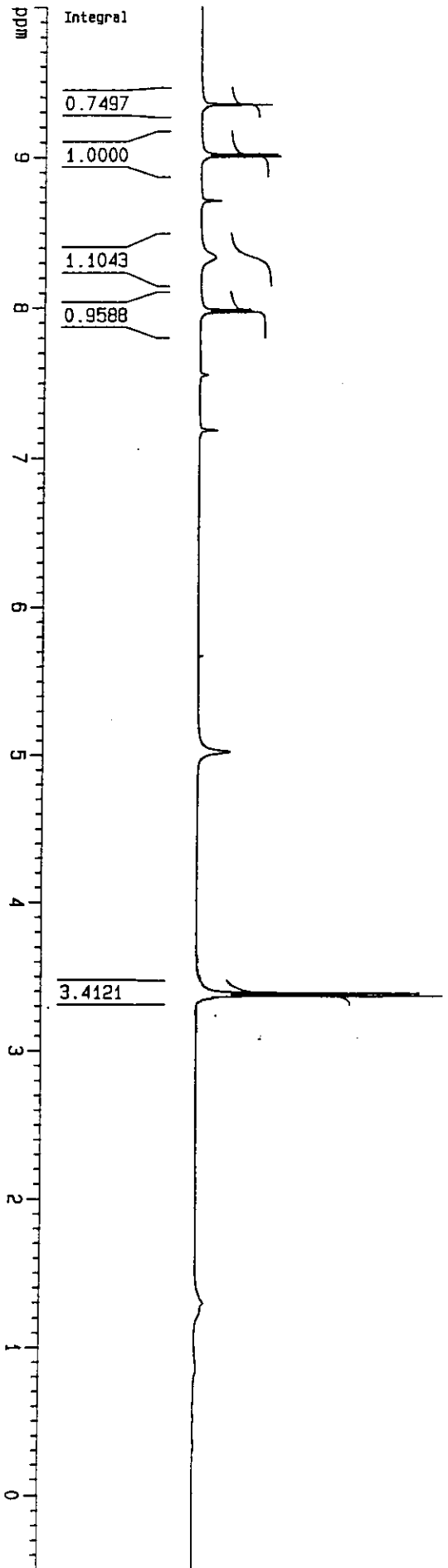




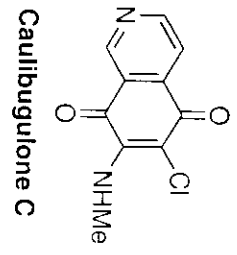
Caulibuglone B in pyridine-d5

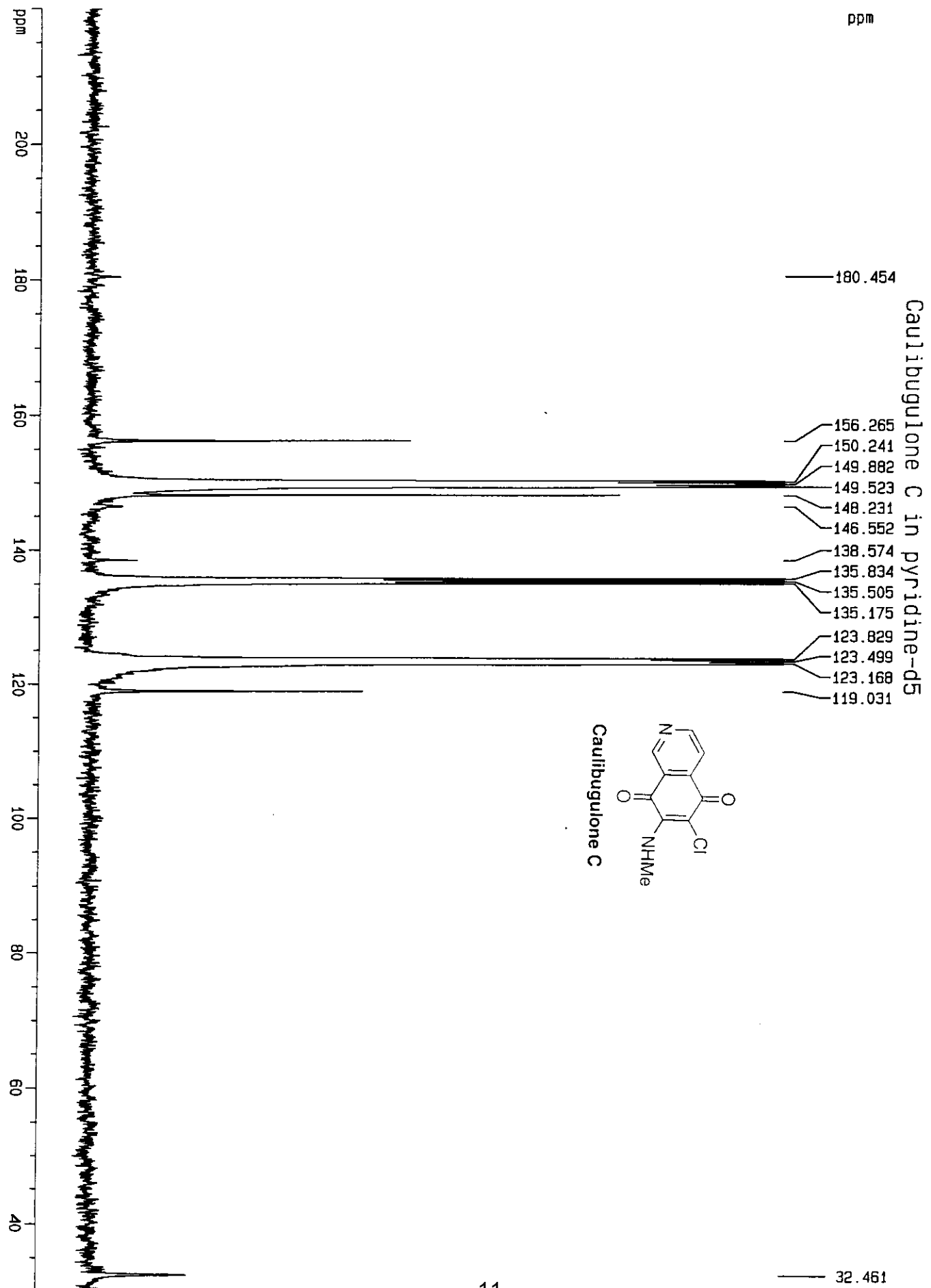




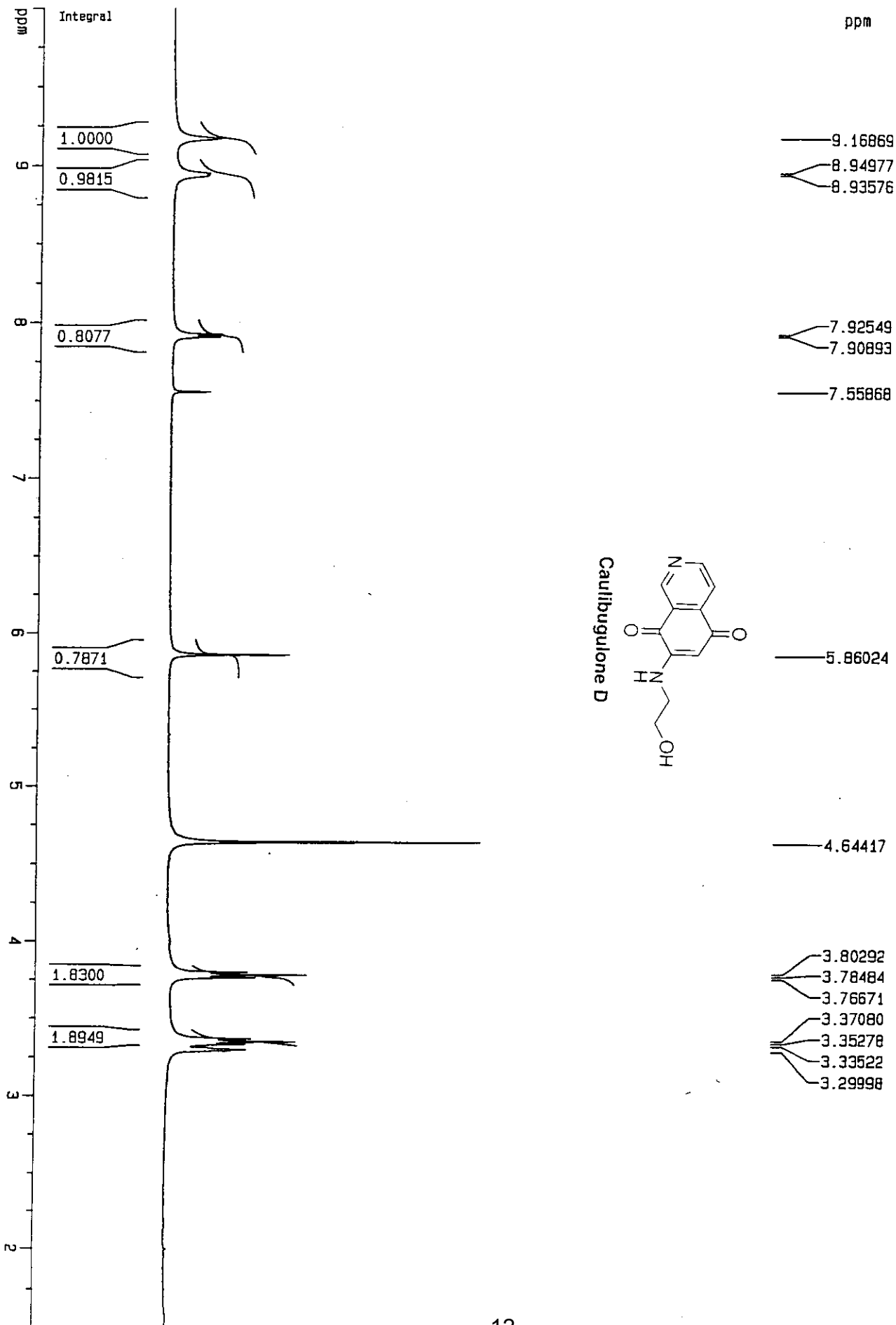
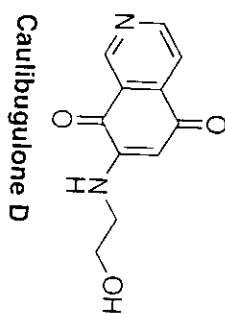


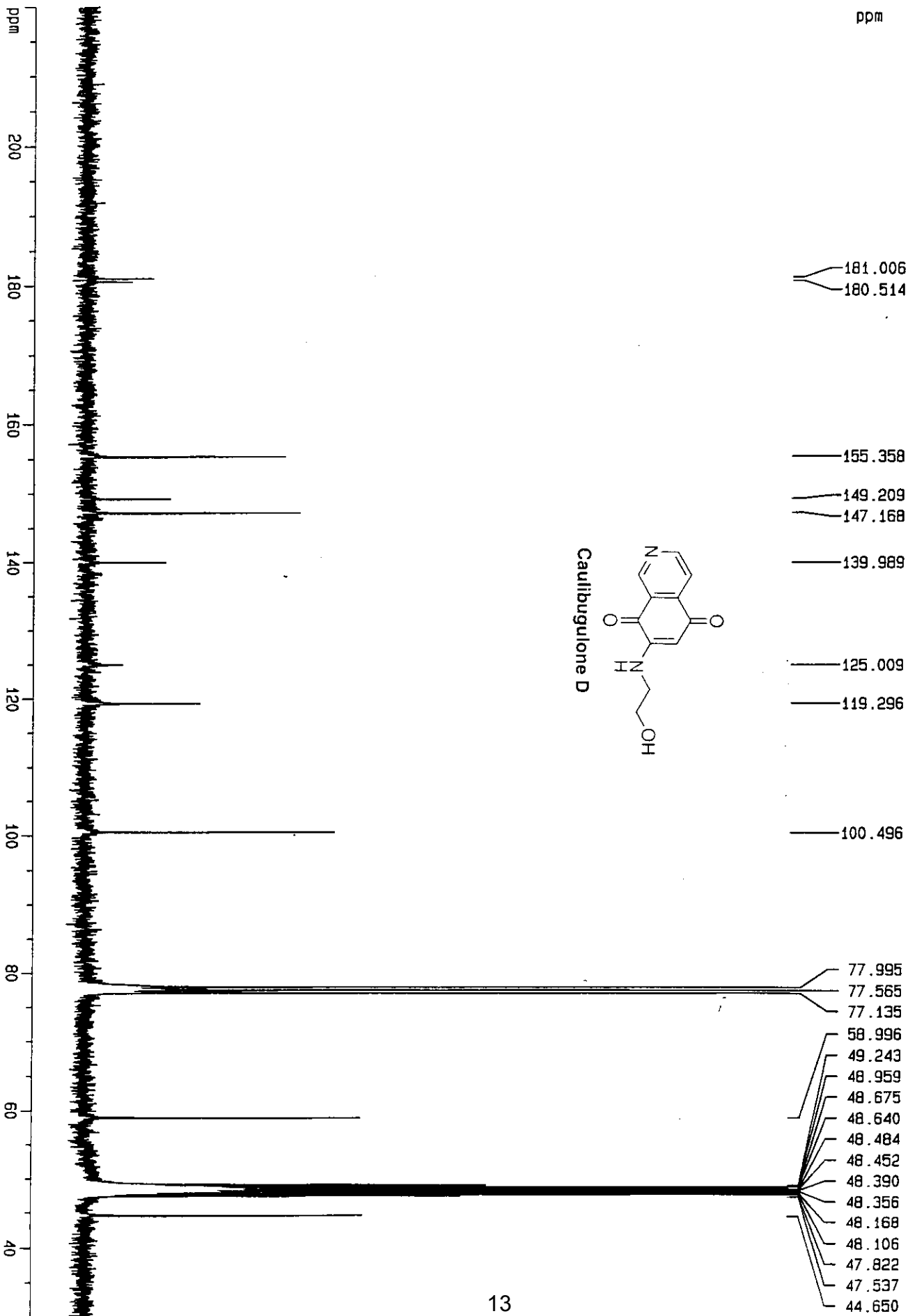
Caulibuglione C in pyridine-d5

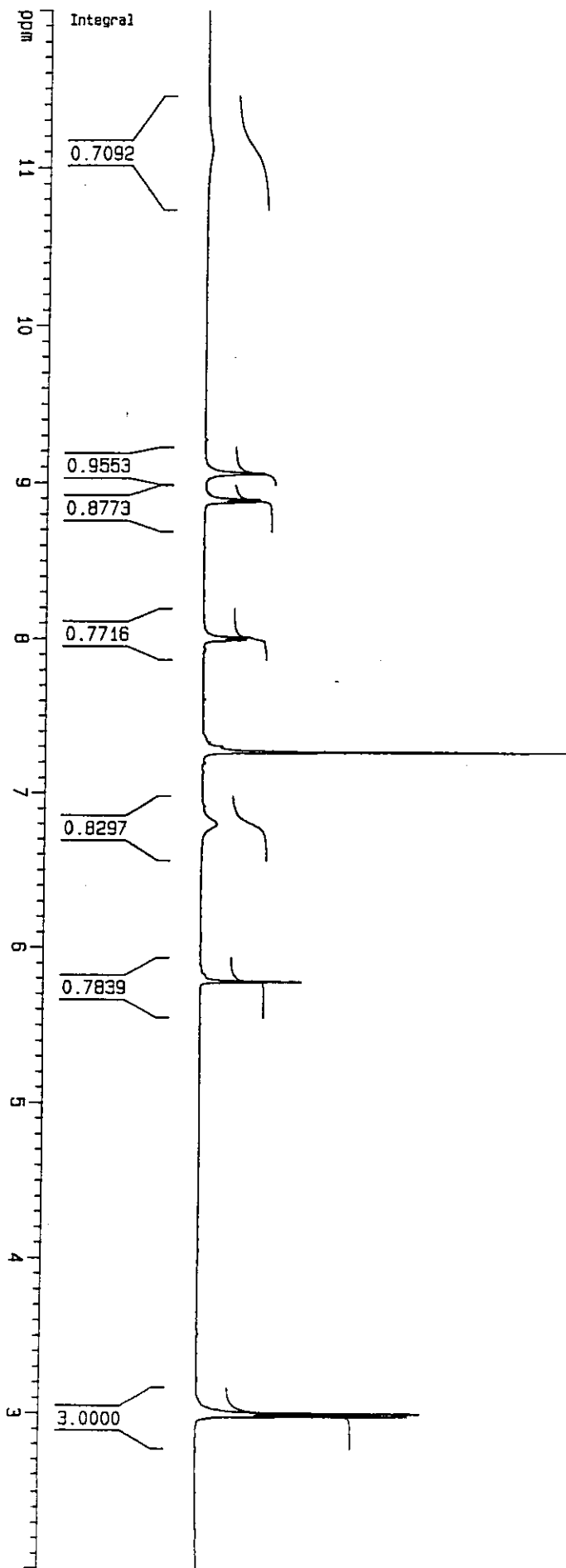




jun reaction 1363 in cdcl3-MeOHd4







ppm

Caulibuglione E in $cdcl_3$

9.06082
8.89653
8.88020

8.01264
7.99636

7.26936

5.78402

3.00540
2.98776

