

Total Synthesis of the Caged Indole Alkaloid Arboridinine Enabled by *Aza*-Prins and Metal-Mediated Cyclizations

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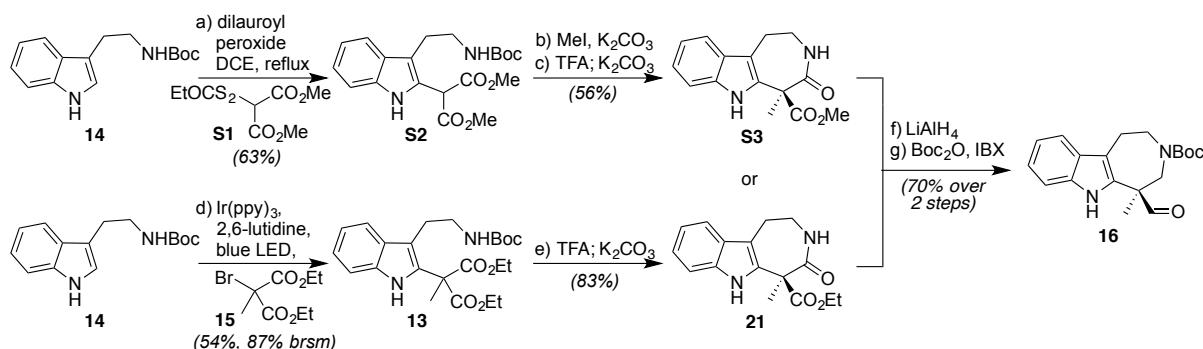
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Experimental Data for Compounds

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, dimethylformamide (DMF), diethyl ether (Et₂O) and dichloromethane (CH₂Cl₂) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (¹H and ¹³C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. SiliCycle silica gel plates (60F-254) using UV light as visualizing agent, and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker 500 MHz and 400 MHz instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on an Agilent 6244 Tof-MS using ESI (Electrospray Ionization) at the University of Chicago Mass Spectroscopy Core Facility.

Abbreviations. EtOAc = ethyl acetate, THF = tetrahydrofuran, LiAlH₄ = lithium aluminum hydride, MsOH = methanesulfonic acid, Bz = benzoyl, Ac = acetyl, Ir(ppy)₃ = tris[2-phenylpyridinato-C²,N]iridium(III), DIBAL-H = diisobutylaluminum hydride, DMSO = dimethyl sulfoxide, IBX = 2-iodoxybenzoic acid, Boc = *tert*-butyloxycarbonyl, *n*-BuLi = *n*-butyllithium, MeCN = acetonitrile, HMPA = hexamethylphosphoramide, TFA = trifluoroacetic acid, TFE = 2,2,2-trifluoroethanol, HFIP = hexafluoroisopropanol, EDTA = ethylenediaminetetraacetic acid, TCCA = trichlororisorcyanuric acid, DCE = 1,2-dichloroethane, DLP = dilauroyl peroxide.

Scheme S1. Synthesis of aldehyde **16**.



Reagents and conditions: a) **14** (1.0 equiv), xanthate **S1** (2.5 equiv) in refluxing degassed DCE (0.6 M) was added DLP (1.8 equiv) portionwise, then reflux for 4 h; b) **S2** (1.0 equiv), K₂CO₃ (9.0 equiv), Mel (4.5 equiv), MeCN (0.13 M); c) CH₂Cl₂/TFA (2/1), 23 °C, 30 min, then concentrate, K₂CO₃ (9.0 equiv), MeOH (0.13 M), 23 °C, 3 h; d) **14** (1.0 equiv), **15** (1.0 equiv), Ir(ppy)₃ (0.01 equiv), 2,6-lutidine (1.0 equiv), MeCN (1.0 M), blue LED, 23 °C, 24 h; e) **13** (1.0 equiv) CH₂Cl₂/TFA (2/1), 23 °C, 30 min, then concentrate, K₂CO₃ (9.0 equiv), EtOH/MeOH (2/1, 0.05 M), 23 °C, 3 h; f) **S3** or **21** (1.0 equiv) in THF (0.04 M), LiAlH₄ (10.0 equiv), 0 °C for 0.5 h, then 45 °C for 4 h; g) Boc₂O (1.1 eq), CH₂Cl₂ (0.04 M), 23 °C for 1 h, then DMSO (0.18 M), IBX (3.0 equiv), 23 °C for 18 h.

Boc-protected Tryptamine (14). Prepared according to the literature procedure of Zhao and co-workers¹ on decagram scale. **14:** $R_f = 0.60$ (silica gel, EtOAc/hexanes, 2/1); IR (film) ν_{max} 3421, 3317, 3064, 2991, 2923, 1701, 1510, 1457, 1395, 1364, 1277, 1246, 1173, 1089 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.36 (s, 1 H), 7.62 (d, $J = 8.0$ Hz, 1 H), 7.37 (d, $J = 8.0$ Hz, 1 H), 7.22 (t, $J = 7.5$ Hz, 1 H), 7.14 (t, $J = 7.5$ Hz, 1 H), 6.99 (s, 1 H), 4.70 (s, 1 H), 3.49 (t, $J = 6.0$ Hz, 2 H), 2.97 (t, $J = 6.0$ Hz, 2 H), 1.48 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.0, 136.4, 127.3, 122.0, 121.9, 119.2, 118.7, 112.9, 111.2, 79.1, 40.9, 28.4, 25.7; HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_2^+ [\text{M} + \text{H}^+]$ 261.1603, found 261.1616.

Lactam S3. Prepared according to the literature procedure of Martínez, Miranda and co-workers in 3 steps on multigram scale.² All spectroscopic data matched that reported in Ref. 2.

Ethyl Malonate 13 (small scale). Following the literature procedure described by Stephenson and co-workers,³ to a 20 mL Schlenk tube equipped with a magnetic bar was added Ir(ppy)₃ (0.010 g, 1 mol %, 0.015 mmol, 0.01 equiv), bromomalonate (0.35 mL, 1.85 mmol, 1.2 equiv), 2,6-lutidine (0.18 mL, 1.54 mmol, 1.0 equiv) and *N*-Boc protected tryptamine **14** (0.400 g, 1.54 mmol, 1.0 equiv). Dry MeCN (2 mL) was then added at 23 °C, and the reaction contents were sparged with bubbling Ar for 15 min. Next, the reaction contents were stirred under an argon atmosphere at 23 °C for 24 h surrounded by two strings of 4W blue LEDs. Upon completion, the reaction contents were concentrated directly and purified by flash column chromatography (silica gel, EtOAc/hexanes, 1/5) to afford **13** (0.360 g, 54% yield) as a light yellow oil along with recovered *N*-Boc protected tryptamine **14** (0.086 g, 87% yield of **13** based on recovered starting material). **13:** $R_f = 0.61$ (silica gel, EtOAc/hexanes, 2/1); IR (film) ν_{max} 3471, 2982, 2939, 1742, 1507, 1447, 1378, 1367, 1264, 1172, 1117, 1070, 1018 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.71 (s, 1 H), 7.63 (d, $J = 7.5$ Hz, 1 H), 7.36 (d, $J = 7.5$ Hz, 1 H), 7.19 (t, $J = 7.5$ Hz, 1 H), 7.10 (t, $J = 7.5$ Hz, 1 H), 4.69 (s, 1 H), 4.34–4.20 (m, 4 H), 3.38 (t, $J = 7.0$ Hz, 2 H), 2.89 (t, $J = 7.0$ Hz, 2 H), 1.93 (s, 3 H), 1.45 (s, 9 H), 1.27 (t, $J = 7.3$ Hz, 6 H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.9, 155.8, 134.5, 130.8, 128.5, 122.1, 119.4, 119.0, 111.0, 109.7, 78.9, 62.2, 54.0, 40.6, 28.4, 25.1, 24.0, 13.9; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{33}\text{N}_2\text{O}_6^+ [\text{M} + \text{H}^+]$ 433.2339, found 433.2343.

Ethyl Malonate 13 (large scale). Following the literature procedure described by Stephenson and co-workers,³ to a 50 mL flask equipped with a magnetic bar was added Ir(ppy)₃ (0.101 g, 1 mol %, 0.154 mmol, 0.1 equiv), bromomalonate (3.52 mL, 18.5 mmol, 1.2 equiv), 2,6-lutidine (1.79 mL, 15.4 mmol, 1.0 equiv) and *N*-Boc protected tryptamine **14** (4.00 g, 15.4 mmol, 1.0 equiv). Dry MeCN (20 mL) was then added at 23 °C, and the reaction contents were sparged with bubbling Ar for 15 min. Next, the reaction contents were stirred under an argon atmosphere at 23 °C for 36 h surrounded by two strings of 4W blue LEDs. Upon completion, the reaction contents were concentrated directly and purified by flash column chromatography (silica gel, EtOAc/hexanes, 1/5) to afford **13** (3.025 g, 46% yield) as a light yellow oil along with recovered *N*-Boc protected tryptamine **14** (1.320 g, 79% yield of **13** based on recovered starting material). All spectral data for **13** matched that delineated above.

Lactam 21 (small scale). Ethyl malonate **13** (0.069 g, 0.16 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (1.5 mL) and then TFA (0.5 mL) was added at 23 °C. The resultant solution was stirred for 30 min at 23 °C. Upon completion, the reaction contents were concentrated directly and the crude residue was dissolved in a mixture of dry EtOH (2 mL) and dry MeOH (1 mL). K_2CO_3 (0.200 g, 1.44 mmol, 9.0 equiv) was added, and the resultant suspension was stirred at 23 °C for 4 h. Upon completion, the solids were removed by filtration, washing with EtOAc (3×2 mL). The combined filtrate was then concentrated and the resultant residue was purified

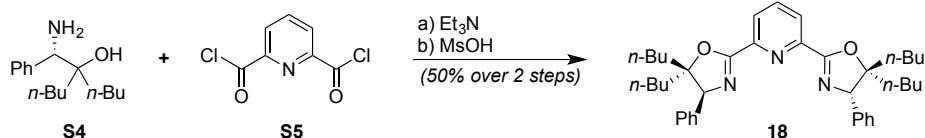
by flash column chromatography (silica gel, EtOAc/hexanes, 1/4→2/1) to afford lactam **21** (0.038 g, 83% yield) as a white solid. **21**: $R_f = 0.32$ (silica gel, EtOAc/hexanes, 2/1); IR (film) ν_{max} 3342, 2958, 2925, 1727, 1665, 1567, 1459, 1380, 1343, 1233, 1168, 1105, 1018 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.12 (s, 1 H), 7.47 (d, $J = 7.9$ Hz, 1 H), 7.34 (d, $J = 7.9$ Hz, 1 H), 7.20 (t, $J = 7.1$ Hz, 1 H), 7.11 (t, $J = 7.1$ Hz, 1 H), 6.27–6.24 (m, 1 H), 4.34–4.16 (m, 2 H), 3.69–3.52 (m, 1 H), 3.51–3.44 (m, 1 H), 3.17–2.91 (m, 2 H), 1.99 (s, 3 H), 1.25 (t, $J = 7.1$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.3, 171.5, 135.0, 128.3, 127.9, 122.7, 119.7, 118.3, 111.8, 110.8, 62.3, 53.6, 39.8, 26.0, 21.4, 14.0; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_3^+ [\text{M} + \text{H}^+]$ 287.1395, found 287.1393.

Lactam 21 (large scale). Ethyl malonate **13** (2.28 g, 5.28 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (20 mL) and then TFA (10 mL) was added at 23 °C. The resultant solution was stirred for 30 min at 23 °C. Upon completion, the reaction contents were concentrated directly and the crude residue was dissolved in a mixture of dry EtOH (20 mL) and dry MeOH (5 mL). K_2CO_3 (6.56 g, 47.5 mmol, 9.0 equiv) was added, and the resultant suspension was stirred at 23 °C for 4 h. Upon completion, the solids were removed by filtration, washing with EtOAc (10×3 mL). The combined filtrate was then evaporated to dryness and the resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1/4→2/1) to afford lactam **21** (1.027 g, 68% yield) as a white solid. All spectral data for **21** matched that delineated above.

Aldehyde 16. To a slurry of lactam **21** (1.17 g, 4.30 mmol, 1.0 equiv) in THF (100 mL) at 0 °C under an argon atmosphere was carefully added LiAlH₄ powder (1.63 g, 43.0 mmol, 10 equiv) in one portion. After stirring the reaction contents at 0 °C for 30 min, the ice bath was removed and the contents were allowed to warm to 23 °C; the reaction flask was then heated at 45 °C for 4 h with vigorous stirring. Upon completion, noting that TLC analysis at this point showed UV activity only on the baseline when developing with pure EtOAc, the resultant grey slurry was cooled to 0 °C and solid $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ (10.0 g) was added carefully with vigorous stirring. After all gas evolution ceased, the reaction mixture was then diluted with EtOAc (50 mL) and the resulting contents were stirred at 23 °C for 2 h. Stirring was then stopped, and once the white solids formed had settled, they were separated by filtration, washing the residue with EtOAc (3×20 mL). The filtrates were then combined and concentrated directly. Pressing forward without any additional purification, the resulting yellow oil (0.92 g, 4.0 mmol assumed, 1.0 equiv) was dissolved in CH_2Cl_2 (100 mL), Boc_2O (0.87 g, 4.0 mmol, 1.0 equiv) was added at 23 °C, and the resultant mixture was stirred at 23 °C for 1 h. Upon completion, the reaction contents were concentrated directly and the crude residue was dissolved in DMSO (20 mL). IBX (2.49 g, 10.8 mmol, 3.0 equiv) was then added at 23 °C, and the resultant mixture was stirred at 23 °C for 18 h. Upon completion, the reaction contents were quenched by first diluting with EtOAc (20 mL) and then adding saturated aqueous Na_2SO_3 (10 mL). The contents were then poured into a separatory funnel. After separating the resultant layers, the organic phase was washed with H_2O (5×20 mL), dried (MgSO_4), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1/9→1/4) to give aldehyde **16** (0.990 g, 70% yield over two steps) as a yellow oil. [Note: the same LiAlH₄ reduction/IBX oxidation sequence could be applied to lactam **S3** to afford aldehyde **16** in comparable yields]. **16**: $R_f = 0.45$ (silica gel, EtOAc/hexanes, 1/2); IR (film) ν_{max} 3348, 2975, 2930, 1723, 1670, 1467, 1417, 1367, 1250, 1154 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3 , 2 rotamers, ~0.5:0.5) δ 9.72 (s, 0.5 H), 9.71 (s, 0.5 H), 8.68 (s, 0.5 H), 8.66 (s, 0.5 H), 7.57 (d, $J = 7.5$ Hz, 1 H), 7.31 (d, $J = 7.5$ Hz, 1 H), 7.23–7.16 (m, 2 H), 4.35 (d, $J = 14.5$ Hz, 0.5 H), 4.20–4.02 (m, 1 H), 4.05 (dt, $J = 12.2, 5.6$ Hz, 0.5 H), 3.60 (d, $J = 14.5$ Hz, 0.5 H), 3.57 (d, $J = 14.5$ Hz, 0.5 H), 3.50 (dt, $J = 12.7,$

6.0 Hz, 0.5 H), 3.42 (ddd, J = 13.0, 8.9, 3.8 Hz, 0.5 H), 3.23–3.11 (m, 2 H), 1.56 (s, 4.5 H), 1.53 (s, 4.5 H), 1.51 (s, 1.5 H), 1.50 (s, 1.5 H); ^{13}C NMR (125 MHz, CDCl_3 , 2 rotamers, ~0.5:0.5) δ 200.4, 200.1, 155.7, 154.5, 135.4, 132.5, 131.9, 128.3, 128.1, 122.1, 122.0, 119.3, 119.2, 118.1, 117.9, 113.4, 112.8, 110.8, 110.7, 80.7, 80.1, 54.0, 53.4, 52.5, 50.9, 48.4, 48.0, 28.2, 28.1, 23.7, 18.6, 18.1; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_3^+ [\text{M} + \text{H}^+]$ 329.1865, found 329.1850.

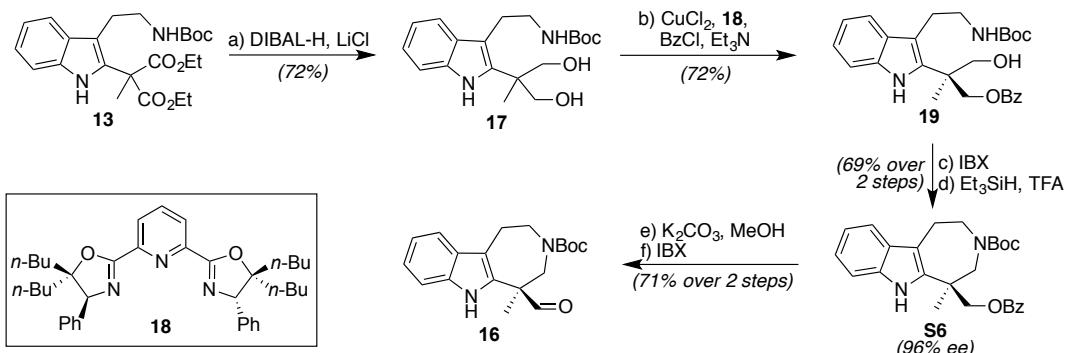
Scheme S2. Synthesis of Ligand **18**.



Reagents and conditions: a) **S4** (2.0 equiv), **S5** (1.0 equiv), Et_3N (4.0 equiv), CH_2Cl_2 (0.05 M), 0–23°C, 18 h; b) MsOH (10.0 equiv), CH_2Cl_2 (0.04 M), 0–50 °C, 18 h.

Pybox 18. To a solution of amine **S4** (0.410 g, 1.64 mmol, 2.0 equiv) in CH_2Cl_2 (20 mL) at 0 °C was added Et_3N (0.46 mL, 3.29 mmol, 4.0 equiv) followed by the slow addition of a solution of acid chloride **S5** (0.167 g, 0.822 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL). The reaction contents were then warmed to 23 °C and stirred for 18 h. Upon completion, the reaction was diluted with CH_2Cl_2 (100 mL), poured into a separatory funnel, and then washed with 1 M HCl (50 mL), H_2O (50 mL), saturated aqueous NaHCO_3 (50 mL), and saturated aqueous NaCl (50 mL). The organic layer was then dried (Na_2SO_4) and concentrated. The resulting yellow solid (0.485 g, 0.770 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (20 mL), cooled to 0 °C, and then MsOH (0.50 mL, 7.70 mmol, 10.0 equiv) was added dropwise. The resultant mixture was then heated at reflux for 18 h. Upon completion, the reaction contents were cooled to 23 °C, diluted with CH_2Cl_2 (50 mL), and then poured into a separatory funnel containing saturated aqueous NaHCO_3 (30 mL). After separating the resultant layers, the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phases were washed with H_2O (50 mL), saturated aqueous NaCl (50 mL), dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash column chromatography (silica gel, EtOAc/hexanes , 1/4→1/2) to give ligand **18** (0.244 g, 50% yield over 2 steps) as a yellow oil. All spectral data matched that as reported by Kang and co-workers.⁴

Scheme S3. Enantioselective Synthesis of Aldehyde **16**.



Reagents and conditions: a) DIBAL-H (1.0 M in toluene, 10 equiv), LiCl (10 equiv), THF (0.1 M), 0–23 °C, 18 h; b) CuCl_2 (0.1 equiv), **18** (0.1 equiv), BzCl (1.5 equiv), Et_3N (1.1 equiv), CH_2Cl_2 (0.1 M), –78 °C, 14 h; c) IBX (1.5 equiv), DMSO (0.15 M), 23 °C, 5 h; d) Et_3SiH (2.5 equiv), TFA (0.85 equiv), MeCN (0.1 M), 0–23 °C, 18 h; e) K_2CO_3 (5.0 equiv), MeOH (0.1 M), CH_2Cl_2 (0.1 M), 23 °C, 0.75 h; f) IBX (3.0 equiv), DMSO , 23 °C, 18 h.

Diol 17. To a reaction flask containing diethylmalonate **13** (0.100 g, 0.23 mmol, 1.0 equiv), LiCl (0.097 g, 2.3 mmol, 10 equiv) and THF (2.3 mL, 0.1 M in substrate) under argon at 0 °C was added DIBAL-H (2.30 mL, 1.0 M in toluene, 10 equiv). After the addition was complete, the ice bath was removed and the reaction contents were allowed to warm to 23 °C and stirred for an additional 18 h. Upon completion, the reaction was cooled to 0 °C and quenched by the addition of a solution of Rochelle's salt (5 mL), followed by the addition of EtOAc (5 mL). The reaction contents were then warmed to 23 °C and stirred at that temperature for 3 h. When the separation between organic and aqueous layers were clear, the mixture was poured into a separatory funnel and separated. The aqueous layer was extracted with EtOAc (3×4 mL) and the combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1/4→1/2) to give diol **17** (0.058 g, 72% yield) as a colorless oil. **17:** $R_f = 0.12$ (silica gel, EtOAc/hexanes, 1/1); IR (film) ν_{max} 3445, 3402, 3054, 2985, 1700, 1422, 1169 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.50 (s, 1 H), 7.51 (d, $J = 7.8$ Hz, 1 H), 7.31 (d, $J = 7.9$ Hz, 1 H), 7.13 (t, $J = 7.3$ Hz, 1 H), 7.08 (t, $J = 7.1$ Hz, 1 H), 4.78 (t, $J = 5.5$ Hz, 1 H), 4.10 (d, $J = 8.9$ Hz, 2 H), 3.94 (d, $J = 10.8$ Hz, 2 H), 3.72 (br s, 2 H), 3.45 (q, $J = 6.7$ Hz, 2 H), 3.04 (t, $J = 6.7$ Hz, 2 H), 1.26–1.22 (m, 12 H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.3, 137.6, 134.9, 129.3, 121.5, 119.1, 118.1, 110.9, 108.5, 79.4, 71.1, 42.7, 41.3, 28.2, 26.0, 19.9; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{29}\text{N}_2\text{O}_4$ [$\text{M} + \text{H}^+$] 349.2127, found 349.2120.

Ester 19. To a reaction flask under an atmosphere of N_2 at 23 °C was added CuCl_2 (0.029 g, 0.215 mmol, 0.1 equiv) followed by a solution of Pybox ligand **18** (0.128 g, 0.215 mmol, 0.1 equiv) in CH_2Cl_2 (17 mL). The resulting mixture was stirred at 23 °C for 4 h. Next, a solution of diol **17** (0.750 g, 2.15 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) was added and the reaction contents were cooled to –78 °C. Benzoyl chloride (0.37 mL, 3.23 mmol, 1.5 equiv) and Et_3N (0.33 mL, 2.37 mmol, 1.1 equiv) were then added sequentially dropwise and the reaction mixture was stirred at –78 °C for 14 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (5 mL) and warmed to 23 °C. The mixture was diluted with saturated aqueous NH_4Cl (30 mL) and poured into a separatory funnel. After separating the resultant layers, the aqueous phase was extracted with EtOAc (3×50 mL). The combined organic layers were then washed with saturated aqueous NaCl (100 mL), dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1/4→1/2) to give ester **19** (0.702 g, 72% yield) as a white solid. **19:** $R_f = 0.26$ (silica gel, EtOAc/hexanes, 1/2); $[\alpha]_D^{23} = +14.5^\circ$ ($c = 1.4$, CHCl_3); IR (film) ν_{max} 3451, 3398, 3054, 2983, 1708, 1507, 1271, 1176 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.54 (s, 1 H), 8.06 (d, $J = 7.4$ Hz, 2 H), 7.61 (t, $J = 7.4$ Hz, 1 H), 7.58 (d, $J = 7.9$ Hz, 1 H), 7.48 (t, $J = 7.7$ Hz, 2 H), 7.34 (d, $J = 8.0$ Hz, 1 H), 7.17 (t, $J = 7.4$ Hz, 1 H), 7.10 (t, $J = 7.3$ Hz, 1 H), 4.95 (d, $J = 11.5$ Hz, 1 H), 4.75 (t, $J = 5.8$ Hz, 1 H), 4.34 (d, $J = 11.4$ Hz, 1 H), 3.93 (d, $J = 12.1$ Hz, 1 H), 3.73 (d, $J = 12.0$ Hz, 1 H), 3.49–3.43 (m, 2 H), 3.13 (t, $J = 7.0$ Hz, 2 H), 1.55 (s, 3 H), 1.40 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 167.6, 156.1, 136.3, 135.0, 133.6, 129.8, 129.5, 128.9, 128.6, 121.9, 119.3, 118.4, 110.9, 109.5, 79.2, 67.8, 67.6, 42.6, 41.5, 28.4, 26.2, 20.0; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{33}\text{N}_2\text{O}_5$ [$\text{M} + \text{H}^+$] 453.2390, found 453.2400. Note: the enantiopurity could not conclusively be determined at this stage due to incomplete separation by chiral HPLC (AD-H column, 4.6 × 250 mm, 9:1 hexanes/*i*-PrOH, 1 mL/min, UV detector at 220 nm) $R_T = 20.9$ min (major), $R_T = 22.4$ min (minor). The major enantiomer elutes first, completely overlapping the minor enantiomer signal. Using the opposite enantiomer of Pybox **18** to prepare the opposite

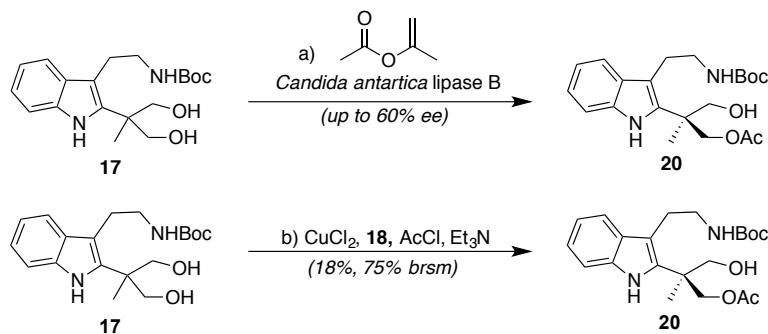
enantiomer of ester **19**, the minor enantiomer elutes first and can be observed. The enantiopurity was found to be approximately 98% ee.

Tricycle S6. To a solution of IBX (0.497 g, 1.77 mmol, 1.5 equiv) in DMSO (4 mL) at 23 °C was added slowly a solution of alcohol **19** (0.535 g, 1.18 mmol, 1.0 equiv) in DMSO (4 mL). After stirring the resultant solution at 23 °C for 5 h, the reaction contents were diluted with saturated aqueous NaHCO₃ (20 mL) and poured into a separatory funnel. After separating the layers, the aqueous phase was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layers were then washed with H₂O (100 mL), saturated aqueous NaCl (100 mL), dried (Na₂SO₄), and concentrated. The resulting residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1/4) to afford the desired intermediate aldehyde (0.437 g, 0.970 mmol, 82% yield) as a white solid. This intermediate aldehyde was immediately dissolved in MeCN (10 mL). After cooling the resultant solution to 0 °C, Et₃SiH (0.39 mL, 2.42 mmol, 2.5 equiv) and TFA (0.063 mL, 0.824 mmol, 0.85 equiv) were added sequentially dropwise. The reaction contents were then allowed to warm slowly to 23 °C and were stirred at that temperature for a further 18 h. Upon completion, the reaction mixture was quenched with saturated aqueous NaHCO₃ (20 mL) and poured into a separatory funnel. After separating the layers, the aqueous phase was extracted with EtOAc (3 × 50 mL), dried (Na₂SO₄) and concentrated. The resulting residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 0/1 → 1/8) to afford **S6** (0.352 g, 84% yield, 69% yield over 2 steps) as a white solid. **S6:** R_f = 0.63 (silica gel, EtOAc/hexanes, 1/2); [α]_D²³ = +42.9° (c = 2.1, CHCl₃); IR (film) ν_{max} 3054, 2985, 1718, 1686, 1461, 1421, 1266, 1161 cm⁻¹; ¹H NMR (500 MHz, CDCl₃, 2 rotamers, ~0.5:0.5) δ 8.38 (s, 1 H), 8.00 (t, J = 6.5 Hz, 2 H), 7.56 (d, J = 7.9 Hz, 1 H), 7.52 (d, J = 7.7 Hz, 1 H), 7.42 (d, J = 5.6 Hz, 2 H), 7.31 (d, J = 4.9 Hz, 1 H), 7.18–7.11 (m, 2 H), 4.66 (dd, J = 16.1, 11.6 Hz, 1 H), 4.43 (dd, J = 15.1, 11.7 Hz, 1 H), 4.11 (d, J = 14.1 Hz, 0.5 H), 3.97 (d, J = 14.5 Hz, 0.5 H), 3.90–3.82 (m, 1 H), 3.72 (dd, J = 21.6, 14.5 Hz, 1 H), 3.65–3.59 (m, 1 H), 3.08 (br s, 2 H), 1.53–1.49 (m, 12 H); ¹³C NMR (125 MHz, CDCl₃, 2 rotamers, ~0.5:0.5) δ 166.50, 166.46, 155.9, 155.3, 137.6, 137.3, 134.8, 133.3, 133.1, 130.1, 129.9, 129.63, 129.60, 128.6, 128.5, 128.4, 121.84, 121.77, 119.4, 118.2, 117.9, 111.9, 111.7, 110.6, 110.5, 80.3, 79.8, 70.1, 69.4, 53.9, 52.3, 48.8, 48.4, 43.1, 42.8, 28.5, 24.2, 21.7, 21.6; HRMS (ESI) calcd for C₂₆H₃₁N₂O₄ [M + H⁺] 435.2284, found 435.2293. The enantiopurity was determined using chiral HPLC (OD-H column, 4.6 × 250 mm, 9:1 hexanes/i-PrOH, 1 mL/min, UV detector at 280 nm) R_T = 14.3 min (minor), R_T = 20.8 min (major), ee = 96%.

Chiral Aldehyde 16. To a solution of ester **S6** (0.352 g, 0.810 mmol, 1.0 equiv) in CH₂Cl₂ (8 mL) at 23 °C was sequentially added MeOH (8 mL) and K₂CO₃ (0.560 g, 4.05 mmol, 5.0 equiv). The resultant slurry was stirred at 23 °C for 45 min. Upon completion, the reaction contents were diluted with CH₂Cl₂ (100 mL), poured into a separatory funnel, and the organic phase was washed with H₂O (50 mL) and saturated aqueous NaCl (50 mL), dried (Na₂SO₄), and concentrated. The resulting residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1/4) to afford the desired alcohol intermediate (0.251 g, 0.760 mmol, 94% yield) as a white solid. Pressing forward, this new material was immediately dissolved in DMSO (2.5 mL) and then was added to a solution of IBX (0.638 g, 2.28 mmol, 3.0 equiv) in DMSO (2.5 mL) at 23 °C. The resulting mixture was stirred at 23 °C for 18 h. Upon completion, the reaction contents were diluted with EtOAc (50 mL), H₂O (25 mL), and saturated aqueous Na₂SO₃ (25 mL), and poured into a separatory funnel. After separating the layers, the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H₂O (2 × 100 mL), saturated aqueous NaCl (100 mL), dried (Na₂SO₄), and concentrated. The

resultant residue was filtered through silica gel, eluting with EtOAc/hexanes (1/4). The filtrate was then concentrated, redissolved in CH₂Cl₂ (200 mL), washed with saturated aqueous NaHCO₃ (100 mL) and saturated aqueous NaCl (100 mL), dried (Na₂SO₄), and concentrated to afford aldehyde **16** (0.189 g, 76% yield, 71% yield over 2 steps) as a white solid. All spectroscopic data were in full agreement with the racemic compound. **16**: [α]_D²³ = +235.0° (*c* = 2.3, CHCl₃).

Scheme S4. Enantioselective acetate protection by enzymatic or chemical process.



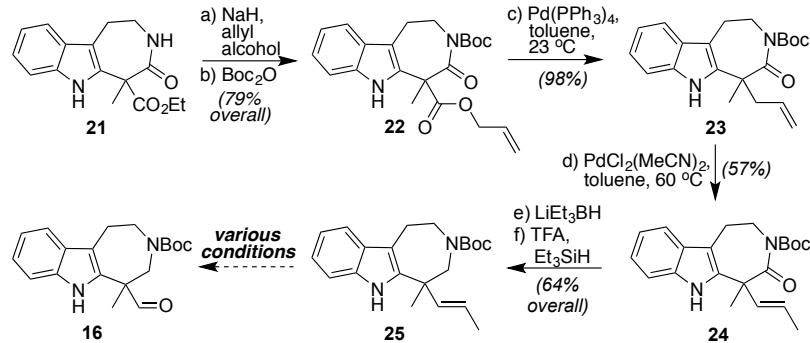
Reagents and conditions: a) **17** (1.0 equiv), isopropenyl acetate (5.0 equiv), CALB (100 wt%), EtOAc, 40 °C, 9 d; b) CuCl₂ (0.1 equiv), **18** (0.1 equiv), AcCl (1.5 equiv), Et₃N (1.1 equiv), CH₂Cl₂ (0.1 M), -78 °C, 18 h.

Ester 20 (enzymatic). To a solution of diol **17** (31.0 mg, 0.089 mmol, 1.0 equiv) in EtOAc (0.9 mL) at 25 °C was added *Candida antarctica* Lipase B (31.0 gm, 100 wt %, immobilized on Immobead 150, recombinant from *Aspergillus oryzae*, 1922 U/g) followed by isopropenyl acetate (0.048 mL, 0.445 mmol, 5.0 equiv). The resulting suspension was then heated at 40 °C for 9 d. Upon completion, the reaction contents were cooled to 23 °C, filtered through Celite, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1/2→1/1) to afford recovered diol **17** (13.1 mg) as well as ester **20** (13.7 mg, 39% yield, 68% yield based on recovered starting material) as a colorless oil. **20**: R_f = 0.36 (silica gel, EtOAc/hexanes, 1/1); IR (film) ν_{max} 3452, 3054, 2984, 1709, 1507, 1265, 1169 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.38 (s, 1 H), 7.55 (d, *J* = 7.8 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 7.16 (t, *J* = 7.5 Hz, 1 H), 7.09 (t, *J* = 7.4 Hz, 1 H), 4.72 (br s, 1 H), 4.64 (d, *J* = 11.5 Hz, 1 H), 4.14 (d, *J* = 11.5 Hz, 1 H), 3.88 (dd, *J* = 11.3, 7.0 Hz, 1 H), 3.68 (d, *J* = 12.0 Hz, 1 H), 3.60 (br s, 1 H), 3.43–3.41 (m, 2 H), 3.07 (t, *J* = 6.7 Hz, 2 H), 2.13 (s, 3 H), 1.46 (s, 3 H), 1.39 (s, 9 H); ¹³C NMR (125 MHz, CDCl₃) δ 172.2, 156.0, 136.2, 134.9, 128.9, 121.9, 119.3, 118.4, 110.9, 109.4, 79.2, 67.6, 42.3, 41.4, 29.7, 28.4, 26.1, 20.9, 19.9; HRMS (ESI) calcd for C₂₁H₃₀N₂O₅Na [M + Na⁺] 413.2053, found 413.2050. The enantiopurity was determined using chiral HPLC (AD-H column, 4.6 × 250 mm, 9:1 hexanes/*i*-PrOH, 1 mL/min, UV detector at 280 nm), R_T = 16.1 min (major), R_T = 20.6 min (minor), ee = 34%. In additional runs we found that by decreasing the reaction time to 48 h the enantioselectivity could be increased up to 60% ee, but with significantly lower yields of ester **20** (10–20%).

Ester 20 (chemical). To a reaction flask under an atmosphere of N₂ at 23 °C was added CuCl₂ (1.9 mg, 0.0143 mmol, 0.1 equiv) followed by a solution of Pybox ligand **18** (8.5 mg, 0.0143 mmol, 0.1 equiv) in CH₂Cl₂ (1.1 mL), and the resulting mixture was stirred at 23 °C for 3 h. Next, a solution of diol **17** (50.0 mg, 0.143 mmol, 1.0 equiv) in CH₂Cl₂ (0.6 mL) was added and the reaction contents were cooled to -78 °C. Next, acetyl chloride (0.015 mL, 0.215 mmol, 1.5 equiv) and Et₃N (0.022 mL, 0.158 mmol, 1.1 equiv) were added sequentially dropwise and

the reaction mixture was stirred at -78°C for 18 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (1 mL) and warmed to 23°C . The mixture was diluted with saturated aqueous NH_4Cl (5 mL) and poured into a separatory funnel. After separating the resultant layers, the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic layers were then washed with saturated aqueous NaCl (20 mL), dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash column chromatography (silica gel, $\text{EtOAc}/\text{hexanes}$, $1/2 \rightarrow 1/1$) to afford recovered diol **17** (37.9 mg) as well as ester **20** (10.2 mg, 18% yield, 75% yield based on recovered starting material) as a colorless oil. All spectroscopic data were in full agreement with the compound prepared by enzymatic desymmetrization. The enantiopurity was determined using chiral HPLC (AD-H column, 4.6×250 mm, 9:1 hexanes/*i*-PrOH, 1 mL/min, UV detector at 280 nm), $R_T = 16.1$ min (major), $R_T = 20.7$ min (minor), ee = 66%. The absolute configuration is the same as that obtained as the enzymatically acetylated product.

Scheme S5. Explorations into a potential Tsuji-Trost allylation strategy for the synthesis of aldehyde **16**.^a



Reagents and conditions: a) allyl alcohol/THF (5/2), NaH (1.5 equiv), 23°C , 3 h; b) Boc_2O (1.3 equiv), 4-DMAP (0.1 equiv), Et_3N (3.0 equiv), CH_2Cl_2 , 23°C , 4 h; c) $\text{Pd}(\text{PPh}_3)_4$ (0.1 equiv), toluene, 23°C , 30 min; d) $\text{PdCl}_2(\text{MeCN})_2$ (0.15 equiv), toluene, 60°C , 3 h; e) LiEt_3BH (1.5 equiv), THF, -78°C , 1 h; f) TFA (2.0 equiv), Et_3SiH (10 equiv), CH_2Cl_2 , 0°C , 15 min.

Allyl Ester 22. To a slurry of lactam **21** (0.200 g, 0.70 mmol, 1.0 equiv) in THF (2.0 mL) and allyl alcohol (5.0 mL) at 0°C was added NaH (60% dispersion in mineral oil, 0.042 g, 1.05 mmol, 1.5 equiv). After stirring the reaction contents at 0°C for 30 min, the contents were allowed to warm to 23°C and stirred for an additional 3 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (5 mL) and diluted with EtOAc (10 mL). The mixture was then transferred to a separatory funnel and the layers were separated. The organic phase was washed with brine (2×5 mL), dried (MgSO_4), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, $\text{EtOAc}/\text{hexanes}$, 1/2) to give the desired transesterification product (0.194 g, 93% yield). Pressing forward, the newly-synthesized transesterification product (0.194 g, 0.65 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (10 mL), and Boc_2O (0.184 g, 0.85 mmol, 1.3 equiv), 4-DMAP (0.008 g, 0.065 mmol, 0.1 equiv) and Et_3N (0.27 mL, 1.95 mmol, 3.0 equiv) were added sequentially at 23°C . The resultant reaction mixture was then stirred at 23°C for 3 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (10 mL) and diluted with EtOAc (20 mL). The mixture was then transferred to a separatory funnel and the layers were separated. The organic phase was washed with brine (2×10 mL), dried (MgSO_4), and concentrated. The resultant crude material was purified by flash column chromatography (silica gel, $\text{EtOAc}/\text{hexanes}$, 1/4 \rightarrow 1/2) to give the desired allyl ester **22** (0.220 g, 85% yield) as a pale yellow solid. **22:** $R_f = 0.65$ (silica gel, $\text{EtOAc}/\text{hexanes}$, 1/2); IR (film) ν_{max}

2924, 2852, 1718, 1580, 1507, 1459, 1366, 1302, 1150, 1048 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 78.10 (s, 1 H), 7.48 (d, $J = 7.9$ Hz, 1 H), 7.34 (d, $J = 8.1$ Hz, 1 H), 7.23–7.19 (m, 1 H), 7.12 (t, $J = 7.5$ Hz, 1 H), 5.93–5.80 (m, 1 H), 5.30 (dt, $J = 17.2, 1.5$ Hz, 1 H), 5.27–5.23 (m, 1 H), 4.66 (d, $J = 7.1$ Hz, 2 H), 4.51 (dt, $J = 15.8, 3.6$ Hz, 1 H), 3.65 (ddd, $J = 15.5, 12.7, 2.5$ Hz, 1 H), 3.11 (ddd, $J = 16.6, 12.7, 3.8$ Hz, 1 H), 3.01 (dt, $J = 17.0, 2.8$ Hz, 1 H), 2.08–2.01 (m, 3 H), 1.54 (d, $J = 1.5$ Hz, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.9, 168.5, 152.8, 135.2, 130.9, 128.1, 127.1, 122.9, 119.9, 119.6, 118.5, 111.8, 110.9, 83.5, 66.7, 42.7, 28.2, 28.0, 24.6, 21.8; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_5^+ [\text{M}^+]$ 398.1842, found 398.1823.

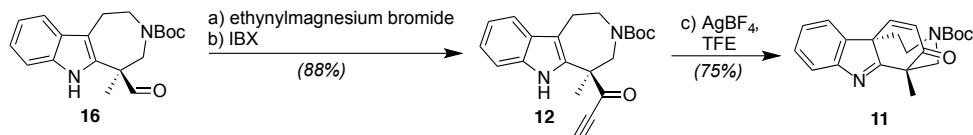
Allylation Product 23. To a solution of allyl ester **22** (0.044 g, 0.11 mmol, 1.0 equiv) in toluene (5.0 mL) at 23 °C was added $\text{Pd}(\text{PPh}_3)_4$ (0.056 g, 0.011 mmol, 0.1 equiv), and the resultant mixture was stirred at 23 °C for 30 min. Upon completion, the reaction contents were concentrated directly and the resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1/2) to give allylation product **23** (0.038 g, 98% yield) as a colorless oil. **23:** $R_f = 0.68$ (silica gel, EtOAc/hexanes, 1/2); IR (film) ν_{max} 3395, 2924, 2692, 1727, 1557, 1463, 1377, 1166, 1063 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.88 (s, 1 H), 7.47 (d, $J = 7.8$ Hz, 1 H), 7.32 (d, $J = 8.0$ Hz, 1 H), 7.22–7.17 (m, 1 H), 7.12 (t, $J = 7.5$ Hz, 1 H), 5.69 (ddt, $J = 17.2, 10.1, 7.2$ Hz, 1 H), 5.17–5.12 (m, 1 H), 5.10 (dd, $J = 10.3, 1.7$ Hz, 1 H), 4.25 (ddd, $J = 14.7, 5.9, 4.0$ Hz, 1 H), 4.08 (ddd, $J = 14.7, 8.3, 4.1$ Hz, 1 H), 3.11–3.02 (m, 2 H), 2.91 (dd, $J = 14.4, 7.1$ Hz, 1 H), 2.77 (dd, $J = 14.4, 7.3$ Hz, 1 H), 1.72 (s, 3 H), 1.51 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 176.3, 153.8, 134.8, 134.8, 133.3, 133.1, 128.0, 122.3, 119.6, 119.0, 118.1, 111.1, 110.5, 82.7, 46.0, 43.7, 28.0, 25.5, 24.2; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{27}\text{N}_2\text{O}_3^+ [\text{M}^+ \text{H}^+]$ 355.2021, found 355.2019.

Alkene Isomerization Product 24. To a solution of the allylation product **23** (0.038 g, 0.11 mmol, 1.0 equiv) in toluene (5.0 mL) at 23 °C was added $\text{PdCl}_2(\text{MeCN})_2$ (0.004 g, 0.017 mmol, 0.15 equiv). The resultant mixture was then warmed to 60 °C and heated at that temperature for 3 h. Upon completion, the reaction contents were cooled to 23 °C and concentrated directly. The resultant residue was then purified by flash column chromatography (silica gel, EtOAc/hexanes, 1/2) to give the desired alkene isomerization product **24** (0.022 g, 57% yield) as a colorless oil. **24:** $R_f = 0.37$ (silica gel, EtOAc/hexanes, 1/4); IR (film) ν_{max} 3379, 2980, 2934, 1761, 1718, 1460, 1369, 1342, 1300, 1226, 1147, 1048 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.98 (s, 1 H), 7.48 (d, $J = 7.9$ Hz, 1 H), 7.34 (d, $J = 8.1$ Hz, 1 H), 7.20 (t, $J = 7.7$ Hz, 1 H), 7.12 (t, $J = 7.4$ Hz, 1 H), 5.82 (dt, $J = 15.3, 1.8$ Hz, 1 H), 5.33 (dq, $J = 15.8, 6.5$ Hz, 1 H), 4.41 (ddd, $J = 15.1, 12.5, 2.5$ Hz, 1 H), 4.28 (dt, $J = 15.1, 3.8$ Hz, 1 H), 3.09 (ddd, $J = 16.6, 12.5, 3.8$ Hz, 1 H), 2.97 (dt, $J = 16.8, 3.1$ Hz, 1 H), 1.80 (s, 3 H), 1.66 (dd, $J = 6.6, 1.8$ Hz, 3 H), 1.52 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.3, 153.4, 135.7, 134.7, 131.2, 128.4, 126.2, 122.3, 119.6, 118.2, 110.9, 110.6, 83.0, 52.2, 42.4, 28.0, 25.4, 24.6, 17.6; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_3^+ [\text{M}^+]$ 354.1943, found 354.1938.

Reduction product 25. To a solution of alkene isomerization product **24** (6.0 mg, 0.017 mmol, 1.0 equiv) in THF (0.5 mL) at -78 °C was added LiEt_3BH (1.0 M in THF, 25 μL , 0.025 mmol, 1.5 equiv), and the resultant pale yellow solution was stirred at -78 °C for 1 h. Upon completion, the reaction contents were quenched by the addition of excess $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ and warmed to 23 °C. After stirring the reaction mixture at 23 °C for 10 min, the contents were filtered through a pad of Na_2SO_4 (eluting with EtOAc). The filtrate was then concentrated directly, and the resultant residue was redissolved in CH_2Cl_2 (1 mL) and cooled to 0 °C. Et_3SiH (20.2 mg, 0.170 mmol, 10.0 equiv) and TFA (3.9 mg, 0.034 mmol, 2.0 equiv) were then added sequentially at 0 °C. The yellowish reaction solution was then stirred at 0 °C for 15 min. Upon

completion, the reaction contents were quenched by the addition of saturated aqueous NaHCO₃ (1 mL) and warmed up to 23 °C. The reaction contents were transferred to separatory funnel. After separating the layers, the aqueous layer was extracted with CH₂Cl₂ (3 × 2 mL). The organic layer was combined, dried (Na₂SO₄), filtered, and concentrated. The resulting residue was purified by preparative TLC (EtOAc/hexanes, 1/4) to afford reduction product **25** (3.8 mg, 64% yield) as a colorless oil. **25**: R_f = 0.54 (silica gel, EtOAc/hexanes, 1/4); IR (film) ν_{max} 3344, 2972, 2926, 2854, 1672, 1463, 1420, 1366, 1347, 1323, 1233, 1159, 975, 740 cm⁻¹; ¹H NMR (500 MHz, CDCl₃, 2 rotamers, ~0.5:0.5) δ 7.80 (s, 0.5 H), 7.76 (s, 0.5 H), 7.49 (t, J = 7.8 Hz, 1 H), 7.32–7.25 (m, 1 H), 7.11 (dt, J = 20.7, 7.2 Hz, 2 H), 5.68–5.57 (m, 1 H), 5.55–5.45 (m, 0.5 H), 5.45–5.37 (m, 0.5 H), 3.91 (dt, J = 13.1, 5.2 Hz, 0.5 H), 3.78 (dt, J = 13.2, 5.2 Hz, 0.5 H), 3.69 (t, J = 14.8 Hz, 1 H), 3.60–3.43 (m, 2 H), 2.99 (ddd, J = 11.7, 7.2, 3.8 Hz, 2 H), 1.78–1.76 (m, 1.5 H), 1.71 (dd, J = 6.5, 1.5 Hz, 1.5 H), 1.49 (s, 4.5 H), 1.48 (s, 4.5 H), 1.39 (d, J = 2.3 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃, 2 rotamers, ~0.5:0.5) δ 155.7, 155.3, 139.9, 139.4, 135.1, 134.3, 134.3, 128.9, 128.7, 126.0, 121.4, 121.4, 119.2, 118.1, 117.8, 111.2, 110.9, 110.4, 110.3, 79.6, 79.3, 56.6, 55.3, 48.9, 48.3, 45.6, 45.2, 28.5, 28.5, 24.4, 23.7, 23.6, 18.2, 18.0; HRMS (ESI) calcd for C₁₆H₂₅O₄⁺ [M+H⁺] 341.2229, found 341.2222.

Scheme S6. Synthesis of enone **11**.



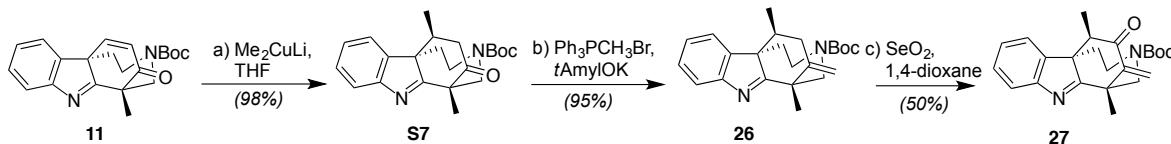
Reagents and conditions: a) 3 (1.0 equiv) in THF (0.06 M), ethynylmagnesium bromide (0.5 M in toluene, 3.0 equiv), -40 °C for 3 h; b) IBX (3.0 equiv), DMSO (0.15 M), 23 °C for 18 h; c) **12** (1.0 equiv) in TFE (0.04 M), AgBF₄ (0.1 equiv), 0 °C for 2 h.

Propargyl Ketone 12. Aldehyde **16** (0.990 g, 3.02 mmol, 1.0 equiv) was dissolved in THF (50 mL) and the resultant solution was cooled to -40 °C under an argon atmosphere before ethynylmagnesium bromide (0.5 M in THF, 18.1 mL, 9.06 mmol, 3.0 equiv) was added over the course of 5 min. The resultant mixture was stirred at -40 °C for 1 h, and slowly warmed up to 0 °C over the course of 3 h. Upon completion, the reaction contents were quenched with saturated aqueous NH₄Cl (10 mL), diluted with EtOAc (20 mL), and poured into a separatory funnel. After separating the resultant layers, the organic layer was washed with saturated aqueous NH₄Cl (20 mL) and brine (2 × 20 mL), dried (MgSO₄), filtered, and concentrated. Pressing forward without any addition purification, the resultant crude product (3.02 mmol assumed, 1.0 equiv) was dissolved in DMSO (20 mL) and IBX (2.08 g, 9.06 mmol, 3.0 equiv) was added at 23 °C. The reaction contents were then stirred at 23 °C for 18 h. Upon completion, the reaction contents were diluted with EtOAc (20 mL), quenched with saturated aqueous Na₂SO₃ (10 mL), and poured into a separatory funnel. After separating the resultant layers, the organic layer was washed with H₂O (5 × 20 mL), dried (MgSO₄), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1/9→1/4) to give propargyl ketone **12** (0.937 g, 88% yield over two steps) as a yellow foam. **12**: R_f = 0.46 (silica gel, EtOAc/hexanes, 1/2); IR (film) ν_{max} 3345, 2977, 2923, 2091, 1670, 1458, 1419, 1367, 1250, 1156, 1034 cm⁻¹; ¹H NMR (500 MHz, CDCl₃, 2 rotamers, ~0.4:0.6) δ 8.55 (s, 1 H), 7.56 (d, J = 7.8 Hz, 1 H), 7.32 (d, J = 7.8 Hz, 1 H), 7.20 (t, J = 7.5 Hz, 1 H), 7.15 (t, J = 7.5 Hz, 1 H), 4.34 (d, J = 14.3 Hz, 0.4 H), 4.30 (d, J = 14.3 Hz, 0.6 H), 4.10–3.90 (m, 1 H), 3.89–3.76 (m, 1 H),

3.69 (ddd, $J = 13.1, 9.2, 3.8$ Hz, 0.4 H), 3.60 (ddd, $J = 13.1, 9.2, 3.8$ Hz, 0.6 H), 3.66–3.55 (m, 3 H), 1.65 (s, 1.2 H), 1.61 (s, 1.8 H), 1.54 (s, 3.6 H), 1.51 (s, 5.4 H); ^{13}C NMR (125 MHz, CDCl_3 , 2 rotamers, ~0.4:0.6) δ 188.3, 188.0, 155.7, 154.8, 135.5, 133.5, 133.4, 128.2, 128.0, 122.2, 122.1, 119.3, 118.2, 118.0, 113.6, 113.1, 110.9, 110.8, 82.8, 82.4, 80.6, 80.5, 79.9, 56.0, 55.9, 52.8, 50.8, 48.5, 48.2, 28.3, 28.2, 23.2, 22.9, 21.5, 20.9; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_3^+ [\text{M} + \text{H}^+]$ 353.1865, found 353.1867.

Enone 11. To a solution of propargyl ketone **12** (0.022 g, 0.06 mmol, 1.0 equiv) in TFE (1.5 mL) at 0 °C under an argon atmosphere was added a solution of AgBF_4 in TFE (0.1 mL, 0.06 M, 0.006 mmol, 0.1 equiv) in a single portion. The resultant reaction mixture was stirred at 0 °C for 2 h. Upon completion, the reaction contents were filtered through Celite, washing with EtOAc (3 × 2 mL), and the combined filtrates were concentrated. The resultant residue was purified by flash column chromatography (silica gel, $\text{EtOAc}/\text{hexanes}$, 1/4 → 1/2) to give enone **11** (0.016 g, 75% yield) as a yellow foam. **11:** $R_f = 0.61$ (silica gel, $\text{EtOAc}/\text{hexanes}$, 1/1); IR (film) ν_{max} 3352, 2976, 2930, 1688, 1611, 1562, 1367, 1458, 1417, 1383, 1280, 1251, 1198 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3 , 2 rotamers, ~0.4:0.6) δ 7.66 (d, $J = 8.0$ Hz, 0.4 H), 7.65 (d, $J = 8.0$ Hz, 0.6 H), 7.41–7.36 (m, 2 H), 7.30–7.27 (m, 1 H), 7.17 (d, $J = 9.6$ Hz, 0.6 H), 7.11 (d, $J = 9.6$ Hz, 0.4 H), 6.26 (d, $J = 9.5$ Hz, 0.4 H), 6.23 (d, $J = 9.6$ Hz, 0.6 H), 4.00 (d, $J = 14.1$ Hz, 0.6 H), 3.95 (d, $J = 14.1$ Hz, 0.4 H), 3.67 (d, $J = 14.1$ Hz, 0.4 H), 3.57–3.54, (m, 1.4 H), 3.41 (t, $J = 5.9$ Hz, 0.6 H), 3.34 (ddd, $J = 14.7, 7.8, 4.6$ Hz, 0.6 H), 2.53 (ddd, $J = 14.4, 7.8, 4.5$ Hz, 0.6 H), 2.42 (dt, $J = 14.4, 5.7$ Hz, 0.4 H), 1.82 (ddd, $J = 14.4, 7.8, 4.5$ Hz, 0.6 H), 1.75 (dt, $J = 14.4, 5.7$ Hz, 0.4 H), 1.66 (s, 1.2 H), 1.64 (s, 1.8 H), 1.42 (s, 3.2 H), 1.38 (s, 5.4 H); ^{13}C NMR (125 MHz, CDCl_3 , 2 rotamers, ~0.4:0.6) δ 200.6, 200.3, 183.8, 183.7, 154.4, 154.1, 153.1, 153.0, 148.2, 147.0, 142.4, 142.2, 130.6, 130.1, 128.6, 128.5, 126.4, 126.3, 121.3, 121.2, 80.7, 80.3, 59.2, 58.9, 58.0, 57.7, 56.8, 55.9, 46.1, 45.6, 36.0, 34.5, 28.2, 28.1, 18.4, 18.0; HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_3^+ [\text{M} + \text{H}^+]$ 353.1865, found 353.1860.

Scheme S7. Synthesis of enone **27**.



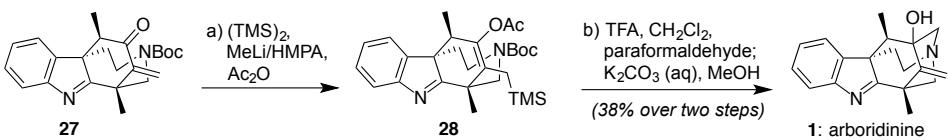
Reagents and conditions: a) CuI (3.0 equiv), MeLi (1.6 M in Et_2O , 6.0 equiv), **11** (1.0 equiv), THF (0.03 M), -78 °C to 0 °C over 4 h; b) **S7** (1.0 equiv), $\text{Ph}_3\text{PCH}_3\text{Br}$ (5.0 equiv), $t\text{AmylOK}$ (1.4 M in toluene, 4.0 equiv), toluene (0.06 M), 80 °C for 1 h; c) SeO_2 (10.0 equiv), 1,4-dioxane, 80 °C for 8 h.

Ketone S7. To a slurry of CuI (0.160 g, 0.84 mmol, 3.0 equiv) in THF (8.0 mL) at 0 °C under an argon atmosphere was added MeLi (1.6 M in Et_2O , 1.03 mL, 1.65 mmol, 6.0 equiv) dropwise during which time the solid disappeared and the solution turned from yellow to colorless. The resulting solution was then stirred at 0 °C for 5 min and was cooled to -78 °C. A solution of enone **11** (0.097 g, 0.28 mmol, 1.0 equiv) in THF (2.0 mL) was then added dropwise. The resultant reaction mixture was then stirred at -78 °C for 30 min and slowly warmed to -40 °C over the course of 4 h. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NH_4Cl (10 mL), diluted with EtOAc (10 mL), and poured into a separatory funnel. After separating the resultant layers, the organic layer was washed repeatedly with saturated aqueous NH_4Cl (4 × 5 mL) until the aqueous phase no longer had a blue color. The organic layer was then dried (MgSO_4), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, $\text{EtOAc}/\text{hexanes}$, 1/4 → 1/2) to give ketone

S7 (0.096 g, 95% yield) as a yellow foam. **S7**: $R_f = 0.74$ (silica gel, EtOAc/hexanes, 1/1); IR (film) ν_{max} 3376, 2977, 2950, 1714, 1694, 1561, 1457, 1417, 1367, 1382, 1159 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3 , 2 rotamers, ~0.2:0.8) δ 7.55 (d, $J = 7.5$ Hz, 1 H), 7.31–7.21 (m, 3 H), 4.49 (d, $J = 13.4$ Hz, 0.2 H), 4.33 (d, $J = 13.4$ Hz, 0.8 H), 3.98 (d, $J = 13.4$ Hz, 0.8 H), 3.80 (d, $J = 13.4$ Hz, 0.2 H), 2.87–2.80 (m, 2 H), 2.47–2.44 (m, 3 H), 2.36 (t, $J = 13.5$ Hz, 1 H), 2.22 (t, $J = 13.5$ Hz, 1 H), 1.48 (s, 3 H), 1.45 (s, 9 H), 0.30 (d, $J = 6.9$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3 , 2 rotamers, ~0.2:0.8) δ 211.1, 186.0, 154.4, 154.1, 146.1, 127.9, 126.4, 121.7, 121.6, 120.8, 80.8, 80.5, 62.0, 59.6, 58.4, 57.4, 47.5, 44.0, 43.6, 36.1, 35.7, 33.2, 32.0, 28.3, 28.0, 17.3, 15.5; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{29}\text{N}_2\text{O}_3^+ [\text{M} + \text{H}^+]$ 369.2178, found 369.2179.

Enone 27. Methyltriphenylphosphonium bromide (0.231 g, 0.65 mmol, 5.0 equiv) and ketone **S7** (0.048 g, 0.13 mmol, 1.0 equiv) were dissolved in toluene (2 mL) under an argon atmosphere at 23 °C and the resultant solution was then heated to 80 °C at which time potassium *tert*-pentyloxide solution (20% in toluene, 0.37 mL, 0.52 mmol, 4.0 equiv) was added in a single portion. The resultant reaction mixture was then stirred at 80 °C for 1 h before being cooled to 23 °C and quenched by the addition of saturated aqueous NH_4Cl (2 mL). The reaction contents were then poured into a separatory funnel and the resultant layers were separated. The aqueous layer was then extracted with EtOAc (2×5 mL) and the combined organic layers were washed with brine (2×10 mL), dried (MgSO_4), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1/5) to afford the desired methylenated product **26** (0.044 g, 95% yield) as a colorless oil. Pressing forward, the newly-formed alkene **26** (0.044 g, 0.13 mmol, 1.0 equiv) was dissolved in 1,4-dioxane (5 mL) at 23 °C, SeO_2 (0.133 g, 1.20 mmol, 10.0 equiv) was added, and the resultant mixture was heated to 80 °C. After stirring at 80 °C for 8 h, the reaction contents were cooled to 23 °C and quenched by the addition of saturated aqueous NaHCO_3 (5 mL) and diluted with EtOAc (10 mL). The mixture was then transferred to a separatory funnel and the resultant layers were separated. The organic layer was washed with brine (2×10 mL), dried (MgSO_4), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1/4) to afford enone **27** (0.023 g, 50% yield) as a yellow oil. **27**: $R_f = 0.69$ (silica gel, EtOAc/hexanes, 1/1); IR (film) ν_{max} 3374, 3050, 2976, 2931, 2872, 1695, 1576, 1456, 1415, 1367, 1320, 1298, 1278, 1162, 1129, 995, 970 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3 , 2 rotamers ~0.5:0.5) δ 7.63 (d, $J = 7.6$ Hz, 1 H), 7.37 (td, $J = 7.4, 1.6$ Hz, 1 H), 7.29–7.23 (m, 2 H), 6.65 (s, 0.5 H), 6.63 (s, 0.5 H), 5.95 (s, 0.5 H), 5.82 (s, 0.5 H), 4.60 (d, $J = 13.6$ Hz, 0.5 H), 4.35 (d, $J = 13.6$ Hz, 0.5 H), 3.93 (dd, $J = 13.6, 4.8$ Hz, 0.5 H), 3.74 (dd, $J = 14.8, 5.2$ Hz, 0.5 H), 3.10–2.90 (m, 2 H), 2.93–2.77 (m, 1 H), 2.33 (dd, $J = 14.5, 4.9$ Hz, 1 H), 2.16–1.86 (m, 2 H), 1.68 (s, 1.5 H), 1.67 (s, 1.5 H), 1.45–1.39 (m, 9 H), 0.51 (dd, $J = 7.4, 3.0$ Hz, 1.5 H), 0.45 (dd, $J = 7.4, 3.0$ Hz, 1.5 H); ^{13}C NMR (100 MHz, CDCl_3 , 2 rotamers ~0.5:0.5) δ 199.8, 199.4, 186.2, 185.8, 155.3, 155.2, 154.8, 154.2, 145.2, 144.4, 142.4, 142.2, 129.4, 128.5, 127.9, 126.4, 126.3, 122.1, 122.0, 120.8, 120.7, 80.3, 80.2, 61.2, 61.0, 60.5, 59.5, 51.8, 47.9, 45.2, 44.9, 33.5, 33.1, 28.3, 28.2, 24.1, 23.9, 12.7, 12.6; HRMS (ESI-APCI) calcd for $\text{C}_{23}\text{H}_{29}\text{N}_2\text{O}_3^+ [\text{M} + \text{H}^+]$ 381.2178, found 381.2183.

Scheme S8. Completion of the synthesis of arboridinine (**1**).

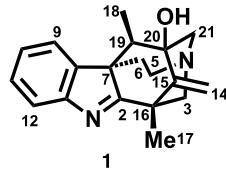


Reagents and conditions: a) $(\text{TMS})_2$ (10 equiv), MeLi (1.6 M in Et_2O , 9.0 equiv), HMPA (1.0 M), 0 °C, then **27** (1.0 equiv), Ac_2O (10 equiv), THF (0.1 M) -78 °C for 30 min; b) **28** (1.0 equiv) in $\text{TFA}/\text{CH}_2\text{Cl}_2$ (1/2, 0.01 M), 23 °C for 30 min; remove volatiles, re-dissolve in CH_2Cl_2 , add paraformaldehyde (50 equiv), 23 °C for 2 h; saturated K_2CO_3 (aq), MeOH (0.01M), 23 °C for 18 h.

Arboridinine (1). Following the modified procedure of Hwu,⁵ a solution of hexamethyldisilane (0.09 mL, 0.45 mmol, 10.0 equiv) in HMPA (0.05 mL) was cooled to 0 °C under an argon atmosphere. MeLi (1.6 M in Et_2O , 0.25 mL, 0.41 mmol, 9.0 equiv) was then added and the resultant orange solution was stirred at 0 °C for 5 min. The reaction contents were then cooled to -78 °C and a solution of enone **27** (16.5 mg, 0.045 mmol, 1.0 equiv) in THF (0.5 mL) was added at -78 °C. The cold bath was removed, and the resultant reaction mixture was stirred for an additional 20 min, during which time it warmed to 0 °C and at which point TLC analysis indicated full consumption of enone **27**. Next, the reaction contents were recooled to -78 °C and Ac_2O (0.04 mL, 0.45 mmol, 10.0 equiv) was added in a single portion at -78 °C. The reaction contents were then stirred for an additional 10 min at -78 °C. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous NaHCO_3 (5 mL) and diluted with EtOAc (5 mL). The reaction mixture was then transferred to a separatory funnel and the resultant layers were separated. The organic layer washed with brine (2×5 mL), dried (Na_2SO_4), filtered, and concentrated. The resultant residue was purified by preparative thin layer chromatography (silica gel, $\text{EtOAc}/\text{hexanes}$, 1/1) to afford silylated enol acetate **28** (9.0 mg, 40% yield) as a colorless oil. Pressing forward, silylated enol acetate **28** (9.0 mg, 0.018 mmol, 1.0 equiv) was dissolved in a mixture of CH_2Cl_2 (1.0 mL) and TFA (0.5 mL) at 23 °C and stirred at that temperature for 30 min. Upon completion, the volatiles were removed by rotary evaporation and the resultant crude TFA salt was redissolved in CH_2Cl_2 (1.5 mL) at 23 °C and paraformaldehyde (16.0 mg, 0.90 mmol, 50.0 equiv) was added. The reaction contents were then stirred at 23 °C for another 2 h. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous K_2CO_3 (2.0 mL), diluted with MeOH (2.0 mL), and the resultant contents were stirred at 23 °C for 18 h. To the mixture was then added saturated aqueous NaHCO_3 (1.0 mL) and the contents were poured into a separatory funnel. After separating the resultant layers, the aqueous layer was extracted with EtOAc (3×5 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The resultant residue was purified by preparative thin-layer chromatography (silica gel, $\text{EtOAc}/\text{Et}_3\text{N}$, 100/1) to afford arboridinine (**1**, 5.0 mg, 38% yield over two steps) as a white solid. X-ray diffraction quality crystals were obtained by slow evaporation of a CH_2Cl_2 solution of **1** in a vial capped with a rubber septum in a refrigerator at 4 °C. **1**: $R_f = 0.39$ (silica gel, $\text{EtOAc}/\text{Et}_3\text{N}$, 100/1); IR (film) ν_{max} 3346, 2978, 2932, 2848, 1645, 1561, 1458, 1373, 1265, 1199, 1164, 1071, 1043 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.54 (d, $J = 7.5$ Hz, 1 H), 7.26 (dt, $J = 7.5, 1.5$ Hz, 1 H), 7.17 (t, $J = 7.4$ Hz, 1 H), 7.13 (d, $J = 7.4$ Hz, 1 H), 5.01 (s, 1 H), 5.00 (s, 1 H), 3.38 (ddd, $J = 15.2, 9.8, 5.4$ Hz, 1 H), 3.29 (d, $J = 13.2$ Hz, 1 H), 3.18 (ddd, $J = 15.2, 9.8, 5.4$ Hz, 1 H), 3.18 (d, $J = 13.2$ Hz, 1 H), 3.11 (d, $J = 13.6$ Hz, 1 H), 3.02 (d, $J = 13.6$ Hz, 1 H), 2.55 (q, $J = 6.9$ Hz, 1 H), 2.25 (ddd, $J = 14.9, 9.8, 5.2$ Hz, 1 H), 1.52 (ddd, $J = 14.9, 9.8, 5.2$ Hz, 1 H), 1.49 (s, 3 H), 0.39 (d, $J = 6.9$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 189.9, 153.8, 153.4, 145.6, 127.4, 125.3, 122.0, 120.8,

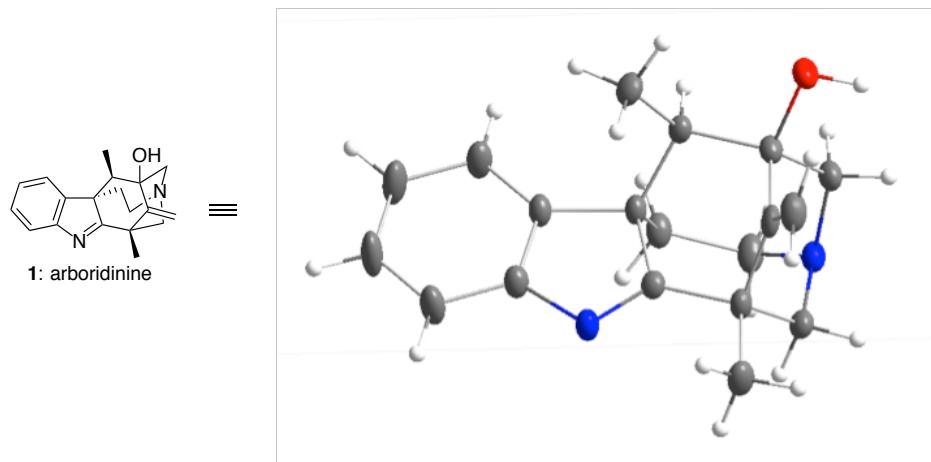
104.2, 74.1, 67.1, 62.8, 61.7, 53.0, 50.0, 48.3, 34.6, 18.0, 12.7; HRMS (ESI-APCI) calcd for C₁₉H₂₃N₂O⁺ [M + H⁺] 295.1810, found 295.1810.

Table S1. Comparison of Literature and Obtained Spectral Values for Arboridinine (**1**).⁶

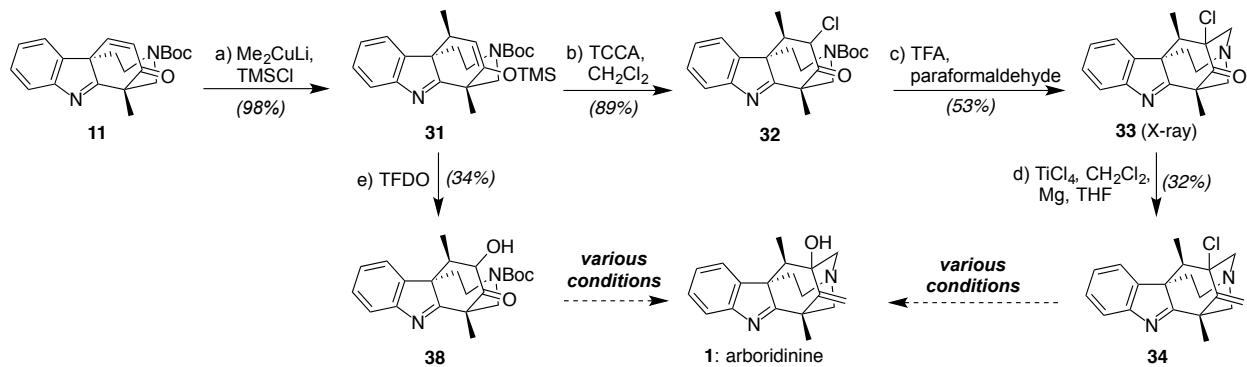


H/C #	Kam: Natural 1 (¹ H NMR, CDCl ₃ , 600 MHz)	This Report: Synthetic 1 (¹ H NMR, CDCl ₃ , 500 MHz)	Kam: Natural 1 (¹³ C NMR, CDCl ₃ , 150 MHz)	This Report: Synthetic 1 (¹³ C NMR, CDCl ₃ , 125 MHz)
2	—	—	189.1	189.9
3	3.09 d (14) 3.11 d (14)	3.02 d (14) 3.11 d (14)	62.3	62.8
5 α	3.20 ddd (15, 10, 5)	3.18 ddd (15, 10, 5)	53.0	53.0
5 β	3.46 ddd (15, 10, 5)	3.38 ddd (15, 10, 5)		
6 α	1.57 ddd (15, 10, 5)	1.52 ddd (15, 10, 5)	34.1	34.6
6 β	2.32 ddd (15, 10, 5)	2.25 ddd (15, 10, 5)		
7	—	—	61.5	61.7
8	—	—	145.4	145.6
9	7.15 d (7.5)	7.13 d (7.4)	122.0	122.0
10	7.18 t (7.5)	7.17 t (7.5)	125.6	125.3
11	7.26 td (7.5, 1)	7.26 td (7.5, 1.5)	127.6	127.4
12	7.55 d (7.5)	7.54 d (7.5)	120.9	120.8
13	—	—	152.8	153.4
14b	5.05 s	5.00 s	105.0	104.2
14a	5.06 s	5.01 s		
15	—	—	153.3	153.8
16	—	—	49.3	50.0
17	1.51 s	1.49 s	18.1	18.0
18	0.39 d (7)	0.39 d (7)	12.6	12.7
19	2.59 q (7)	2.55 q (7)	48.3	48.3
20	—	—	73.7	74.1
21 α	3.26 d (13)	3.18 d (13)	66.2	67.1
21 β	3.36 d (13)	3.29 d (13)		

Figure S1. X-ray crystal structure of arbordinine (**1**).



Scheme S9. The failed attempt at a Mannich strategy for the synthesis of arbordinine **1**.



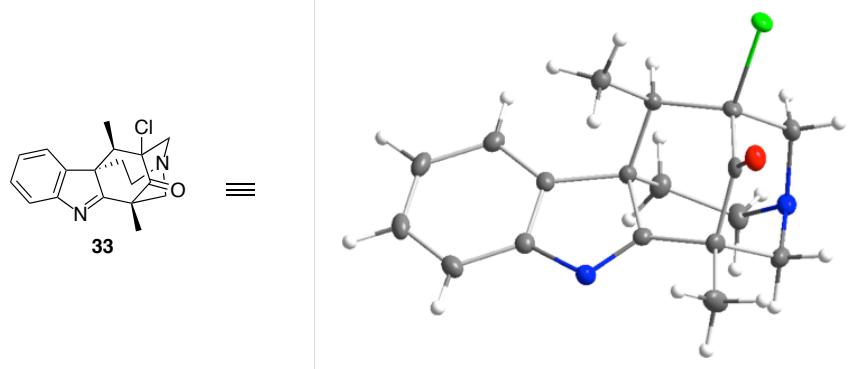
Reagents and conditions: a) CuI (3.0 equiv), MeLi (1.6 M in Et_2O , 6.0 equiv), TMSCl (3.0 equiv), THF (0.03 M), -78°C to -40°C over 4 h; b) TCCA (5.0 equiv), NaHCO_3 (10 equiv), THF (0.035 M), 25°C , 15 min; c) $\text{TFA}/\text{CH}_2\text{Cl}_2$ (1/2, 0.07 M), 25°C , 10 min, then $(\text{CH}_2\text{O})_n$ (10 equiv), 1 h; d) Mg powder (8.0 equiv), TiCl_4 (1.0 M in CH_2Cl_2 , 2.0 equiv), $\text{CH}_2\text{Cl}_2/\text{THF}$ (6/1, 0.15 M), 0°C , 1 h, then 25°C , 20 min; e) 1,1,1-trifluoroacetone (300 equiv), oxone (15 equiv), H_2O (300 equiv), NaHCO_3 (8 equiv), Na_2EDTA (3 equiv), MeCN (0.05 M), rt, 4 h.

Silyl enol ether **31.** To a slurry of CuI (0.057 g, 0.30 mmol, 3.0 equiv) in THF (4.0 mL) at 0°C under an argon atmosphere was added MeLi (1.6 M in Et_2O , 0.38 mL, 0.60 mmol, 6.0 equiv) dropwise until the solid disappeared and the solution turned from yellow to colorless. The resulting solution was stirred at 0°C for 5 min then cooled to -78°C before a solution of enone **11** (0.036 g, 0.102 mmol, 1.0 equiv) in THF (1.0 mL) was added dropwise. The resultant reaction mixture was stirred at -78°C for 30 min and then TMSCl (0.04 mL, 0.30 mmol, 3.0 equiv) was added in one portion. The reaction was then slowly warmed to -40°C over 4 h with stirring. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NaHCO_3 (5 mL) and diluted with EtOAc (5 mL). The mixture was then transferred to a separatory funnel and the resultant layers were separated. The organic phase was washed repeatedly with NH_4Cl (4×5 mL) until the aqueous phase no longer had a blue color. The organic layer was then dried (MgSO_4), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes , 1/4 \rightarrow 1/2) to give the desired silyl enol ether intermediate **31** (0.044 g, 98% yield) as a yellow foam. **31**: $R_f = 0.83$ (silica gel, EtOAc/hexanes , 1/1); IR (film) ν_{max} 3367, 2965, 2925, 1693, 1646, 1457, 1418, 1365, 1282, 1242, 1202, 1169, 1150 cm^{-1} ; $^1\text{H NMR}$ (500 MHz, CDCl_3 , 2 rotamers, $\sim 0.3:0.7$) δ 7.62 (d, $J = 7.5$ Hz, 1 H), 7.32 (t, $J = 7.4$ Hz, 1 H), 7.30–7.20 (m, 2 H), 5.16 (d, $J = 6.0$ Hz, 0.7 H), 5.01 (d, $J = 6.0$ Hz, 0.3 H), 4.68 (d, $J = 13.0$ Hz, 0.3 H), 4.53 (d, $J = 13.0$ Hz, 0.7 H), 3.85 (dd, $J =$

14.6, 4.5 Hz, 0.7 H), 3.70 (dd, J = 14.6, 4.5 Hz, 0.3 H), 2.74–2.56 (m, 2 H), 2.24 (dd, J = 14.1, 5.0 Hz, 1 H), 2.17–2.08 (m, 0.7 H), 2.07–1.99 (m, 0.6 H), 1.92 (dd, J = 14.4, 11.7 Hz, 0.7 H), 1.48 (s, 9 H), 1.43 (d, J = 7.6 Hz, 3 H), 0.29 (d, J = 7.0 Hz, 3 H), 0.25 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3 , 2 rotamers, ~0.3:0.7) δ 188.1, 155.4, 155.2, 155.1, 152.2, 144.6, 127.7, 125.7, 125.6, 122.5, 122.3, 120.5, 110.2, 106.9, 79.5, 79.2, 61.6, 55.2, 54.5, 48.7, 45.7, 45.3, 39.2, 39.0, 35.1, 34.6, 28.4, 28.3, 19.7, 17.9, 0.39, 0.29; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{37}\text{N}_2\text{O}_3\text{Si}^+ [\text{M} + \text{H}^+]$ 441.2573, found 441.2571.

Tertiary Chloride 33. To a solution of silyl enol ether **31** (0.044 g, 0.10 mmol, 1.0 equiv) in THF (5 mL) at 23 °C was added TCCA (0.166 g, 0.5 mmol, 5.0 equiv) in one batch. The reaction was allowed to stir for 15 min at 23 °C before quenching with saturated aqueous NaHCO_3 (5 mL) and diluting with EtOAc (5 mL). The mixture was then transferred to a separatory funnel and the resultant layers were separated. The organic phase was washed with brine (5 mL), dried (MgSO_4), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1/4 → 1/2) to give the desired α -chloroketone product **32** (0.036 g) as a colorless oil in 89% yield. Pressing forward, to a solution of **32** (0.036 g, 0.089 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) at 23 °C was added TFA (0.5 mL) and the resultant contents were stirred for 10 min at 23 °C. Then paraformaldehyde (10 mg, 0.33 mmol, 3.75 equiv) was added to the solution and stirring was continued for another 1 h at 23 °C. Upon completion, the reaction contents were concentrated directly. The resultant residue was redissolved in CH_2Cl_2 (2.0 mL) and solid K_2CO_3 (20 mg, 0.14 mmol, 1.63 equiv) was added at 23 °C. After stirring the resultant slurry for 10 min at 23 °C, the solids were removed by filtration and washed with EtOAc (2 × 3 mL). The combined organic filtrates were concentrated and purified by flash column chromatography (silica gel, EtOAc/hexanes, 1/2 → 1/1) to give the desired tertiary chloride **33** (0.015 g, 53% yield) as a pale yellow solid. X-ray diffraction quality crystals were obtained by slow evaporation of a CH_2Cl_2 solution of **33** in a vial capped with a rubber septum at 23 °C. **33:** R_f = 0.73 (silica gel, EtOAc); IR (film) ν_{max} 3446, 2929, 2852, 1733, 1700, 1684, 1653, 1635, 1576, 1559, 1540, 1457, 1375 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.57 (ddd, J = 7.7, 1.2, 0.7 Hz, 1 H), 7.30 (td, J = 7.5, 1.4 Hz, 1 H), 7.23 (td, J = 7.4, 1.1 Hz, 1 H), 7.17 (ddd, J = 7.4, 1.4 Hz, 1 H), 3.76 (dd, J = 14.3, 2.7 Hz, 1 H), 3.71 (d, J = 14.3 Hz, 1 H), 3.46 (ddd, J = 15.3, 9.7, 3.9 Hz, 1 H), 3.35 (dd, J = 13.8, 2.7 Hz, 1 H), 3.26 (d, J = 13.9 Hz, 1 H), 3.20–3.09 (m, 1 H), 2.80 (q, J = 6.9 Hz, 1 H), 2.38 (ddd, J = 15.0, 9.7, 7.3 Hz, 1 H), 1.80 (ddd, J = 15.0, 9.7, 7.3 Hz, 1 H), 1.54 (s, 3 H), 0.53 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 201.6, 184.4, 153.2, 145.5, 128.0, 126.3, 121.6, 121.3, 78.6, 67.9, 65.5, 64.2, 62.6, 53.2, 47.8, 33.5, 15.3, 14.4; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{20}\text{ClN}_2\text{O}^+ [\text{M} + \text{H}^+]$ 315.1264, found 315.1256.

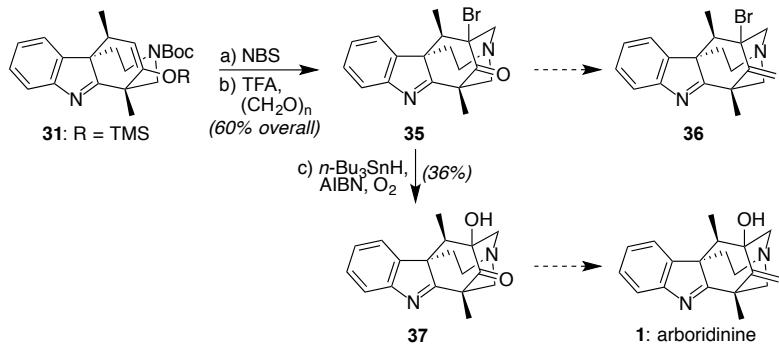
Figure S2. X-ray crystal structure of tertiary chloride **33**.



Alkene 34. Following a slightly modified methylenation procedure described by Yan and co-workers (their method B),⁷ to a suspension of magnesium powder (10 mg, 0.40 mmol, 8.0 equiv) in CH₂Cl₂ (0.2 mL) at 0 °C was sequentially added TiCl₄ (1.0 M in CH₂Cl₂, 0.05 mL, 0.05 mmol, 2.0 equiv) and THF (0.05 mL), with the resultant mixture turning black after 5 min. After stirring at 0 °C for 20 min, a solution of **33** (15 mg, 0.05 mmol) in CH₂Cl₂ (0.3 mL) was added. The reaction was then stirred at 0 °C for 1 h and then at 25 °C for 20 min. Upon completion, the reaction contents were quenched by the addition of saturated aqueous K₂CO₃ (1 mL) and aqueous Rochelle's salt solution (2 mL) and the resultant slurry was stirred at 25 °C for 3 h. The mixture was then transferred to a separatory funnel and the phases were separated. The aqueous layer was extracted with EtOAc (3 × 2 mL) and the combined organic layers were then dried (Na₂SO₄), and concentrated. The resultant residue was purified by preparatory thin-layer chromatography (silica gel, EtOAc) to give alkene **34** (5.0 mg, 32% yield) as a pale yellow solid. **34:** R_f = 0.52 (silica gel, EtOAc/hexanes, 1/1); IR (film) ν_{max} 2926, 2851, 1559, 1457, 1457, 1372, 1260, 1062 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.55 (d, J = 7.7 Hz, 1 H), 7.27 (td, J = 7.4, 1.1 Hz, 1 H), 7.18 (td, J = 7.4, 1.1 Hz, 1 H), 7.13 (dd, J = 7.4, 1.1 Hz, 1 H), 5.36 (s, 1 H), 5.11 (s, 1 H), 3.63 (d, J = 13.9 Hz, 1 H), 3.55 (d, J = 13.9 Hz, 1 H), 3.40 (ddd, J = 15.7, 10.3, 5.9 Hz, 1 H), 3.08 (s, 2 H), 2.77 (q, J = 6.8 Hz, 1 H), 2.27 (ddd, J = 15.3, 9.9, 5.9 Hz, 1 H), 1.57 (td, J = 10.2, 5.1 Hz, 1 H), 1.52 (s, 3H), 0.53 (d, J = 6.8 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 188.3, 153.1, 150.2, 145.9, 127.6, 125.6, 121.9, 120.9, 109.0, 67.9, 62.9, 62.7, 52.9, 51.6, 50.9, 34.3, 29.6, 18.7, 15.5; HRMS (ESI) calcd for C₁₉H₂₂ClN₂⁺ [M + H⁺] 313.1471, found 313.1463.

Alcohol 38. To a solution of **31** (10 mg, 0.023 mmol, 1.0 equiv) in MeCN (0.5 mL) at 23 °C was added NaHCO₃ (15 mg, 0.184 mmol, 8.0 equiv), Na₂EDTA (22 mg, 0.069 mmol, 3.0 equiv), H₂O (0.12 mL, 6.90 mmol, 300 equiv), and 1,1,1-trifluoroacetone (0.6 mL, 6.90 mmol, 300 equiv). The resulting mixture was cooled to 0 °C using an ice bath and then Oxone (0.212 g, 0.345 mmol, 15 equiv) was added. The ice bath was immediately removed and the reaction was allowed to warm to 23 °C and stirred at this temperature for 4 h. Upon completion, the reaction contents were quenched by the addition of H₂O (1 mL), diluted with EtOAc (2 mL), poured into a separatory funnel, and the resultant phases were separated. The organic layer was then washed with saturated aqueous Na₂SO₃ (3 × 2 mL), dried (Na₂SO₄), concentrated, and purified by preparatory thin-layer chromatography (silica gel, EtOAc/hexanes, 1/2) to give alcohol **38** (3.0 mg, 34% yield) as a pale yellow solid. **38:** R_f = 0.32 (silica gel, EtOAc/hexanes, 1/2); IR (film) ν_{max} 3474, 2980, 2932, 1724, 1693, 1569, 1462, 1420, 1386, 1372, 1277, 1251, 1159, 1105 cm⁻¹; ¹H NMR (500 MHz, CDCl₃, 2 rotamers, ~0.3:0.7) δ 7.59 (d, J = 7.4 Hz, 1 H), 7.37–7.28 (m, 3 H), 4.52 (m, 1 H), 4.48 (d, J = 14.0 Hz, 0.3 H), 4.29 (d, J = 14.0 Hz, 0.7 H), 4.08 (d, J = 15.0 Hz, 0.7 H), 3.94 (d, J = 11.0 Hz, 0.3 H), 3.60 (s, 0.3 H), 3.58 (s, 0.7 H), 2.99 (d, J = 13.8 Hz, 0.7 H), 2.90 (t, J = 15.9 Hz, 0.3 H), 2.74–2.65 (m, 1.7 H), 2.58 (d, J = 15.0 Hz, 0.3 H), 2.49–2.43 (m, 1 H), 2.27–2.21 (m, 1 H), 1.55 (s, 3 H), 1.49 (s, 3 H), 1.44 (s, 6 H), 0.17 (d, J = 7.0 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃, 2 rotamers, ~0.3:0.7) δ 211.5, 210.4, 184.2, 154.0, 153.8, 146.1, 128.0, 126.9, 121.7, 121.6, 121.0, 81.4, 75.4, 75.2, 61.9, 60.4, 59.2, 57.7, 56.7, 48.0, 47.8, 42.1, 41.8, 39.9, 33.0, 31.8, 29.7, 28.3, 21.1, 21.0, 20.8, 16.9, 14.2, 8.6; HRMS (ESI) calcd for C₂₂H₂₉N₂O₄⁺ [M + H⁺] 385.2127, found 385.2127.

Scheme S10. Other iminium-based cyclization strategies based on a tertiary bromine which failed to deliver the final target.



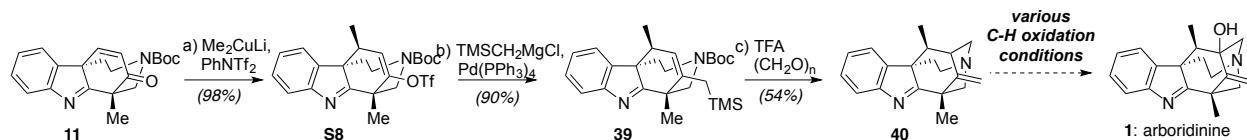
Reagents and conditions: a) NBS (5.0 equiv), THF, 25 °C, 10 min; b) TFA/CH₂Cl₂ (1/2), 25 °C, 10 min, then (CH₂O)_n (10 equiv), 1 h; c) *n*-Bu₃SnH (3.0 equiv), AIBN (1.0 equiv); bubbling O₂, toluene, 80 °C, 20 h.

Tertiary Bromide 35. To a solution of **31** (0.073 g, 0.17 mmol, 1.0 equiv) in THF (5.0 mL) at 23 °C was added NBS (0.15 g, 0.83 mmol, 5.0 equiv) in a single portion. The resultant mixture was then stirred at 23 °C for 15 min. Upon completion, the reaction contents were quenched by the addition of saturated aqueous NaHCO₃ (5 mL) and diluted with EtOAc (5 mL). The mixture was then transferred to a separatory funnel and the layers were separated. The organic phase was washed with brine (5 mL), dried (MgSO₄), and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1/4 → 1/2) to give the desired α-bromoketone product (0.078 g, 99% yield) as a colorless oil. Pressing forward, to a solution of the α-bromoketone product (0.078 g, 0.17 mmol, 1.0 equiv) in CH₂Cl₂ (2.0 mL) at 23 °C was added TFA (1.0 mL) and the resultant solution was stirred for 10 min at 23 °C. Paraformaldehyde (10 mg, 0.33 mmol, 2.0 equiv) was added to the solution and stirring was continued for another 1 h at 23 °C. Upon completion, the reaction contents were concentrated directly. The resultant residue was redissolved in CH₂Cl₂ (5.0 mL) and solid K₂CO₃ (0.23 g, 1.7 mmol, 10 equiv) was added at 23 °C. After stirring the resultant slurry for 10 min at 23 °C, the solids were removed by filtration and washed with EtOAc (2 × 3 mL). The combined organic filtrates were concentrated and the resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1/2 → 1/1) to give the desired tertiary bromide **35** (0.037 g, 61% yield) as a pale yellow solid. **35**: R_f = 0.71 (silica gel, EtOAc); IR (film) ν_{max} 3380, 3059, 2980, 2934, 1770, 1723, 1593, 1458, 1368, 1336, 1290, 1226, 1146, 1110, 1020 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, J = 7.7 Hz, 1 H), 7.30 (td, J = 7.6, 1.4 Hz, 1 H), 7.22 (td, J = 7.4, 1.1 Hz, 1 H), 7.17 (dd, J = 7.5, 1.3 Hz, 1 H), 3.93 (d, J = 14.3 Hz, 1 H), 3.87 (dd, J = 14.4, 3.0 Hz, 1 H), 3.47 (ddd, J = 15.3, 9.7, 3.7 Hz, 1 H), 3.34 (dd, J = 13.9, 3.0 Hz, 1 H), 3.25 (d, J = 13.8 Hz, 1 H), 3.13 (ddd, J = 15.3, 9.8, 7.5 Hz, 1 H), 2.87 (q, J = 7.0 Hz, 1 H), 2.37 (ddd, J = 15.0, 9.7, 7.5 Hz, 1 H), 1.80 (ddd, J = 15.1, 9.8, 3.7 Hz, 1 H), 1.51 (s, 3 H), 0.59 (d, J = 7.0 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 201.1, 184.3, 153.2, 145.7, 127.9, 126.3, 121.6, 121.3, 77.7, 77.3, 77.0, 76.8, 68.8, 65.6, 65.2, 62.8, 53.2, 48.4, 33.3, 17.5, 14.7; HRMS (ESI) calcd for C₁₈H₂₀BrN₂O⁺ [M + H⁺] 359.0759, found 359.0736.

Tertiary Alcohol 37. To a solution of tertiary bromide **35** (0.017 g, 0.047 mmol, 1.0 equiv) and AIBN (3.9 mg, 0.024 mmol, 0.5 equiv) in toluene (2.0 mL) at 23 °C was added *n*-Bu₃SnH (0.019 mL, 0.070 mmol, 1.5 equiv). The resultant mixture was then heated at 80 °C for 5 h with O₂ bubbled through the solution. An additional aliquot of AIBN (3.9 mg, 0.024 mmol, 0.5 equiv) and *n*-Bu₃SnH (0.019 mL, 0.070 mmol, 1.5 equiv) was then added and the reaction was stirred for an additional 15 h at 80 °C, with an O₂ balloon attached to the reaction manifold.

Upon completion, the reaction contents were cooled to 23 °C and concentrated directly. The resultant residue was purified by preparatory thin-layer chromatography (silica gel, EtOAc/hexanes, 1/2) to give the desired tertiary alcohol **37** (5.0 mg, 36% yield) as a white solid. **37**: $R_f = 0.47$ (silica gel, EtOAc); IR (film) ν_{max} 3396, 2924, 2852, 1727, 1557, 1463, 1377 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.56 (d, $J = 7.7$ Hz, 1 H), 7.29 (td, $J = 7.5, 1.6$ Hz, 1 H), 7.24–7.17 (m, 2 H), 3.80 (s, 1 H), 3.56 (dd, $J = 14.1, 3.3$ Hz, 1 H), 3.46–3.38 (m, 2 H), 3.26–3.15 (m, 3 H), 2.70 (q, $J = 7.0$ Hz, 1 H), 2.34 (ddd, $J = 15.7, 9.7, 6.4$ Hz, 1 H), 1.72 (ddd, $J = 14.8, 10.0, 4.6$ Hz, 1 H), 1.50 (s, 3 H), 0.36 (d, $J = 7.0$ Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 211.0, 185.7, 153.4, 145.5, 127.8, 126.1, 121.8, 121.2, 79.0, 67.6, 66.1, 61.9, 61.6, 45.4, 33.6, 29.7, 13.5, 12.9; HRMS (ESI) calcd for C₁₈H₂₁N₂O₂⁺ [M + H⁺] 297.1603, found 297.1559.

Scheme S11. The failed attempt at an aza-Prins strategy for the synthesis of arboridinine (**1**).



Reagents and conditions: a) CuI (3.0 equiv), MeLi (1.6 M in Et₂O, 6.0 equiv), PhNTf₂ (3.0 equiv), THF (0.03 M), -78 °C to 0 °C over 5 h; b) TMSCl₂MgCl (1.0 M in Et₂O, 2.5 equiv), Pd(PPh₃)₄ (0.5 equiv), THF (0.035 M), 65 °C, 3 h; c) TFA/CH₂Cl₂ (1/2, 0.07 M), 25 °C, 10 min, then (CH₂O)_n (10 equiv), 1 h.

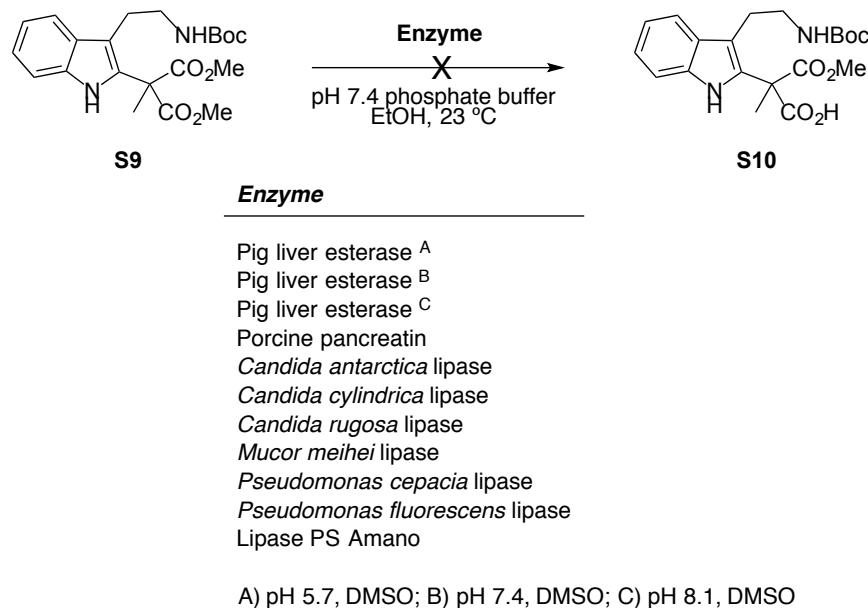
Allyl Silane 39. To a slurry of CuI (0.114 g, 0.60 mmol, 3.0 equiv) in THF (8.0 mL) at 0 °C under an argon atmosphere was added MeLi (1.6 M in Et₂O, 0.75 mL, 1.20 mmol, 6.0 equiv) dropwise until the solid disappeared and the solution turned from yellow to colorless. The resulting solution was stirred at 0 °C for 5 min and then cooled to -78 °C before a solution of ketone **11** (0.070 g, 0.20 mmol, 1.0 equiv) in THF (2.0 mL) was added dropwise. The reaction mixture was stirred for 2 h, during which time the reaction temperature warmed to -40 °C, and then a solution of PhNTf₂ (0.214 g, 0.60 mmol, 3.0 equiv) in THF (1 mL) was added in a single portion. The reaction contents were stirred for another 2 h, during which time the reaction temperature slowly warmed to 0 °C. Upon completion, the reaction was quenched by the addition of saturated aqueous NH₄Cl (5 mL) and diluted with EtOAc (10 mL). The mixture was then transferred to a separatory funnel and the layers were separated. The organic phase was washed repeatedly with saturated aqueous NH₄Cl (4 × 5 mL) until the aqueous phase no longer had a blue color. The organic layer was then dried (MgSO₄), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1/4→1/2) to give vinyl triflate **S8** (0.084 g, 98% yield) as a colorless foam. Pressing forward, a flame-dried flask containing the newly synthesized vinyl triflate **S8** (0.084 g, 0.20 mmol, 1.0 equiv) and Pd(PPh₃)₄ (0.116 g, 0.10 mmol, 0.5 equiv) was evacuated and back-filled with argon three times before THF (5 mL) was added under an argon atmosphere. A solution of TMSCl₂MgCl (1.0 M in Et₂O, 0.5 mL, 0.50 mmol, 2.5 equiv) was added at 23 °C, and the resulting reaction mixture was then heated at 65 °C for 3 h with stirring. Upon completion, the reaction contents were cooled with an ice bath, quenched by the addition of saturated aqueous NH₄Cl (3 mL), and poured into a separatory funnel. After separating the layers, the aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic layers were then washed with brine (2 × 5 mL), dried (Mg₂SO₄), filtered, and concentrated. The resultant residue was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1/4→1/2) to give allyl silane **39** (0.079 g, 90% yield) as a yellow foam. **39**: $R_f = 0.62$ (silica gel, EtOAc/hexanes, 1/2); IR (film) ν_{max} 2956, 2927, 1692, 1663, 1601, 1570, 1495, 1457, 1430, 1384, 1285, 1244, 1211,

1194, 1167, 1143 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3 , 2 rotamers, ~0.5:0.5) δ 7.57 (t, $J = 8.0$ Hz, 1 H), 7.35 (t, $J = 8.0$ Hz, 1 H), 7.30–7.26 (m, 2 H), 7.25–7.20 (m, 1 H), 5.66 (t, $J = 7.5$ Hz, 1 H), 4.58 (d, $J = 13.7$ Hz, 0.5 H), 4.42 (d, $J = 13.7$ Hz, 0.5 H), 3.82 (dd, $J = 14.5, 4.6$ Hz, 0.5 H), 3.64 (dd, $J = 12.9, 4.6$ Hz, 0.5 H), 2.57–2.69 (m, 1.5 H), 2.56 (d, $J = 13.7$ Hz, 0.5 H), 2.20 (ddd, $J = 19.0, 13.8, 4.9$ Hz, 1 H), 1.99 (dddd, $J = 14.0, 11.0, 7.5, 3.9$ Hz, 1 H), 1.85 (dd, $J = 14.0, 11.7$ Hz, 1 H), 1.71 (dd, $J = 15.6, 5.4$ Hz, 1 H), 1.52 (d, $J = 15.6$ Hz, 1 H), 1.46 (s, 5 H), 1.42 (s, 4 H), 1.36 (d, $J = 5.2$ Hz, 3 H), 0.24 (d, $J = 6.9$ Hz, 3 H), 0.04 (s, 5 H), 0.01 (s, 4 H); ^{13}C NMR (125 MHz, CDCl_3 , 2 rotamers, ~0.5:0.5) δ 189.8, 155.0, 154.9, 154.7, 144.8, 144.7, 139.5, 138.4, 134.2, 129.5, 128.7, 128.2, 127.7, 127.2, 125.7, 125.6, 123.7, 123.6, 122.5, 122.3, 121.1, 120.3, 118.6, 80.2, 79.7, 61.5, 61.4, 56.3, 55.6, 48.5, 48.3, 46.0, 45.5, 43.1, 42.7, 34.7, 34.3, 28.4, 28.3, 20.5, 20.3, 20.0, 19.2, 17.2, 17.1, –0.4; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{39}\text{N}_2\text{O}_2\text{Si}^+ [\text{M} + \text{H}^+]$ 439.2780, found 439.2783.

Alkene 40. To a solution of **39** (0.032 g, 0.073 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) at 23 °C was added TFA (0.5 mL) and the resultant solution was stirred for 30 min at 23 °C. Upon completion, the reaction contents were concentrated directly and the resultant residue was redissolved in CH_2Cl_2 (1.0 mL). Paraformaldehyde (10 mg, 0.33 mmol, 4.52 equiv) was added to the solution and stirring was continued for another 2 h at 23 °C. Upon completion, solid K_2CO_3 (20 mg, 0.14 mmol, 1.92 equiv) was added, and the resultant slurry was stirred for 10 min at 23 °C. The solids were then removed by filtration and washed with EtOAc (2×3 mL). The combined organic filtrates were concentrated and purified by preparatory thin-layer chromatography (silica gel, EtOAc) to give alkene **40** (0.011 g, 54% yield) as a pale yellow solid. **40:** $R_f = 0.12$ (silica gel, EtOAc); IR (film) ν_{max} 3446, 2929, 2852, 1733, 1700, 1684, 1653, 1635, 1576, 1559, 1540, 1457, 1375 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.55 (d, $J = 7.8$ Hz, 1 H), 7.26–7.24 (m, 2 H), 7.15–7.16 (m, 2 H), 4.85 (s, 1 H), 4.77 (s, 1 H), 3.43 (dd, $J = 13.7, 2.9$ Hz, 1 H), 3.36–3.27 (m, 2 H), 3.22 (d, $J = 13.7, 2.9$ Hz, 1 H), 3.12 (dd, $J = 13.6, 2.0$ Hz, 1 H), 3.03 (dd, $J = 13.6, 2.0$ Hz, 1 H), 2.63 (qd, $J = 6.9, 3.4$ Hz, 1 H), 2.35 (d, $J = 2.5$ Hz, 1 H), 2.14 (ddd, $J = 14.1, 9.4, 4.2$ Hz, 1 H), 1.47 (s, 3 H), 1.38 (ddd, $J = 15.3, 9.4, 4.2$ Hz, 1 H), 0.43 (d, $J = 7.0$ Hz, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 191.0, 153.7, 152.3, 145.2, 127.3, 125.0, 122.1, 120.6, 106.7, 62.4, 62.0, 61.2, 53.2, 48.5, 48.4, 43.5, 33.9, 29.7, 18.3, 18.0; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{23}\text{N}_2^+ [\text{M} + \text{H}^+]$ 279.1861, found 279.1865.

Screening Table for a Selected Reaction Process

Table S2. Enzymes screened to attempt selective mono-hydrolysis of diester **S9**.



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Crystallographic Experimental Section

Crystal growth of C₁₉H₂₂N₂O: arboridinine (1)

Data collected/reported: Alexander S. Filatov, February/2016 (X-ray Laboratory, Searle B013, Department of Chemistry, the University of Chicago, Chicago, IL).

General information: A colorless block ($0.36 \times 0.18 \times 0.08$ mm³) was cut off the crystals conglomerates and mounted on a Dual-Thickness MicroMounttm (MiTeGen) with 30 μm sample aperture with FluorolubeTM oil. The diffraction data were measured at 100 K on a Bruker D8 VENTURE with PHOTON 100 CMOS detector system equipped with a Cu-target X-ray tube ($\lambda = 1.54178$ Å). Data reduction and integration were performed with the Bruker APEX3 software package (Bruker AXS, version 2015.5-2, 2015). Data were scaled and corrected for absorption effects using the multi-scan procedure as implemented in SADABS (Bruker AXS, version 2014/5, 2015, part of Bruker APEX3 software package). The structure was solved by SHELXT (Version 2014/5: Sheldrick, G. M. *Acta Crystallogr.* **2015**, *A71*, 3-8) and refined by a full-matrix least-squares procedure using OLEX2 (O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann. *J. Appl. Crystallogr.* **2009**, *42*, 339-341) (XL refinement program version 2014/7, Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112-122; Sheldrick, G. M. *Acta Crystallogr.* **2015**, *C71*, 3-8). Crystallographic data and details of the data collection and structure refinement are listed in Table 1.

Specific details for structure refinement: All atoms were refined with anisotropic thermal parameters. Hydrogen atoms were included in idealized positions for structure factor calculations except hydrogen atoms of hydroxyl groups which were refined fully independently. All structures are drawn with thermal ellipsoids at 50% probability.

Table 1 Crystal data and structure refinement for arboridinine (1).

Identification code	arboridinine (1)
Empirical formula	C ₁₉ H ₂₂ N ₂ O
Formula weight	294.38
Temperature/K	100(2)
Crystal system	triclinic
Space group	P-1
a/Å	8.1493(3)
b/Å	11.6100(4)
c/Å	16.2904(6)
$\alpha/^\circ$	85.3610(12)
$\beta/^\circ$	89.3880(12)
$\gamma/^\circ$	85.8876(14)
Volume/Å ³	1532.27(10)
Z	4
$\rho_{\text{calc}}/\text{cm}^3$	1.276
μ/mm^{-1}	0.619
F(000)	632.0
Crystal size/mm ³	0.36 × 0.18 × 0.08
Radiation	CuKα ($\lambda = 1.54178$)
2Θ range for data collection/°	5.442 to 155.338
Index ranges	-9 ≤ h ≤ 8, -14 ≤ k ≤ 14, -19 ≤ l ≤ 20
Reflections collected	20422
Independent reflections	6268 [$R_{\text{int}} = 0.0291$, $R_{\text{sigma}} = 0.0279$]
Data/restraints/parameters	6268/0/409
Goodness-of-fit on F ²	1.045
Final R indexes [I>=2σ (I)]	$R_1 = 0.0398$, $wR_2 = 0.1002$
Final R indexes [all data]	$R_1 = 0.0483$, $wR_2 = 0.1095$
Largest diff. peak/hole / e Å ⁻³	0.32/-0.20

$$R_{\text{int}} = \frac{\sum |F_o|^2 - \langle F_o^2 \rangle}{\sum |F_o|^2}$$

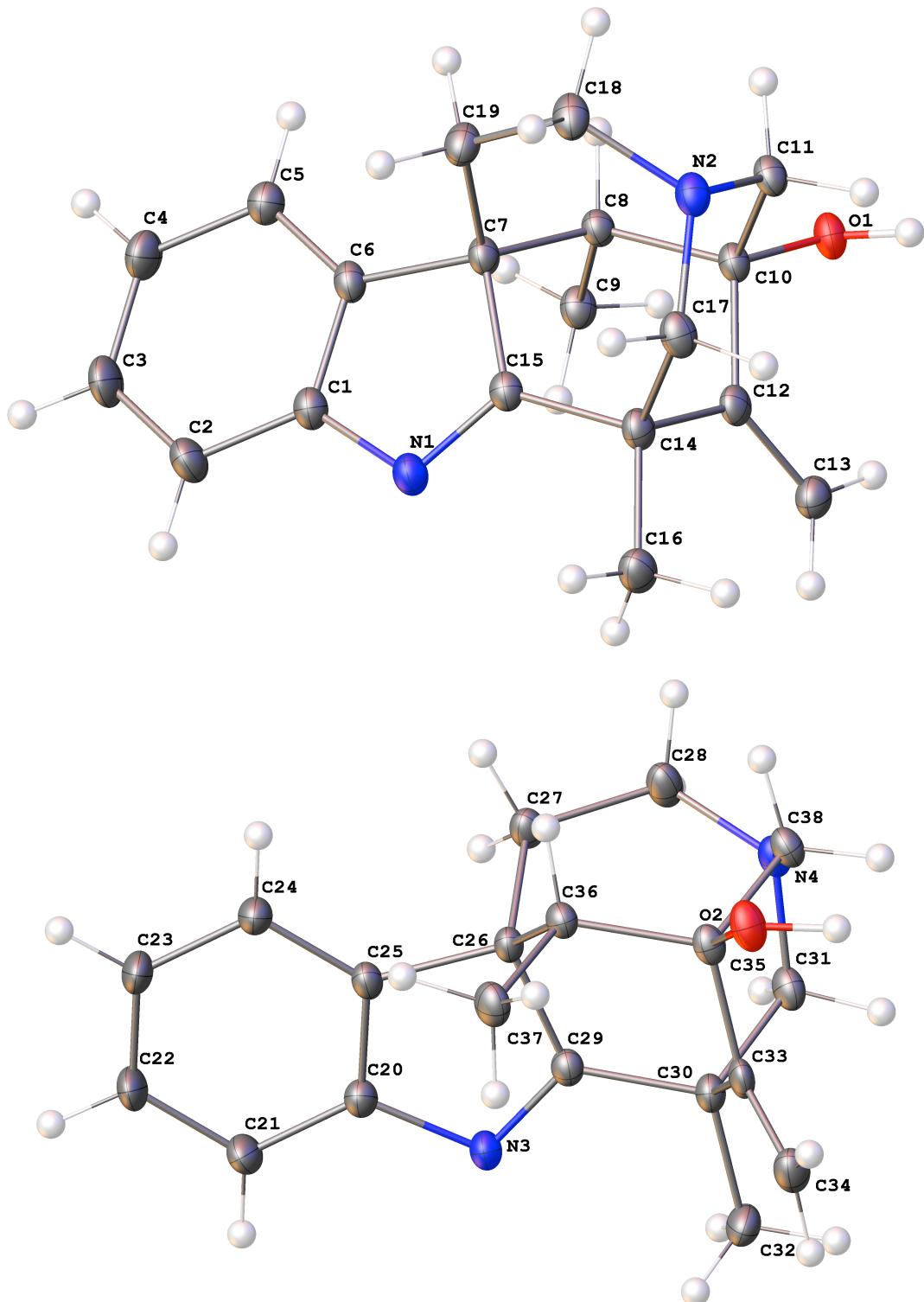
$$R_1 = \frac{\sum |F_o| - |F_c|}{\sum |F_o|}$$

$$wR_2 = [\sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2]]^{1/2}$$

$$\text{Goodness-of-fit} = [\sum [w(F_o^2 - F_c^2)^2] / (n-p)]^{1/2}$$

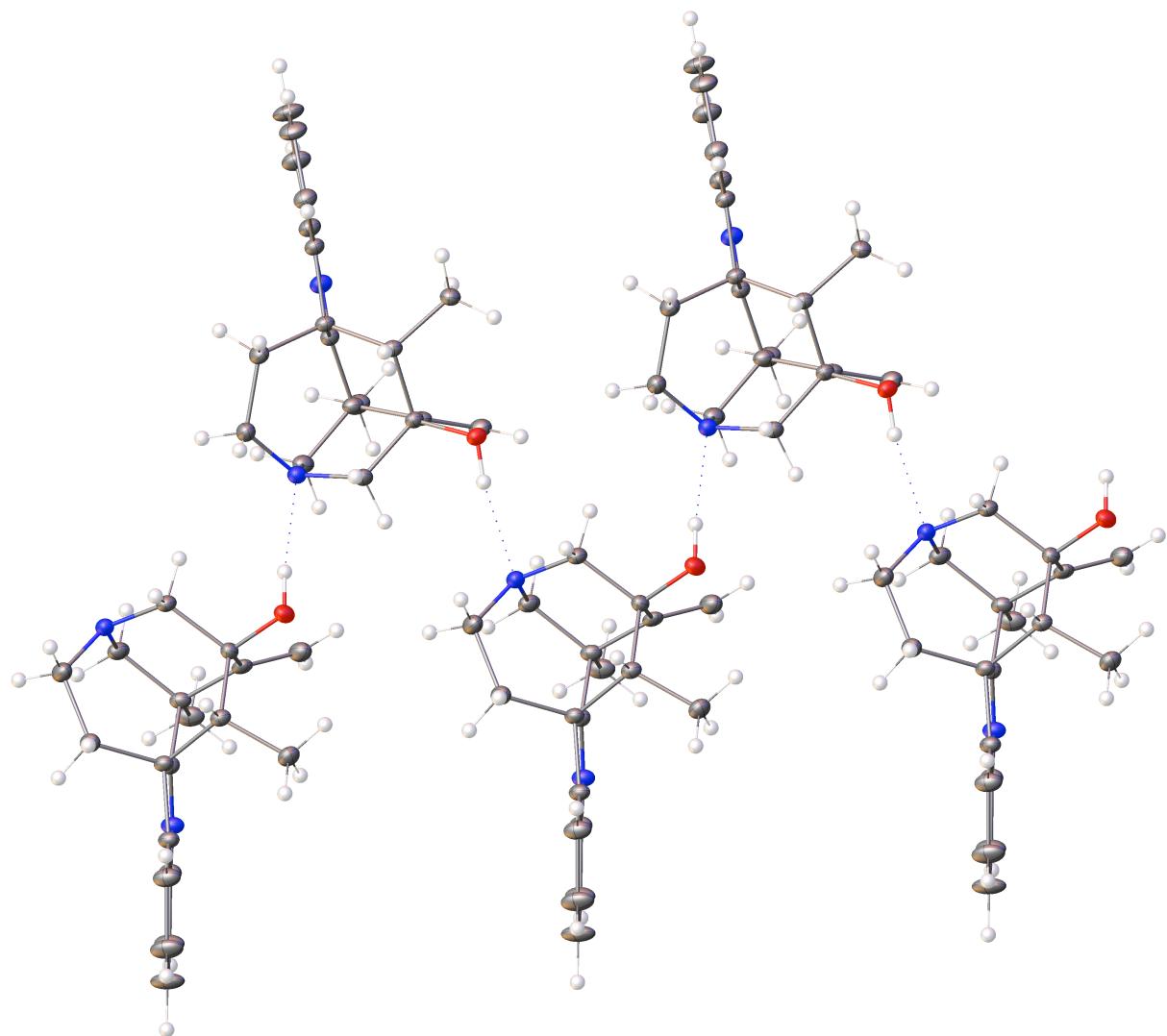
n: number of independent reflections; p: number of refined parameters

Both enantiomers are in the independent unit



Both enantiomers are co-crystallized into a 1D polymeric chain through the OH \cdots N intermolecular hydrogen bonds

D	H	A	d(D-H)/ \AA	d(H-A)/ \AA	d(D-A)/ \AA	D-H-A/ $^\circ$
O1	H1	N4	0.90(2)	2.01(2)	2.8968(14)	168.4(18)



These 1D chains run along the α axis

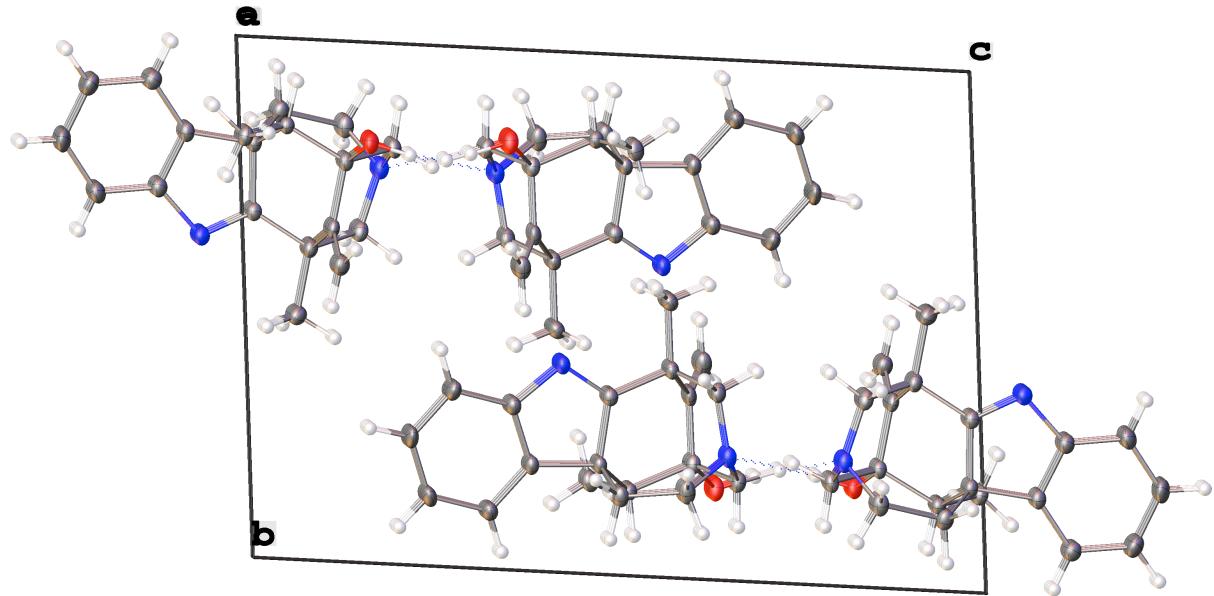


Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for arboridinine (1). U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	x	y	z	U(eq)
O1	4144.9(11)	8088.5(8)	8228.9(6)	22.3(2)
N1	8026.5(14)	6139.7(10)	10575.4(7)	23.0(2)
N2	8705.1(13)	7592.3(10)	8095.9(6)	21.6(2)
C1	7901.8(17)	7028.4(11)	11133.7(8)	23.3(3)
C2	8094(2)	6870.1(13)	11979.2(9)	31.8(3)
C3	7888(2)	7845.5(14)	12422.7(9)	36.2(4)
C4	7522(2)	8938.4(13)	12027.8(9)	31.7(3)
C5	7361.7(17)	9088.6(12)	11172.5(8)	25.5(3)
C6	7535.3(16)	8121.3(11)	10729.4(7)	20.7(3)
C7	7527.4(15)	7971.0(11)	9812.0(7)	18.8(3)
C8	5866.3(15)	8343.2(11)	9365.7(7)	18.6(2)
C9	4407.3(16)	8106.6(11)	9941.8(8)	21.9(3)
C10	5707.1(15)	7702.5(11)	8574.6(7)	18.5(2)
C11	7006.3(15)	8000.0(11)	7910.7(7)	20.4(3)
C12	5895.9(16)	6403.1(11)	8780.7(7)	19.6(3)
C13	4696.4(17)	5708.2(12)	8687.7(8)	24.9(3)
C14	7618.1(16)	5999.6(11)	9093.9(7)	20.8(3)
C15	7811.6(15)	6651.2(11)	9849.3(7)	19.2(3)
C16	7876.1(19)	4699.0(12)	9298.0(8)	27.5(3)
C17	8861.0(16)	6369.4(12)	8404.6(8)	23.2(3)
C18	9604.7(16)	8369.3(12)	8561.5(8)	24.9(3)
C19	9018.9(17)	8595.5(12)	9440.8(8)	24.1(3)
O2	-807.7(11)	8249.4(9)	6342.2(6)	25.9(2)
N3	3059.5(14)	5997.1(9)	4298.0(6)	22.6(2)
N4	3717.2(13)	7619.9(10)	6527.4(6)	20.9(2)
C20	3008.8(17)	6831.2(11)	3604.9(8)	22.9(3)
C21	3281(2)	6595.4(12)	2793.5(8)	30.9(3)
C22	3166(2)	7530.0(13)	2200.5(9)	37.0(4)
C23	2788(2)	8648.4(13)	2417.6(9)	35.6(4)
C24	2534.0(19)	8882.5(12)	3239.3(8)	27.7(3)
C25	2645.9(16)	7955.5(11)	3831.9(7)	21.0(3)
C26	2585.7(15)	7886.0(11)	4766.1(7)	18.5(2)
C27	4137.4(17)	8468.6(12)	5029.5(8)	23.8(3)
C28	4670.4(17)	8323.1(13)	5938.1(8)	27.6(3)
C29	2798.2(15)	6570.2(11)	4936.1(7)	19.1(3)
C30	2539.6(16)	5999.4(11)	5788.2(7)	20.7(3)
C31	3795.6(17)	6382.0(11)	6410.4(8)	23.0(3)

C32	2713.5(19)	4684.1(12)	5785.5(8)	28.9(3)
C33	834.1(16)	6485.1(11)	6035.7(7)	20.8(3)
C34	-423.8(18)	5847.6(13)	6228.4(8)	28.8(3)
C35	734.0(15)	7794.7(11)	6042.7(7)	19.5(3)
C36	965.0(16)	8373.3(11)	5162.0(7)	19.4(3)
C37	-529.3(17)	8211.9(12)	4630.3(8)	25.7(3)
C38	2041.5(16)	8098.2(11)	6653.1(8)	21.3(3)

Table 3 Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for arboridinine (1). The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11} + 2hka^{*}b^{*}U_{12} + \dots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	20.2(5)	30.7(5)	15.9(4)	-2.7(4)	-3.0(3)	0.9(4)
N1	26.4(6)	25.0(6)	17.6(5)	-1.7(4)	-2.8(4)	-0.8(4)
N2	19.1(6)	29.3(6)	16.6(5)	-2.6(4)	0.3(4)	-2.4(4)
C1	26.8(7)	25.8(7)	17.5(6)	-2.4(5)	-2.9(5)	-2.5(5)
C2	46.7(9)	30.5(7)	17.7(7)	1.4(5)	-5.5(6)	-3.8(6)
C3	54.7(10)	39.8(9)	15.0(7)	-3.9(6)	-5.8(6)	-7.7(7)
C4	43.3(9)	32.9(8)	20.6(7)	-9.9(6)	-2.3(6)	-6.0(6)
C5	30.1(7)	26.1(7)	21.0(7)	-4.0(5)	-2.6(5)	-3.4(5)
C6	21.3(6)	26.3(7)	14.8(6)	-2.0(5)	-1.9(4)	-3.0(5)
C7	21.0(6)	22.3(6)	13.2(6)	-2.3(4)	-1.0(4)	-2.0(5)
C8	21.2(6)	19.9(6)	14.5(6)	-1.4(4)	-0.7(4)	-1.0(4)
C9	21.8(7)	27.0(7)	17.0(6)	-3.9(5)	1.4(5)	-1.8(5)
C10	18.4(6)	23.3(6)	13.7(6)	-1.3(4)	-1.3(4)	-1.0(5)
C11	20.4(6)	26.5(6)	14.0(6)	0.1(5)	-0.3(4)	-2.1(5)
C12	23.6(7)	24.2(6)	11.4(5)	-3.8(4)	1.3(4)	-1.8(5)
C13	29.2(7)	27.6(7)	18.6(6)	-3.7(5)	-1.1(5)	-5.4(5)
C14	23.9(7)	23.8(6)	14.8(6)	-3.6(5)	-1.0(5)	-0.2(5)
C15	18.8(6)	22.7(6)	16.1(6)	-2.0(5)	-1.1(4)	-1.4(5)
C16	35.8(8)	24.4(7)	22.2(7)	-4.7(5)	-3.9(5)	1.0(5)
C17	22.5(7)	29.1(7)	17.5(6)	-4.1(5)	1.0(5)	2.6(5)
C18	21.1(7)	35.3(7)	19.0(6)	-2.5(5)	0.0(5)	-6.6(5)
C19	24.1(7)	29.6(7)	19.9(6)	-4.3(5)	-0.6(5)	-7.7(5)
O2	19.5(5)	39.5(6)	18.2(5)	-3.2(4)	1.7(3)	2.4(4)
N3	29.0(6)	23.7(6)	15.1(5)	-1.1(4)	1.3(4)	-3.3(4)
N4	18.8(6)	28.9(6)	15.3(5)	-1.7(4)	-0.5(4)	-4.1(4)
C20	28.6(7)	23.7(6)	16.7(6)	-1.0(5)	1.8(5)	-5.8(5)
C21	49.5(9)	26.4(7)	17.9(7)	-5.0(5)	5.6(6)	-7.9(6)
C22	65.8(11)	33.3(8)	13.5(6)	-2.4(6)	6.3(6)	-13.7(7)
C23	62.5(11)	28.5(7)	16.3(7)	3.3(5)	1.7(6)	-12.7(7)

C24	43.2(9)	22.8(7)	17.8(6)	-0.5(5)	1.1(5)	-8.1(6)
C25	25.4(7)	24.2(6)	13.9(6)	-1.7(5)	0.9(5)	-5.9(5)
C26	22.1(6)	21.0(6)	12.7(6)	-0.5(4)	0.4(4)	-4.5(5)
C27	24.6(7)	29.6(7)	18.0(6)	-1.2(5)	1.3(5)	-9.2(5)
C28	26.1(7)	39.2(8)	18.9(6)	-1.8(5)	-0.7(5)	-12.9(6)
C29	19.5(6)	22.1(6)	15.7(6)	-0.7(5)	-0.5(4)	-2.9(5)
C30	25.8(7)	22.7(6)	13.5(6)	-0.1(5)	0.5(5)	-2.9(5)
C31	24.8(7)	28.0(7)	15.6(6)	-1.3(5)	-2.8(5)	1.6(5)
C32	43.6(9)	23.0(7)	19.6(7)	2.3(5)	1.8(6)	-3.1(6)
C33	25.4(7)	27.5(7)	9.8(5)	0.2(5)	-2.3(4)	-5.4(5)
C34	31.8(8)	36.5(8)	19.2(7)	-1.1(5)	0.8(5)	-11.8(6)
C35	16.5(6)	26.8(6)	15.1(6)	-2.3(5)	0.8(4)	-1.4(5)
C36	23.0(6)	20.6(6)	14.7(6)	-1.4(4)	-1.4(4)	-1.9(5)
C37	25.9(7)	32.2(7)	18.8(6)	0.0(5)	-4.9(5)	-2.7(5)
C38	21.7(7)	27.5(7)	15.2(6)	-4.7(5)	-0.8(5)	-2.0(5)

Table 4 Bond Lengths for arboridinine (1).

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C10	1.4252(15)	O2	C35	1.4243(15)
N1	C1	1.4271(17)	N3	C20	1.4257(16)
N1	C15	1.2879(16)	N3	C29	1.2865(16)
N2	C11	1.4573(17)	N4	C28	1.4628(16)
N2	C17	1.4646(17)	N4	C31	1.4619(17)
N2	C18	1.4642(16)	N4	C38	1.4555(17)
C1	C2	1.3838(19)	C20	C21	1.3837(18)
C1	C6	1.3956(18)	C20	C25	1.3959(18)
C2	C3	1.391(2)	C21	C22	1.392(2)
C3	C4	1.389(2)	C22	C23	1.386(2)
C4	C5	1.3964(19)	C23	C24	1.3977(19)
C5	C6	1.3815(18)	C24	C25	1.3850(18)
C6	C7	1.5187(16)	C25	C26	1.5179(16)
C7	C8	1.5602(17)	C26	C27	1.5562(17)
C7	C15	1.5296(17)	C26	C29	1.5280(17)
C7	C19	1.5519(17)	C26	C36	1.5538(18)
C8	C9	1.5334(17)	C27	C28	1.5398(18)
C8	C10	1.5503(16)	C29	C30	1.5086(16)
C10	C11	1.5419(17)	C30	C31	1.5596(18)
C10	C12	1.5159(17)	C30	C32	1.5239(18)
C12	C13	1.3287(19)	C30	C33	1.5247(18)
C12	C14	1.5271(18)	C33	C34	1.3273(19)

C14	C15	1.5110(17)	C33	C35	1.5177(18)
C14	C16	1.5197(18)	C35	C36	1.5497(17)
C14	C17	1.5593(18)	C35	C38	1.5431(17)
C18	C19	1.5418(18)	C36	C37	1.5329(17)

Table 5 Bond Angles for arboridinine (1).

Atom	Atom	Atom	Angle/ [°]	Atom	Atom	Atom	Angle/ [°]
C15	N1	C1	106.37(11)	C29	N3	C20	106.29(11)
C11	N2	C17	112.25(10)	C31	N4	C28	115.49(11)
C11	N2	C18	114.60(11)	C38	N4	C28	114.03(11)
C18	N2	C17	115.35(10)	C38	N4	C31	112.39(10)
C2	C1	N1	126.02(12)	C21	C20	N3	125.79(12)
C2	C1	C6	121.99(13)	C21	C20	C25	122.15(12)
C6	C1	N1	111.98(11)	C25	C20	N3	112.06(11)
C1	C2	C3	117.54(13)	C20	C21	C22	117.28(13)
C4	C3	C2	121.04(13)	C23	C22	C21	121.08(13)
C3	C4	C5	120.83(13)	C22	C23	C24	121.36(13)
C6	C5	C4	118.45(13)	C25	C24	C23	117.79(13)
C1	C6	C7	107.25(11)	C20	C25	C26	107.08(11)
C5	C6	C1	120.13(12)	C24	C25	C20	120.34(12)
C5	C6	C7	132.46(12)	C24	C25	C26	132.38(12)
C6	C7	C8	115.40(10)	C25	C26	C27	105.40(10)
C6	C7	C15	98.75(10)	C25	C26	C29	98.77(10)
C6	C7	C19	106.14(10)	C25	C26	C36	116.43(10)
C15	C7	C8	108.93(10)	C29	C26	C27	111.18(10)
C15	C7	C19	112.54(10)	C29	C26	C36	110.52(10)
C19	C7	C8	114.13(10)	C36	C26	C27	113.54(10)
C9	C8	C7	110.63(10)	C28	C27	C26	119.31(11)
C9	C8	C10	109.61(10)	N4	C28	C27	118.85(11)
C10	C8	C7	111.28(10)	N3	C29	C26	115.49(11)
O1	C10	C8	106.48(10)	N3	C29	C30	123.12(11)
O1	C10	C11	106.61(9)	C30	C29	C26	121.10(10)
O1	C10	C12	112.96(10)	C29	C30	C31	111.18(10)
C11	C10	C8	113.57(10)	C29	C30	C32	110.98(10)
C12	C10	C8	110.16(10)	C29	C30	C33	104.00(10)
C12	C10	C11	107.13(10)	C32	C30	C31	108.88(11)
N2	C11	C10	116.76(10)	C32	C30	C33	114.17(11)
C10	C12	C14	112.02(10)	C33	C30	C31	107.53(10)
C13	C12	C10	123.29(12)	N4	C31	C30	115.90(10)
C13	C12	C14	124.68(12)	C34	C33	C30	124.54(13)

C12	C14	C17	107.23(10)	C34	C33	C35	123.37(13)
C15	C14	C12	104.29(10)	C35	C33	C30	112.09(10)
C15	C14	C16	111.25(10)	O2	C35	C33	112.59(10)
C15	C14	C17	111.20(10)	O2	C35	C36	107.12(10)
C16	C14	C12	114.01(11)	O2	C35	C38	106.13(10)
C16	C14	C17	108.76(11)	C33	C35	C36	110.70(10)
N1	C15	C7	115.46(11)	C33	C35	C38	107.29(10)
N1	C15	C14	122.81(11)	C38	C35	C36	113.00(10)
C14	C15	C7	121.23(10)	C35	C36	C26	110.90(10)
N2	C17	C14	115.82(10)	C37	C36	C26	111.33(10)
N2	C18	C19	118.71(11)	C37	C36	C35	110.14(10)
C18	C19	C7	119.14(11)	N4	C38	C35	116.72(10)

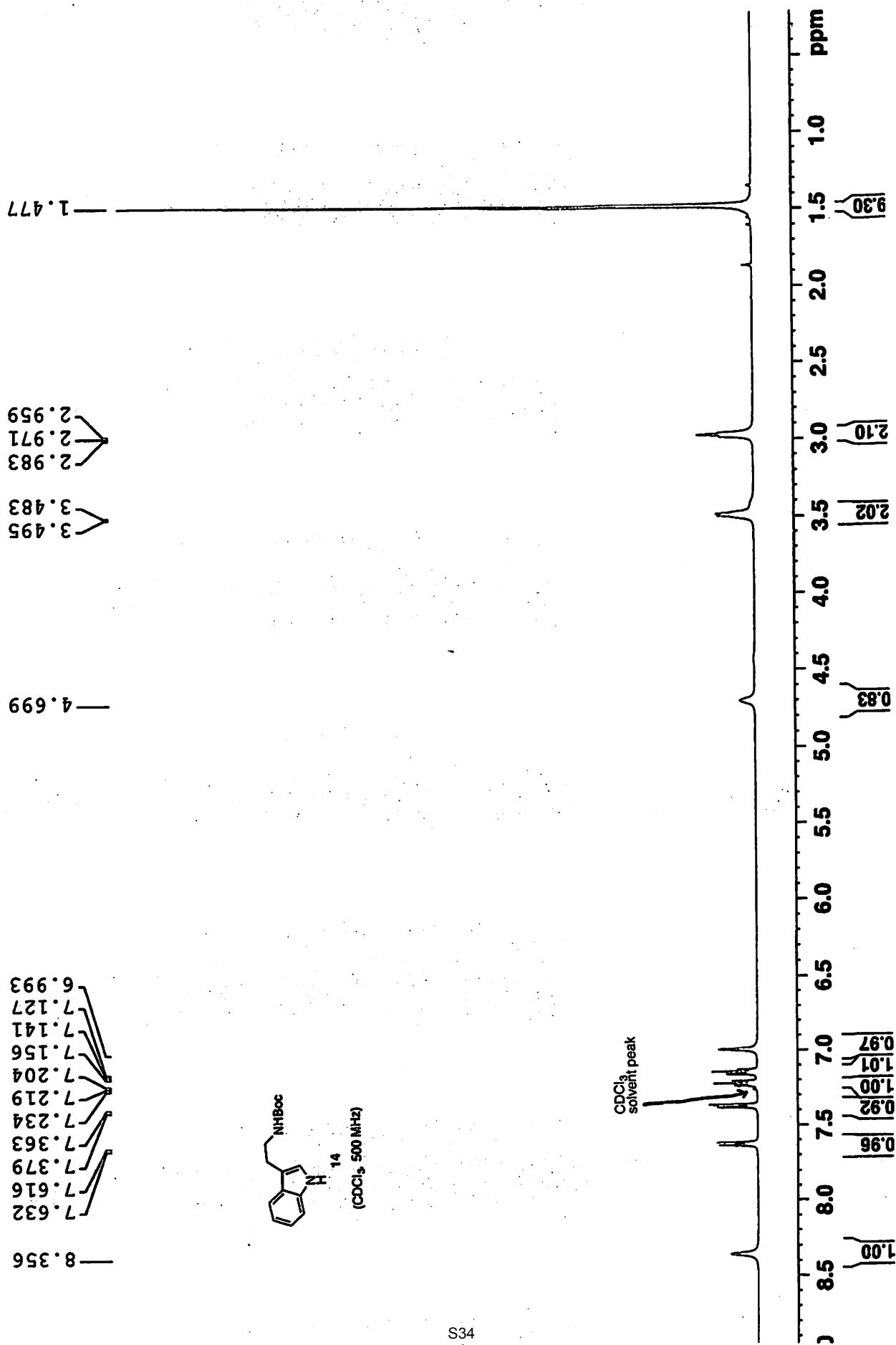
Table 6 Hydrogen Bonds for arboridinine (1).

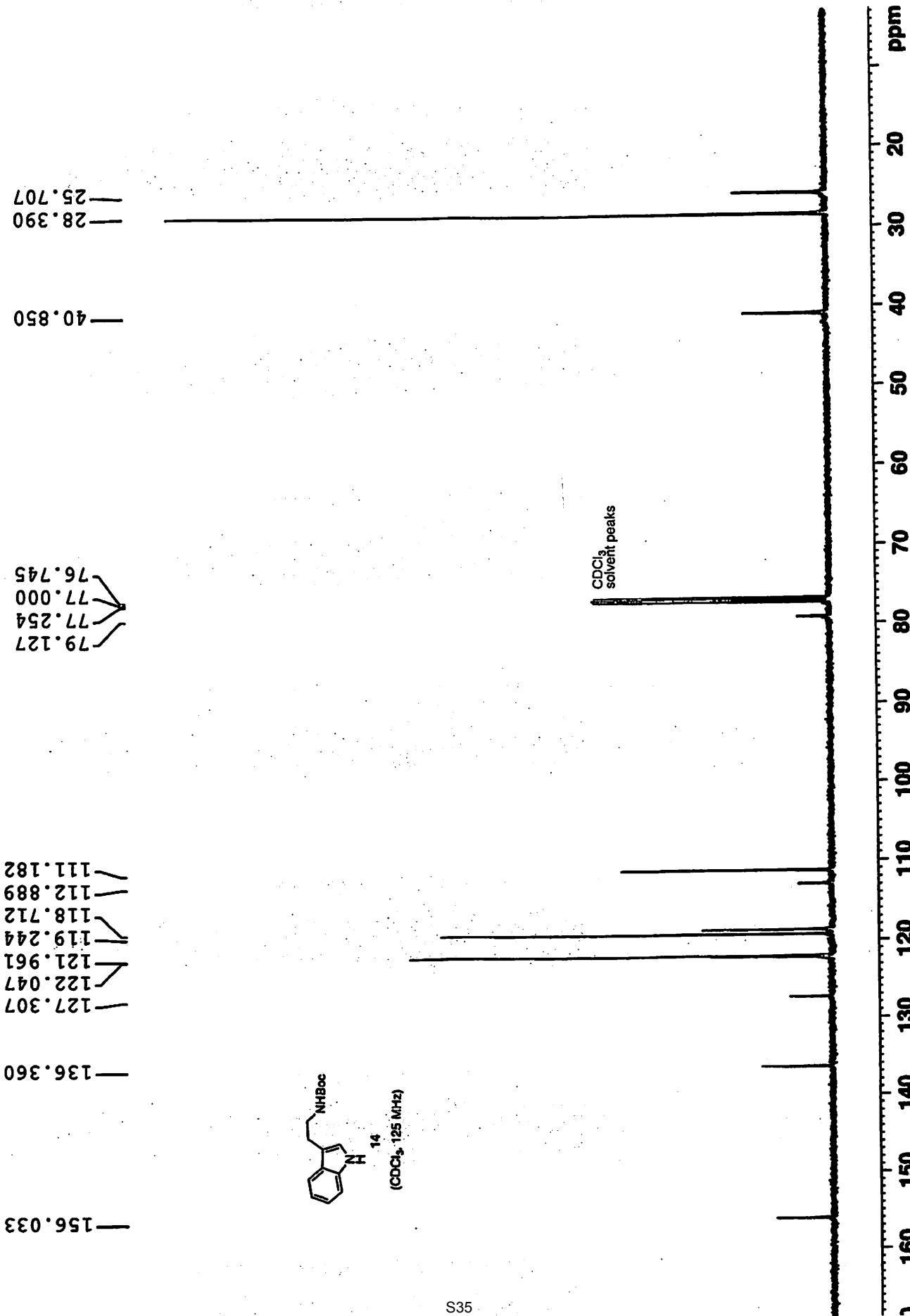
D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
O1	H1	N4	0.90(2)	2.01(2)	2.8968(14)	168.4(18)

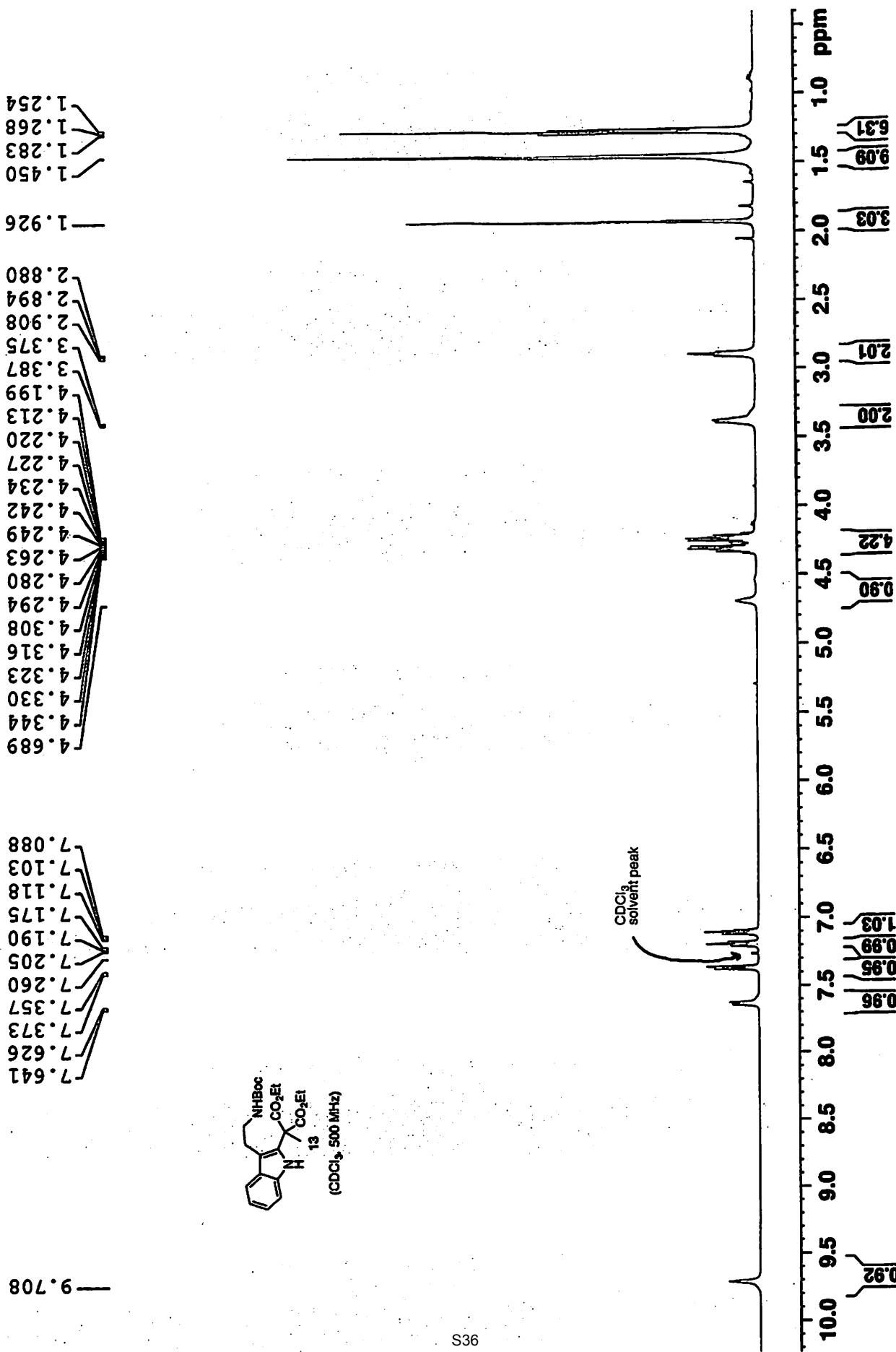
Table 7 Hydrogen Atom Coordinates ($\text{\AA} \times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for arboridinine (1).

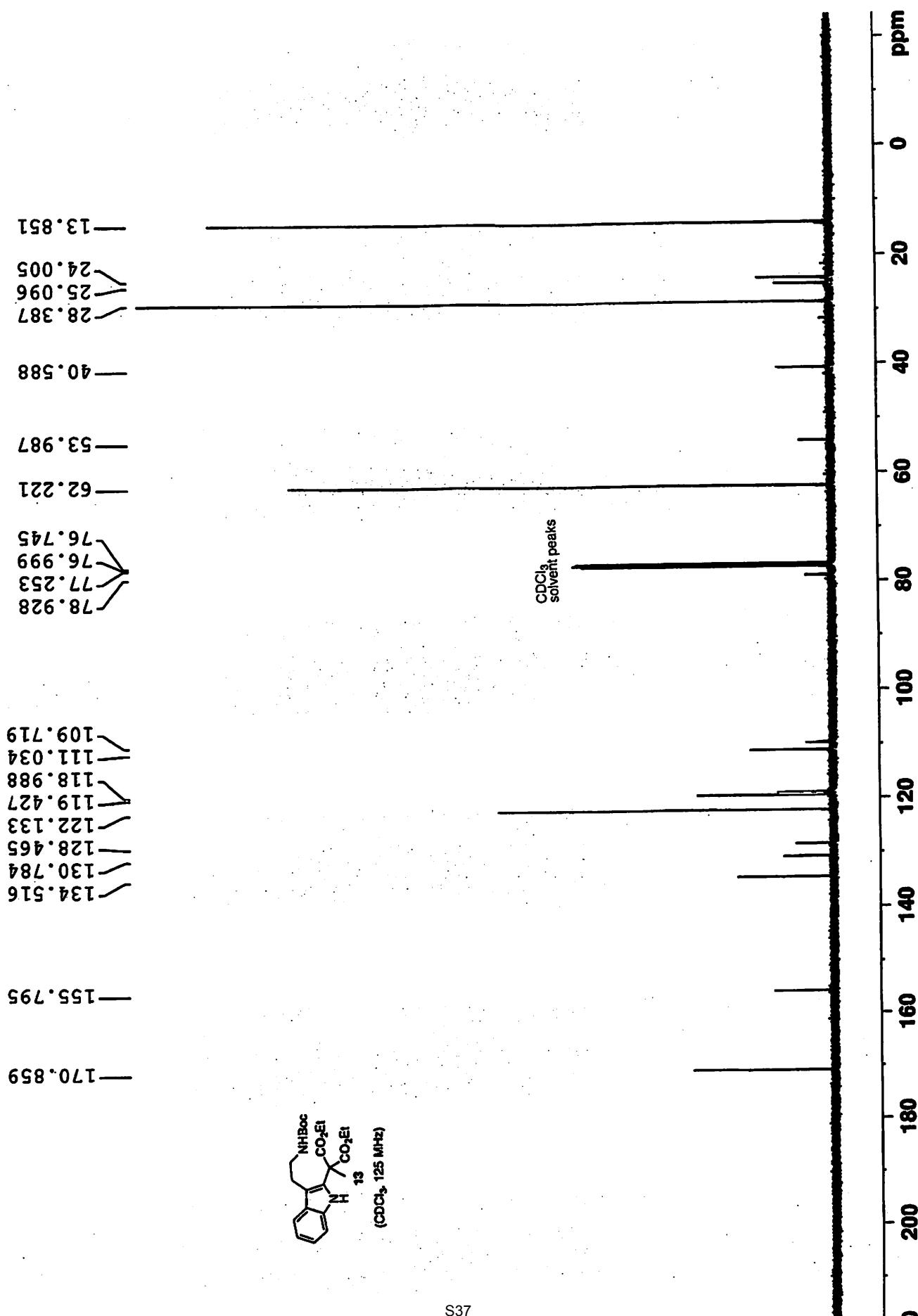
Atom	x	y	z	U(eq)
H1	4150(20)	7891(17)	7704(13)	45(5)
H2	8356.76	6123	12246.79	38
H3	8000	7763.13	13004.78	43
H4	7379.02	9591.56	12343.55	38
H5	7138.37	9838.47	10901.73	31
H8	5833.44	9194.38	9205.52	22
H9A	4559.76	7318.09	10206.58	33
H9B	3386.82	8186.98	9622.99	33
H9C	4343.04	8663.42	10364.19	33
H11A	6692.23	7675.9	7395.74	24
H11B	6958.6	8852.97	7801.43	24
H13A	3657.24	6020.8	8482.92	30
H13B	4877.85	4898.65	8826.09	30
H16A	8995.42	4506.15	9504.57	41
H16B	7718.91	4298.72	8800.68	41
H16C	7080.52	4453.36	9720.38	41
H17A	9989.76	6185.81	8618.79	28
H17B	8728.64	5893.48	7935.24	28
H18A	9591.72	9127.15	8235.16	30

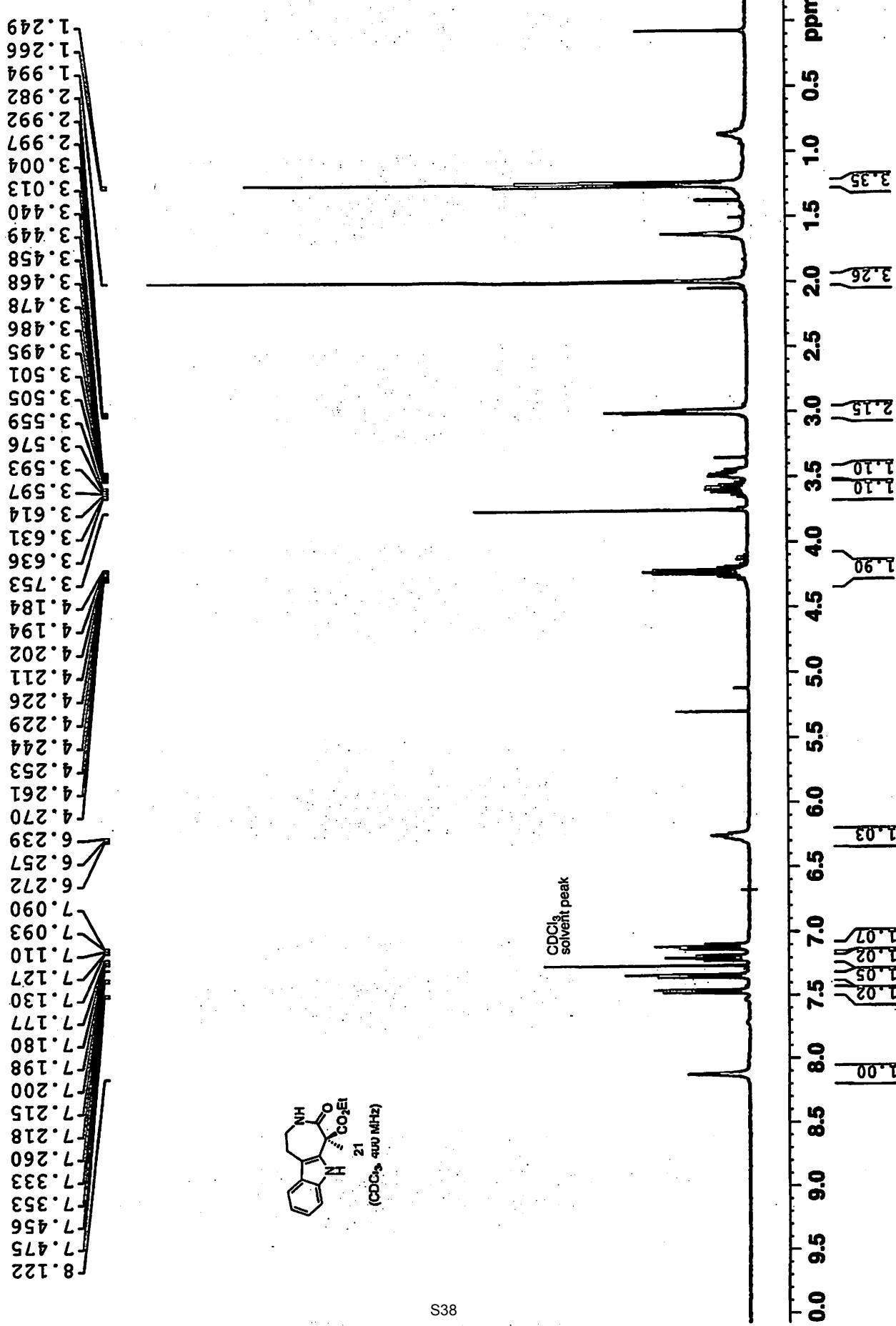
H18B	10765.72	8054.56	8596.58	30
H19A	8750.61	9439.48	9451.68	29
H19B	9962.61	8390.05	9815	29
H2A	-850(20)	7984(17)	6886(13)	49(6)
H21	3535.18	5827.02	2647.24	37
H22	3350.31	7399.15	1637.65	44
H23	2699.81	9268.78	1999.26	43
H24	2292.61	9651.86	3386.51	33
H27A	5075.51	8174.16	4695.99	29
H27B	3958.13	9309.55	4872.38	29
H28A	5821.83	7986.49	5955.99	33
H28B	4673.65	9106.49	6136.83	33
H31A	3620.76	5954.5	6951.38	28
H31B	4919.09	6145.18	6221.42	28
H32A	2502	4333.41	6340.6	43
H32B	3831.45	4438.28	5613.15	43
H32C	1919.04	4434.62	5400.94	43
H34A	-1452.53	6209.13	6380.61	35
H34B	-295.33	5029.65	6214.08	35
H36	1040.49	9222.53	5203.43	23
H37A	-474.37	8702.64	4113.65	39
H37B	-1540.53	8431.19	4927.98	39
H37C	-528.34	7398.54	4509.43	39
H38A	2053.27	8952.32	6629.04	26
H38B	1689.87	7831.45	7215.97	26

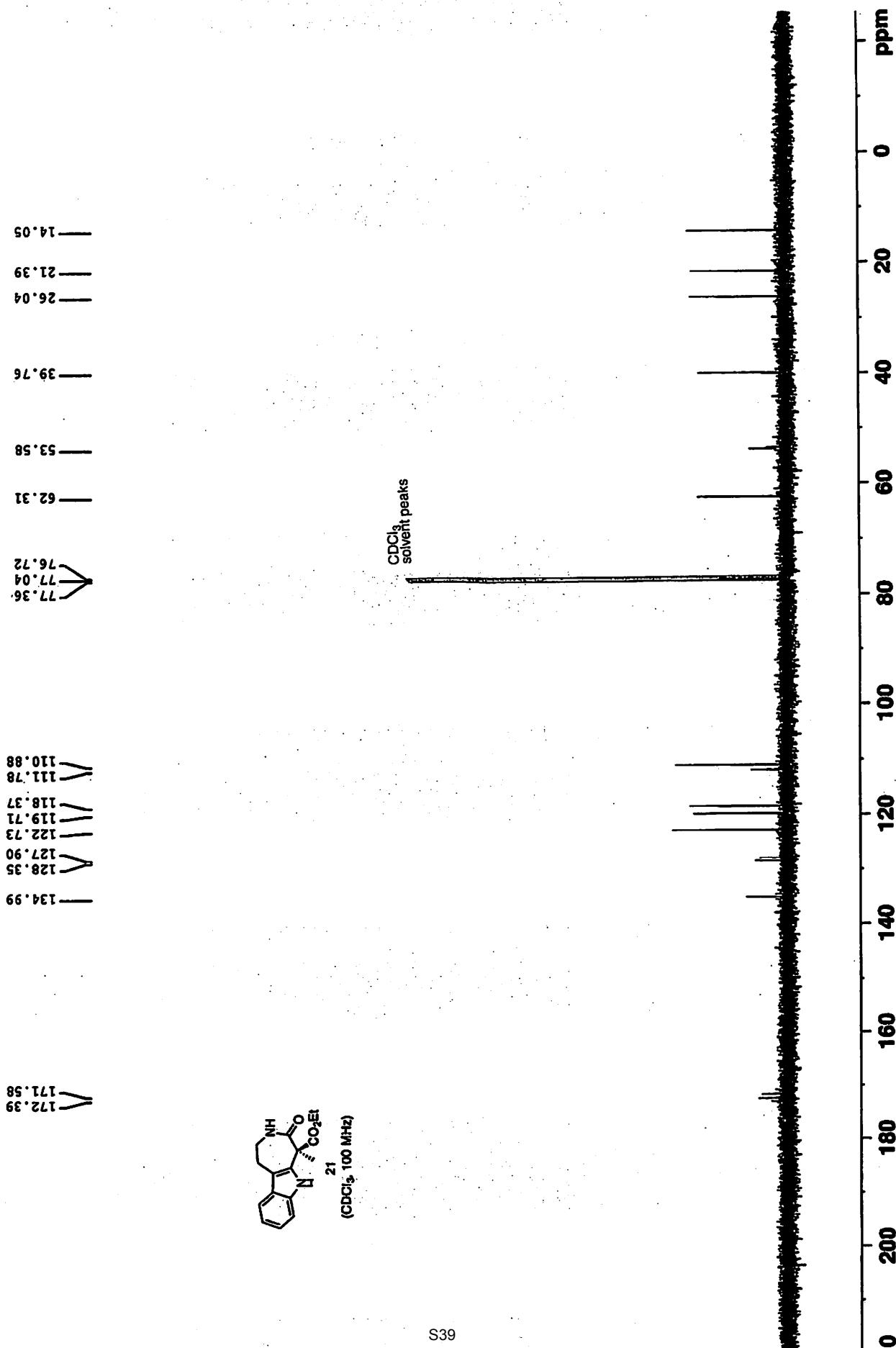


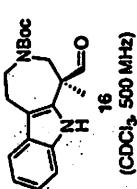
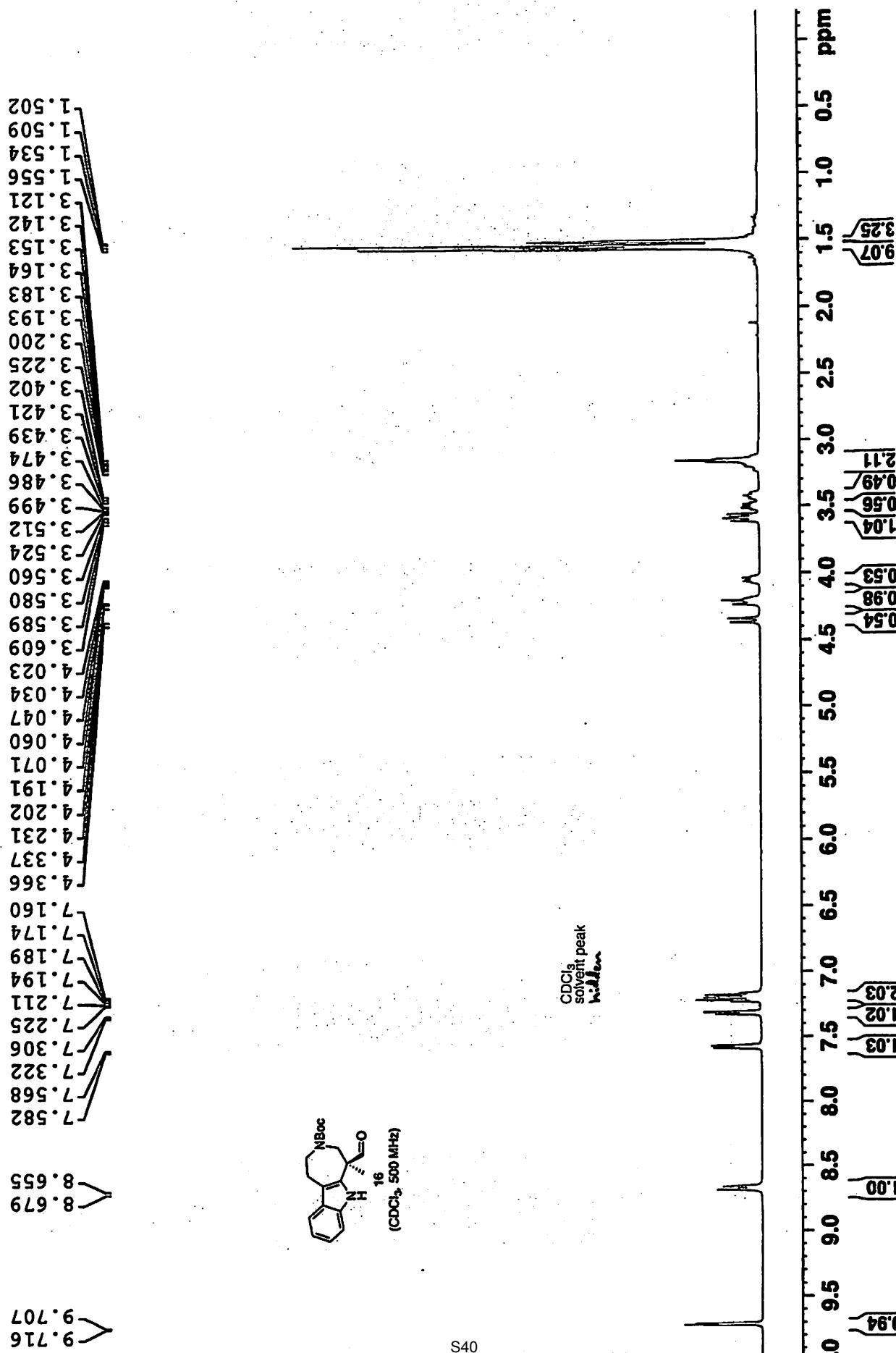


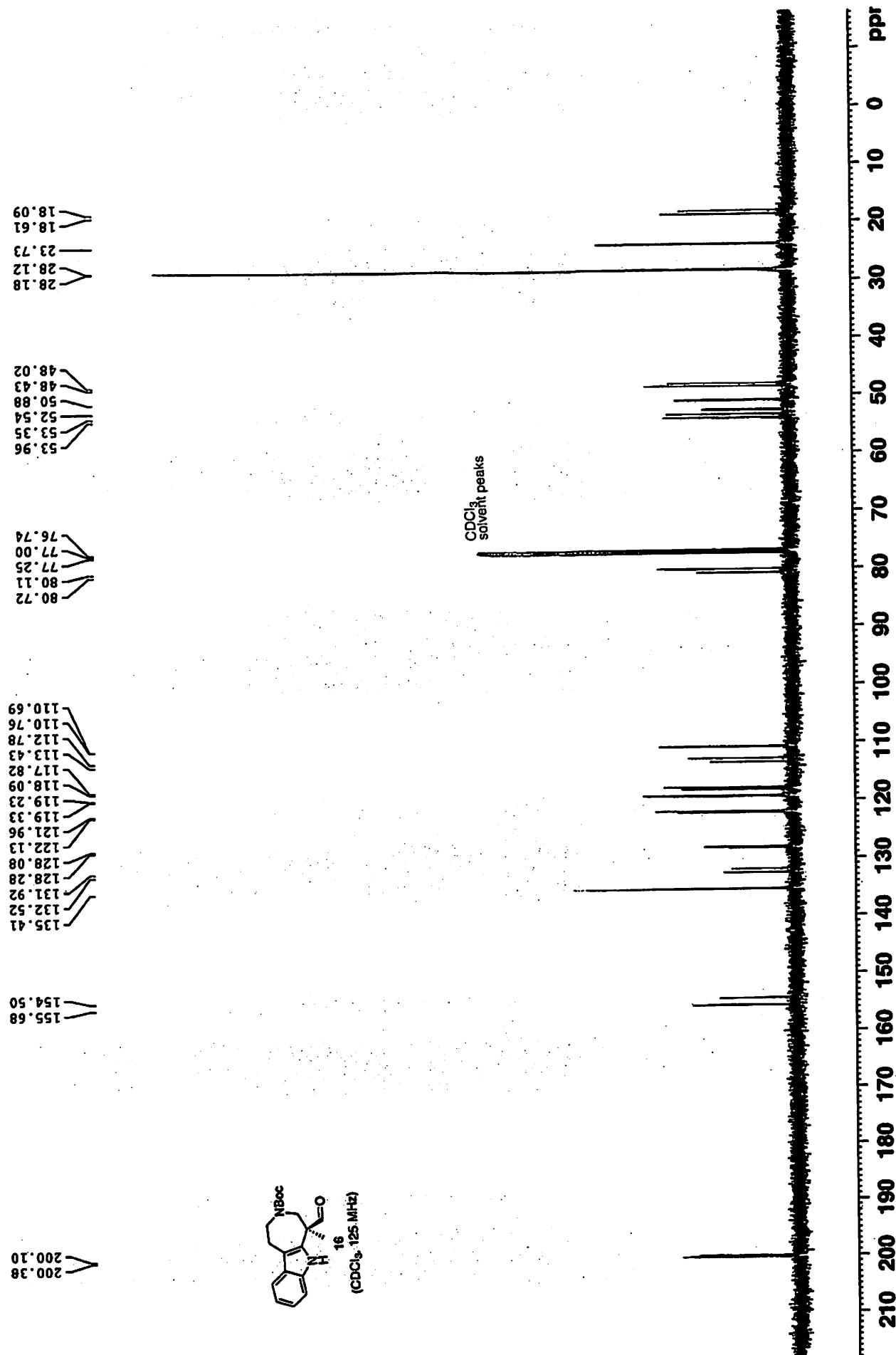


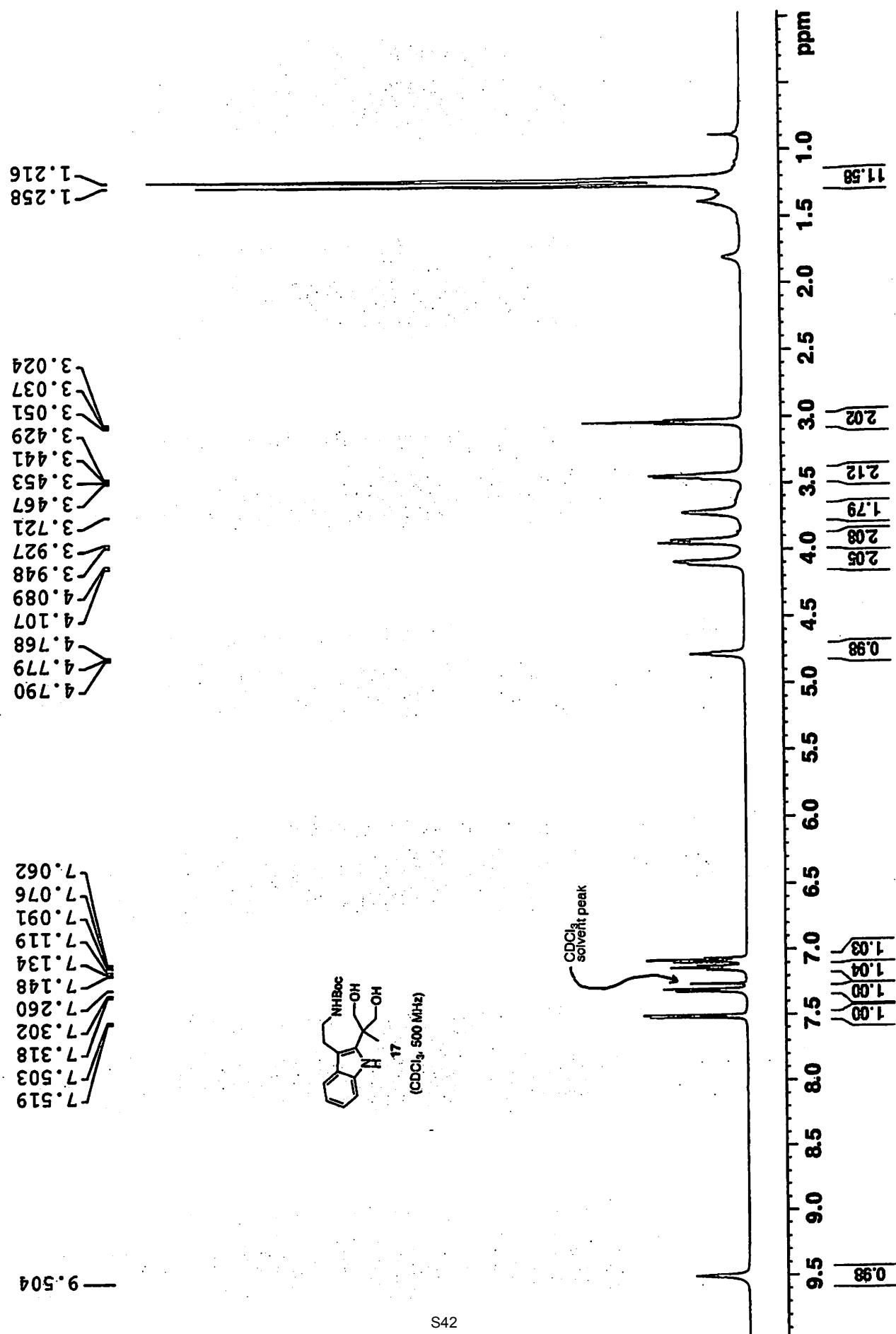


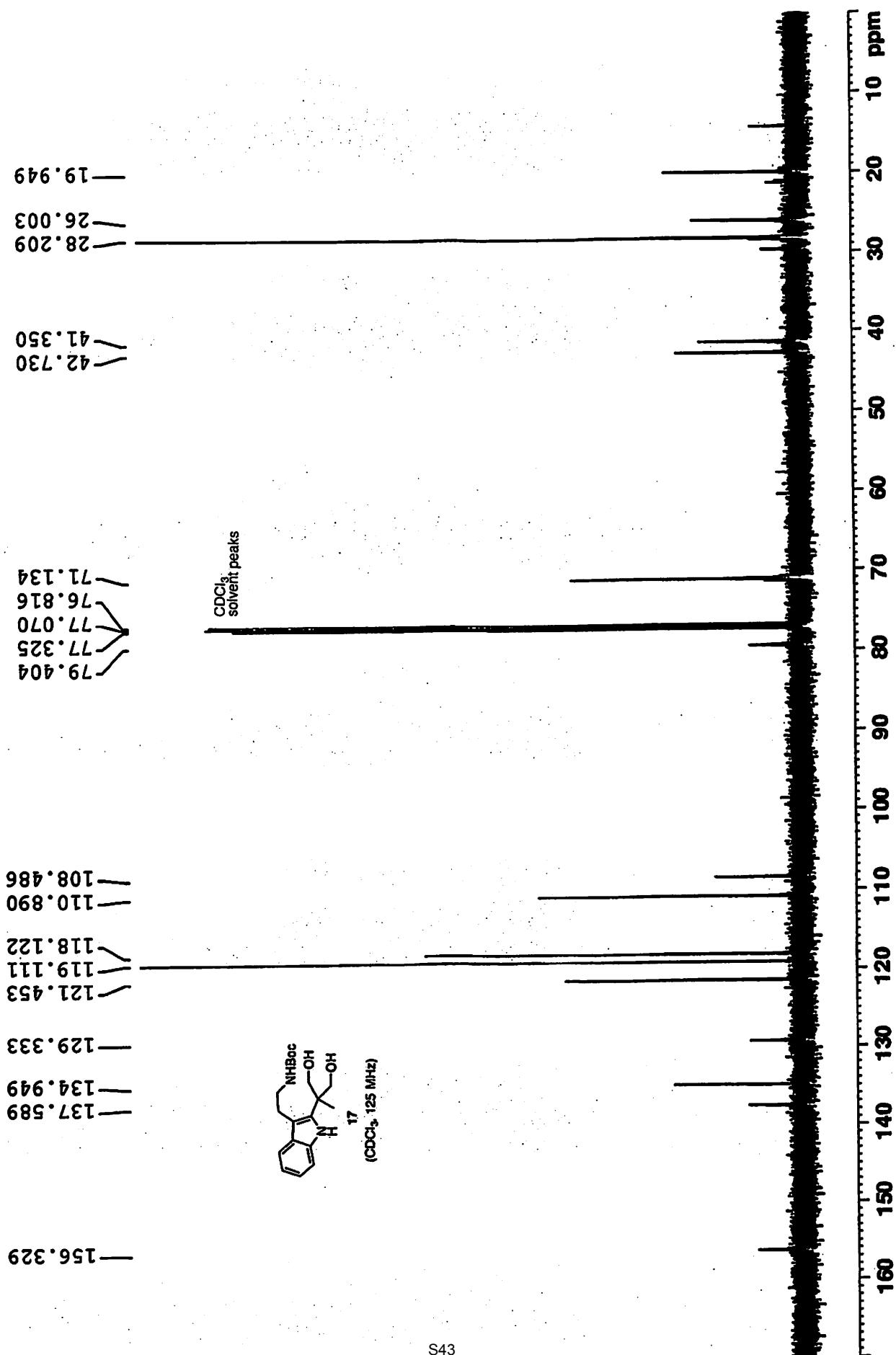


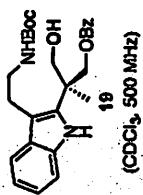
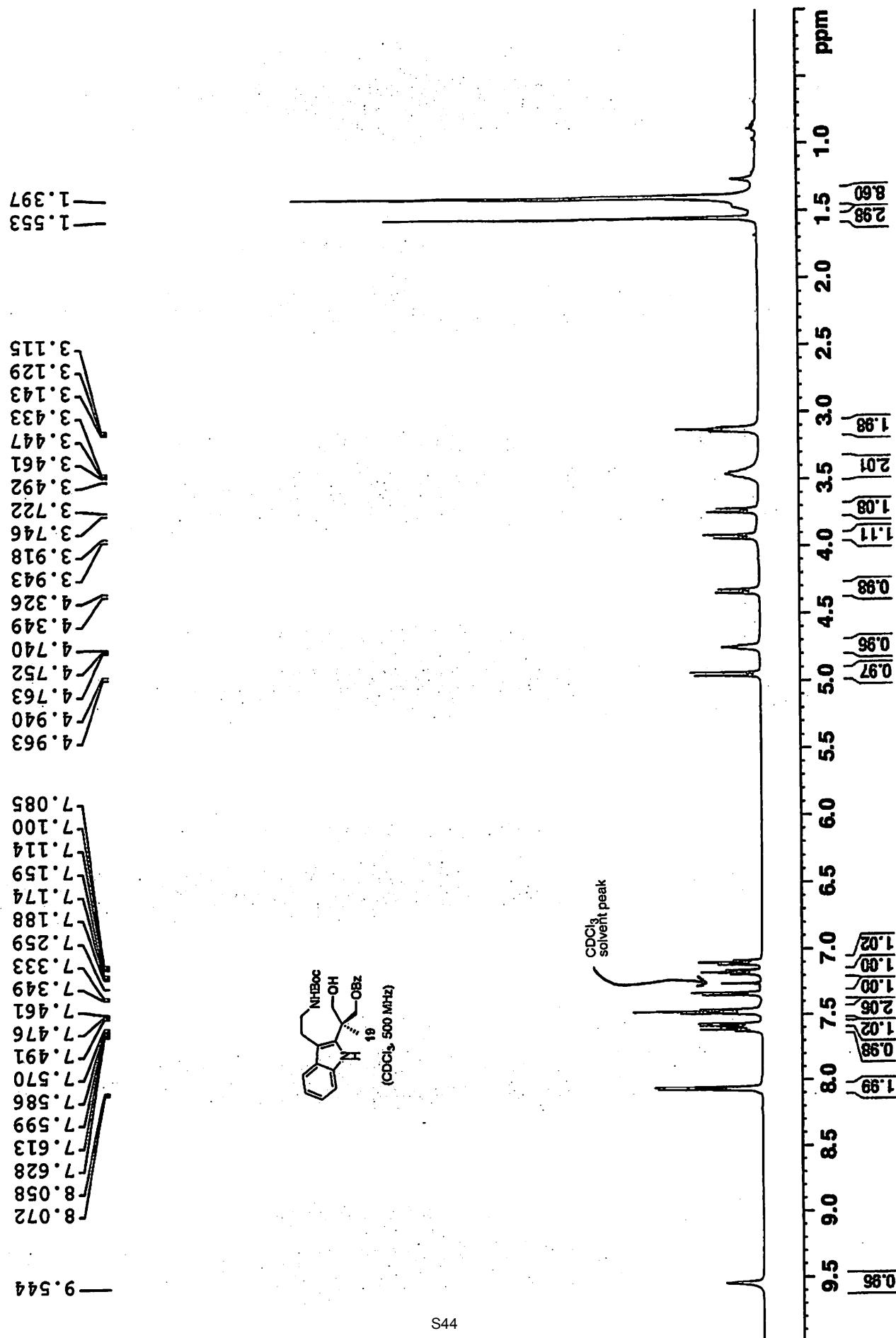


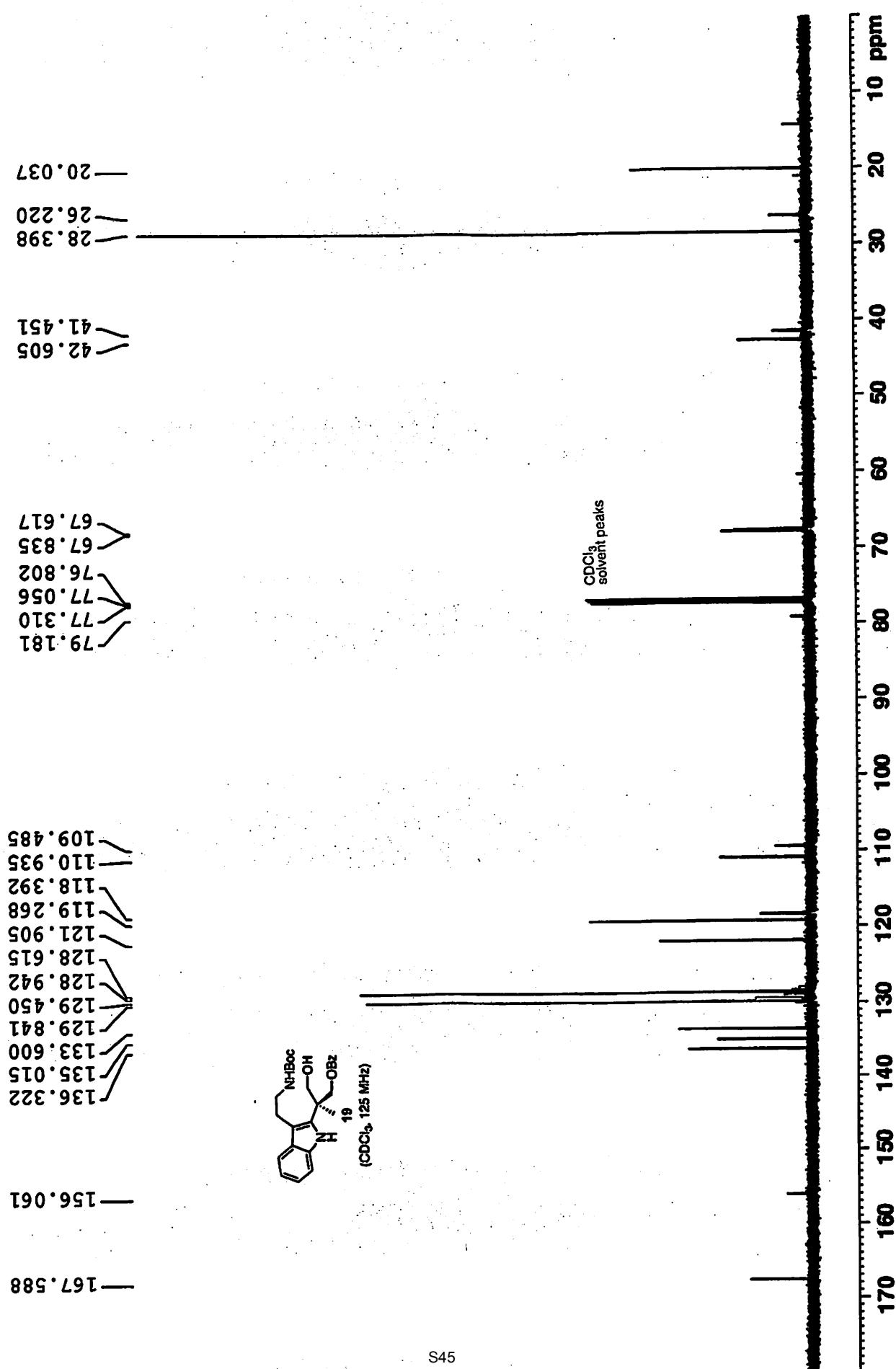


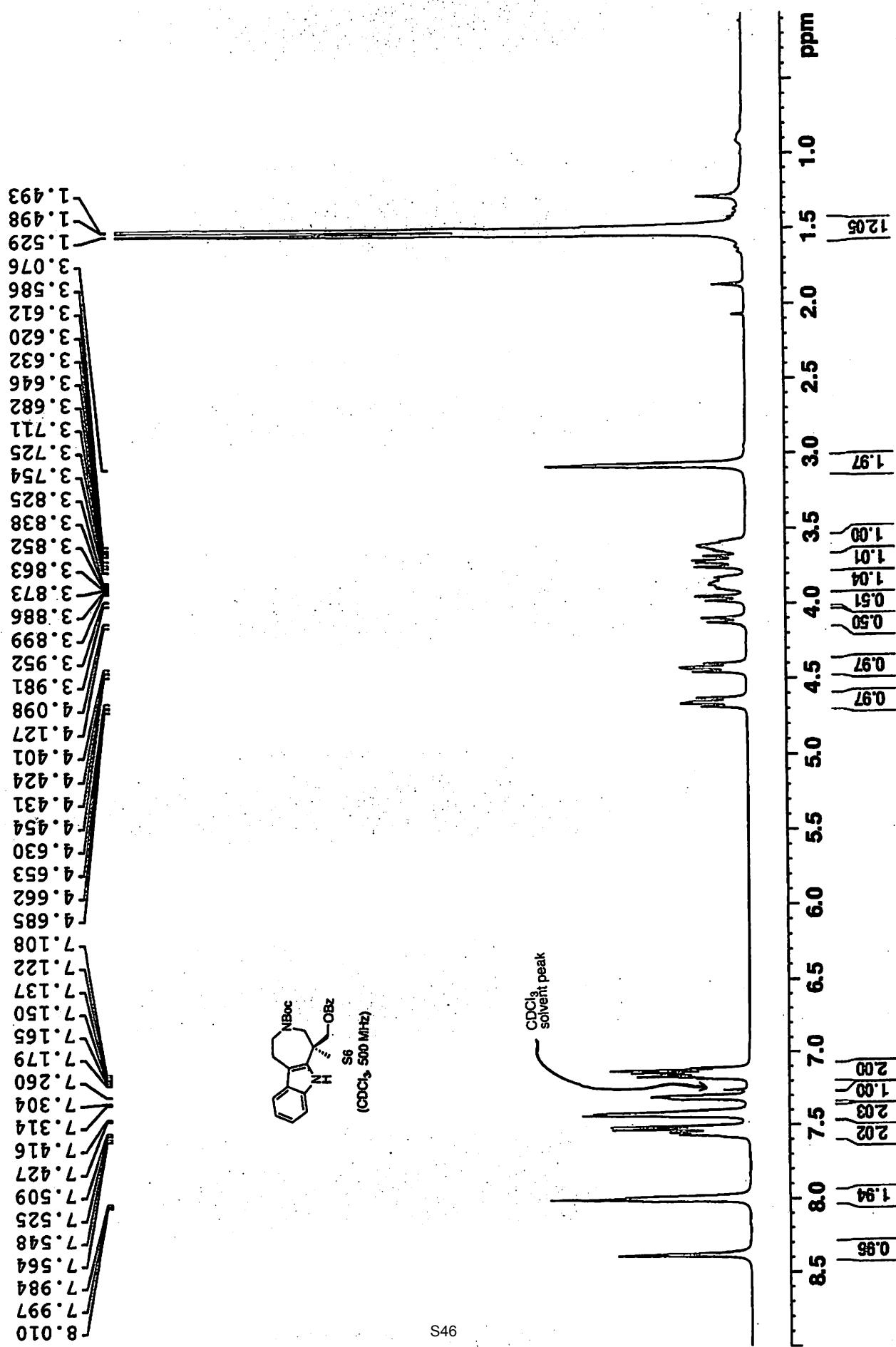


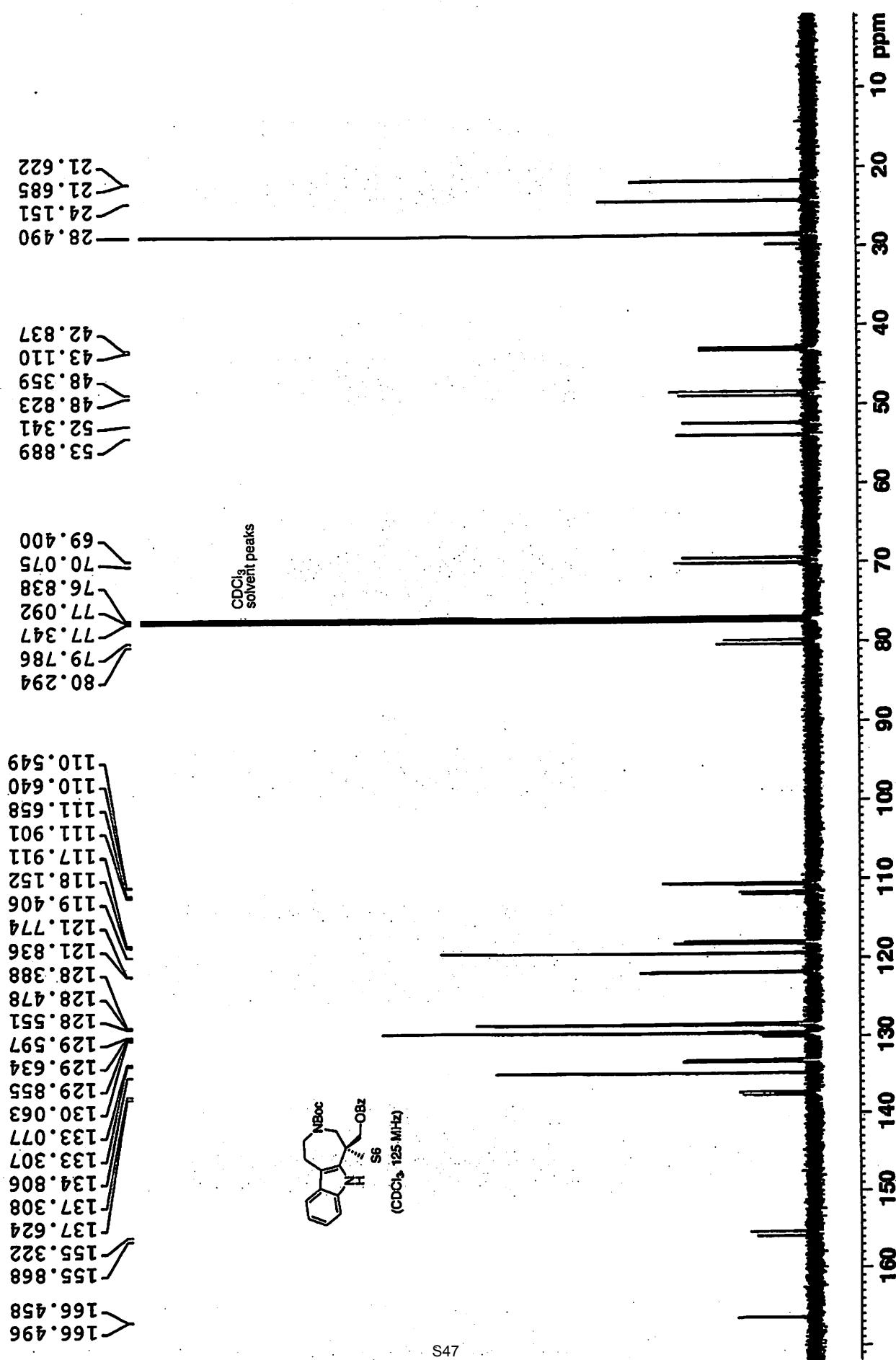


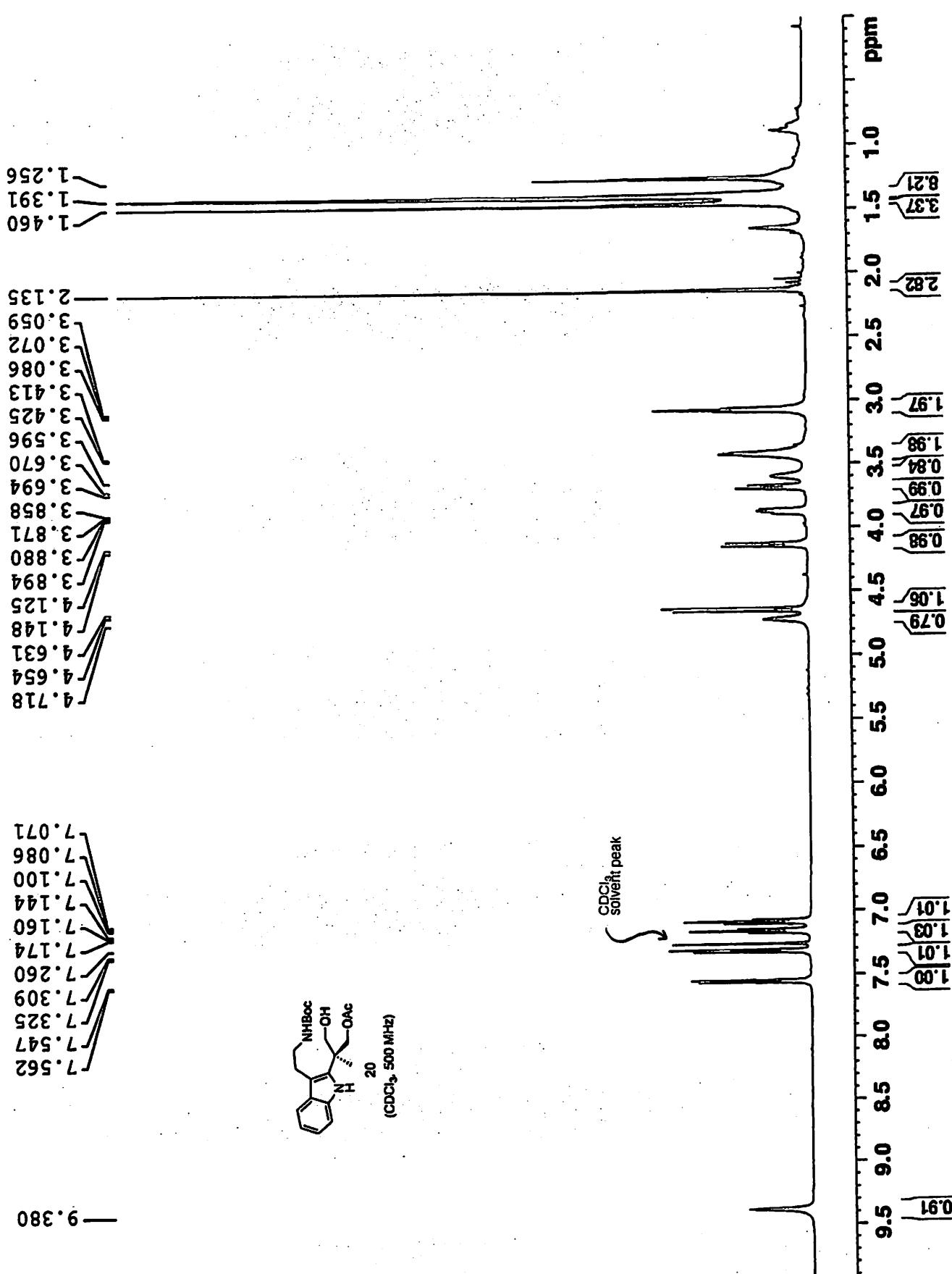


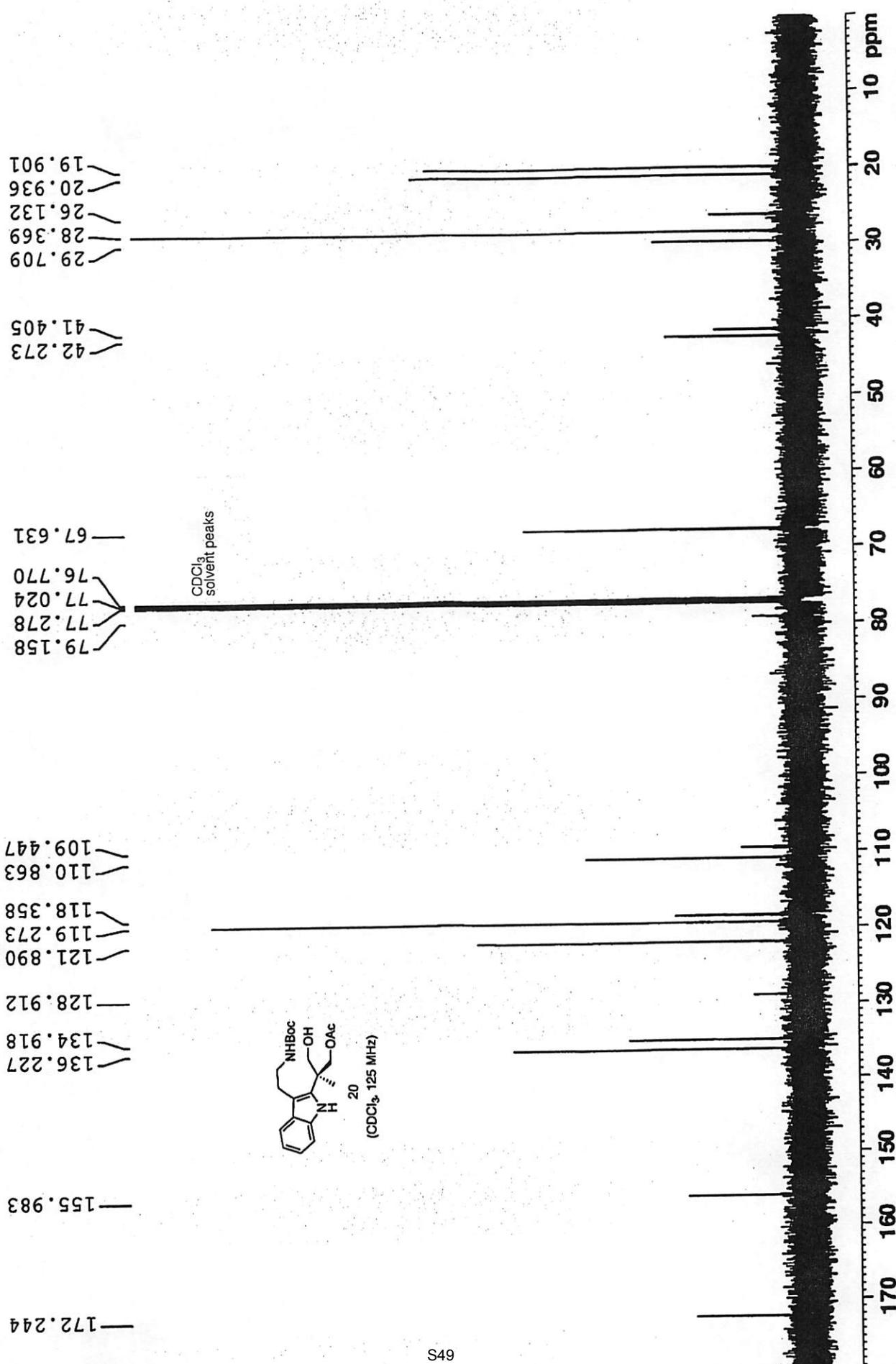


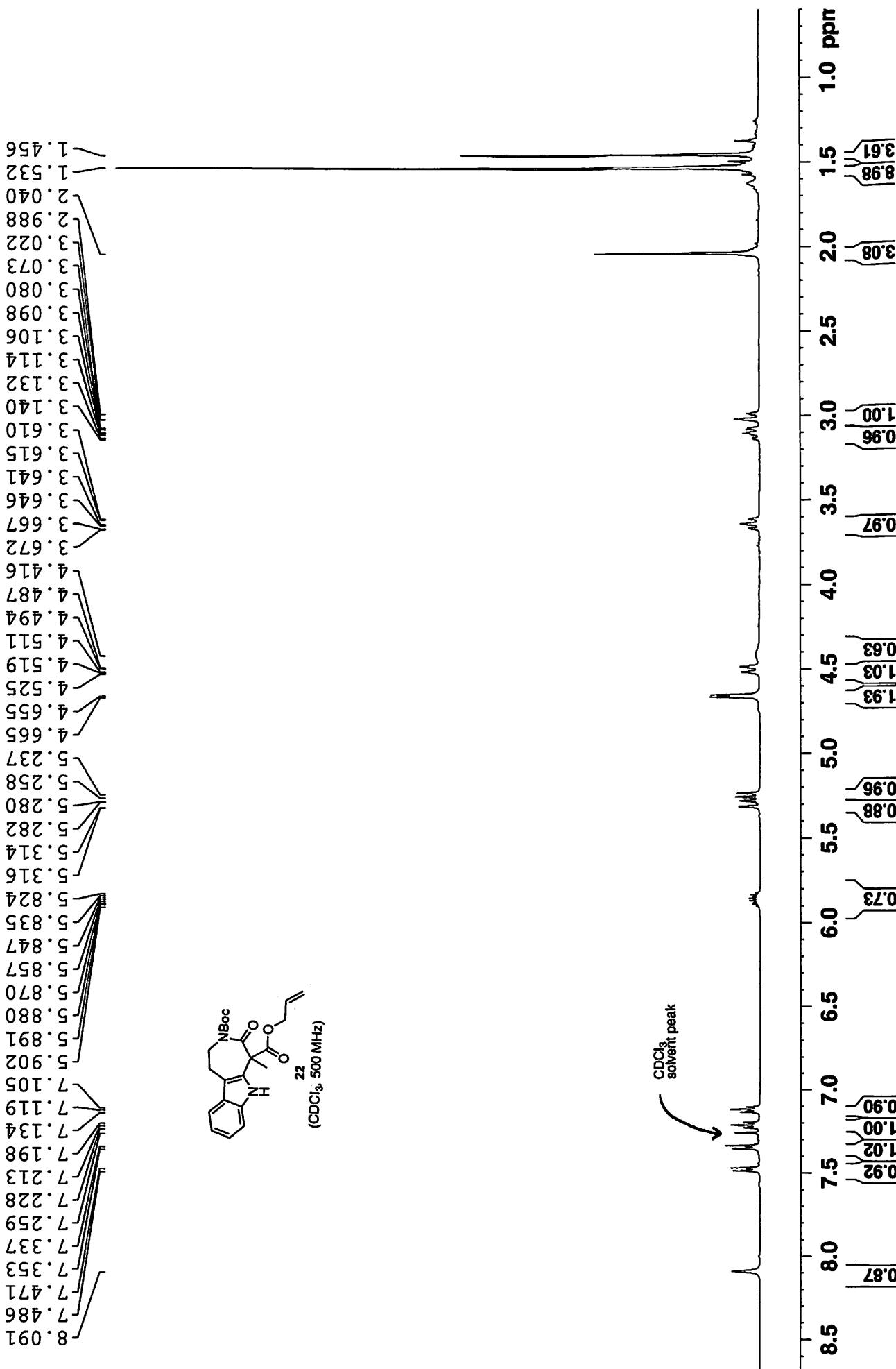


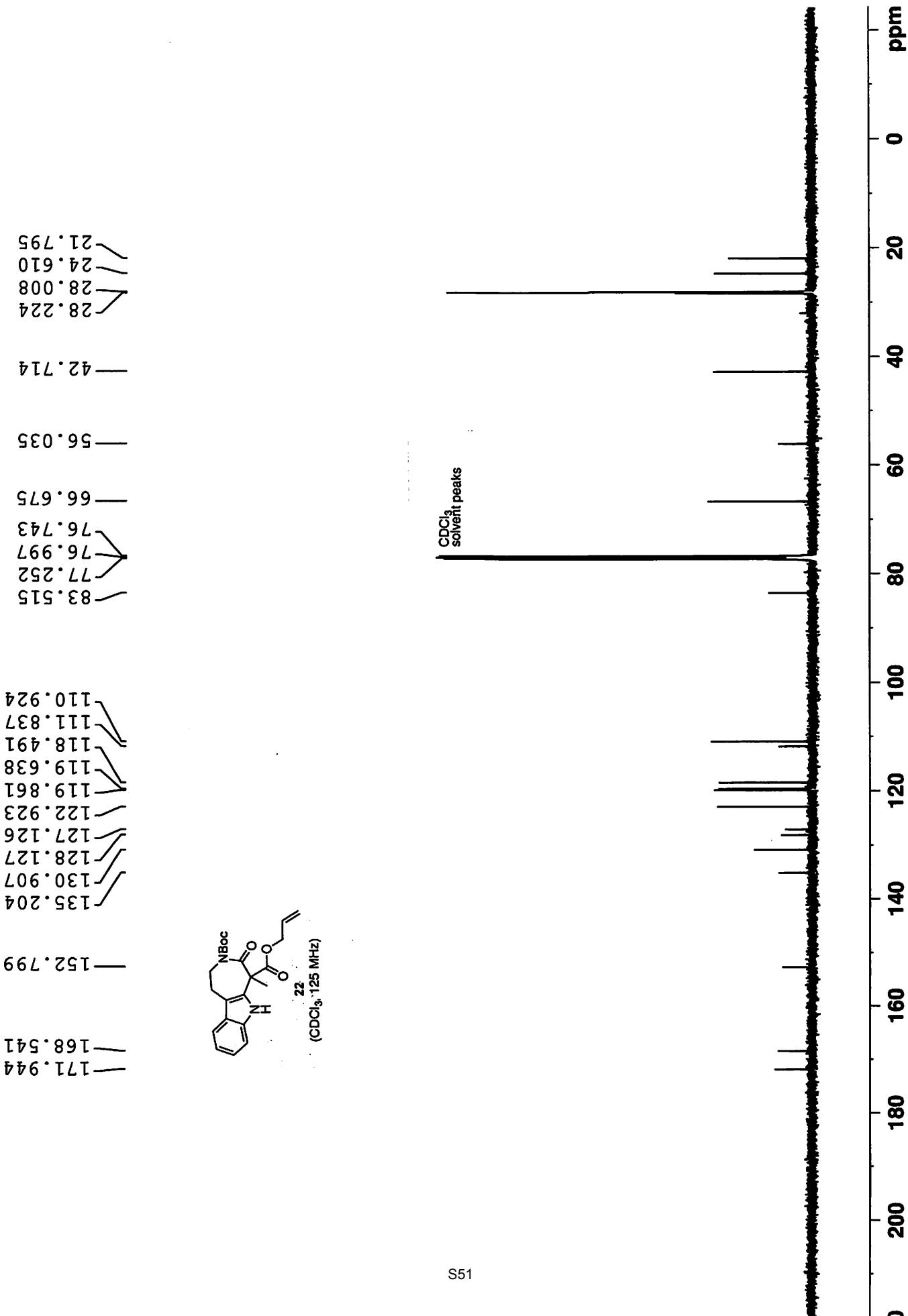


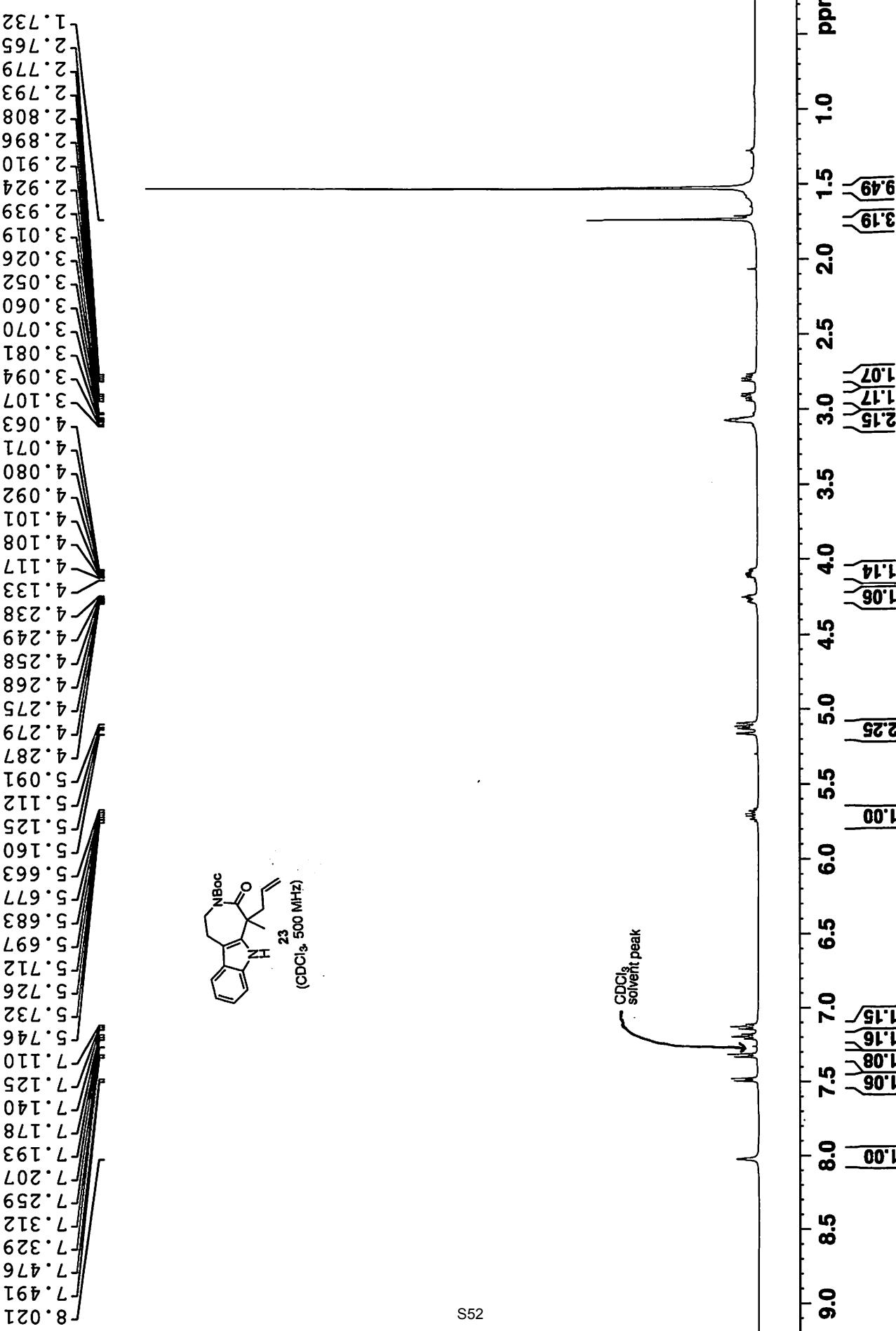


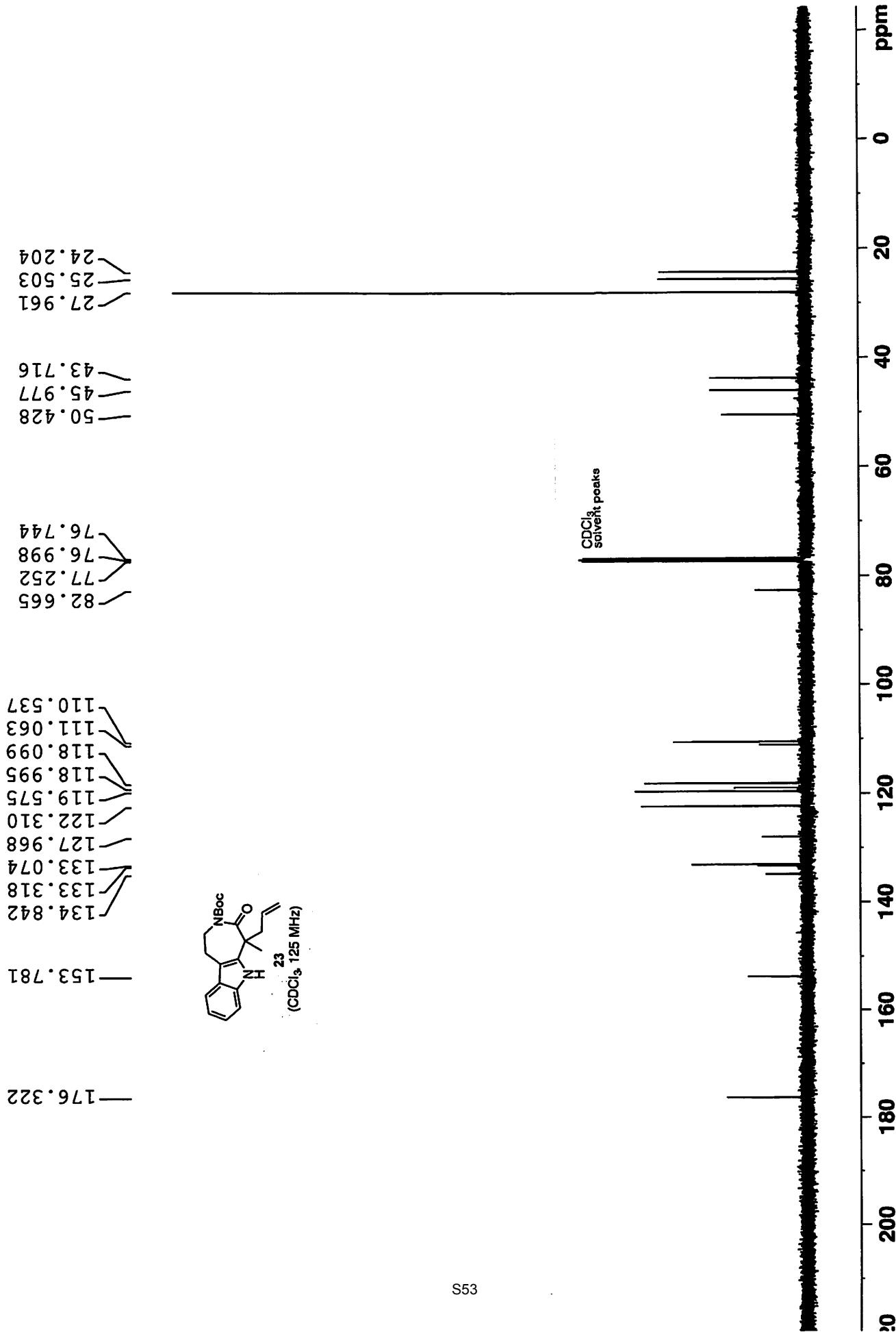


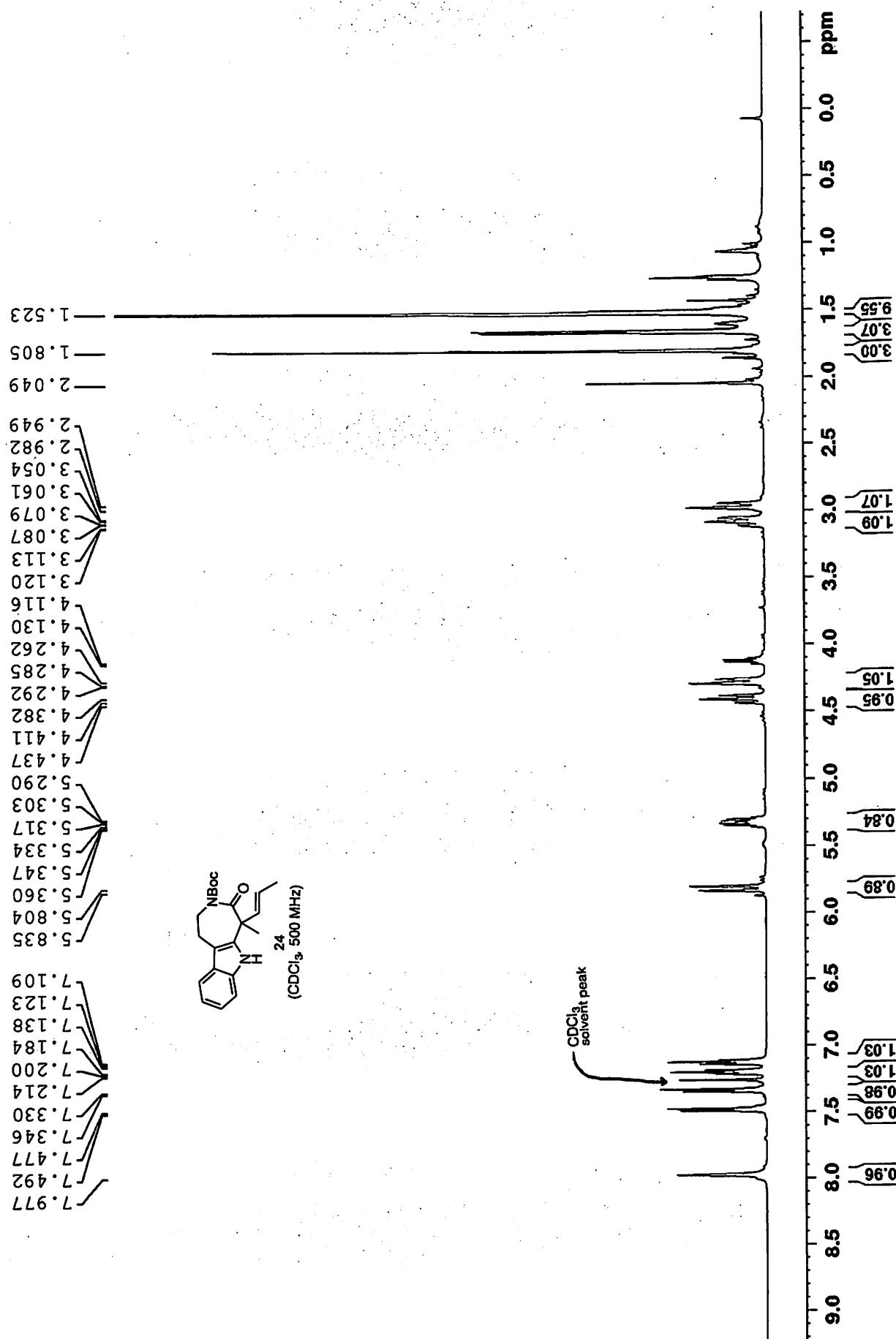


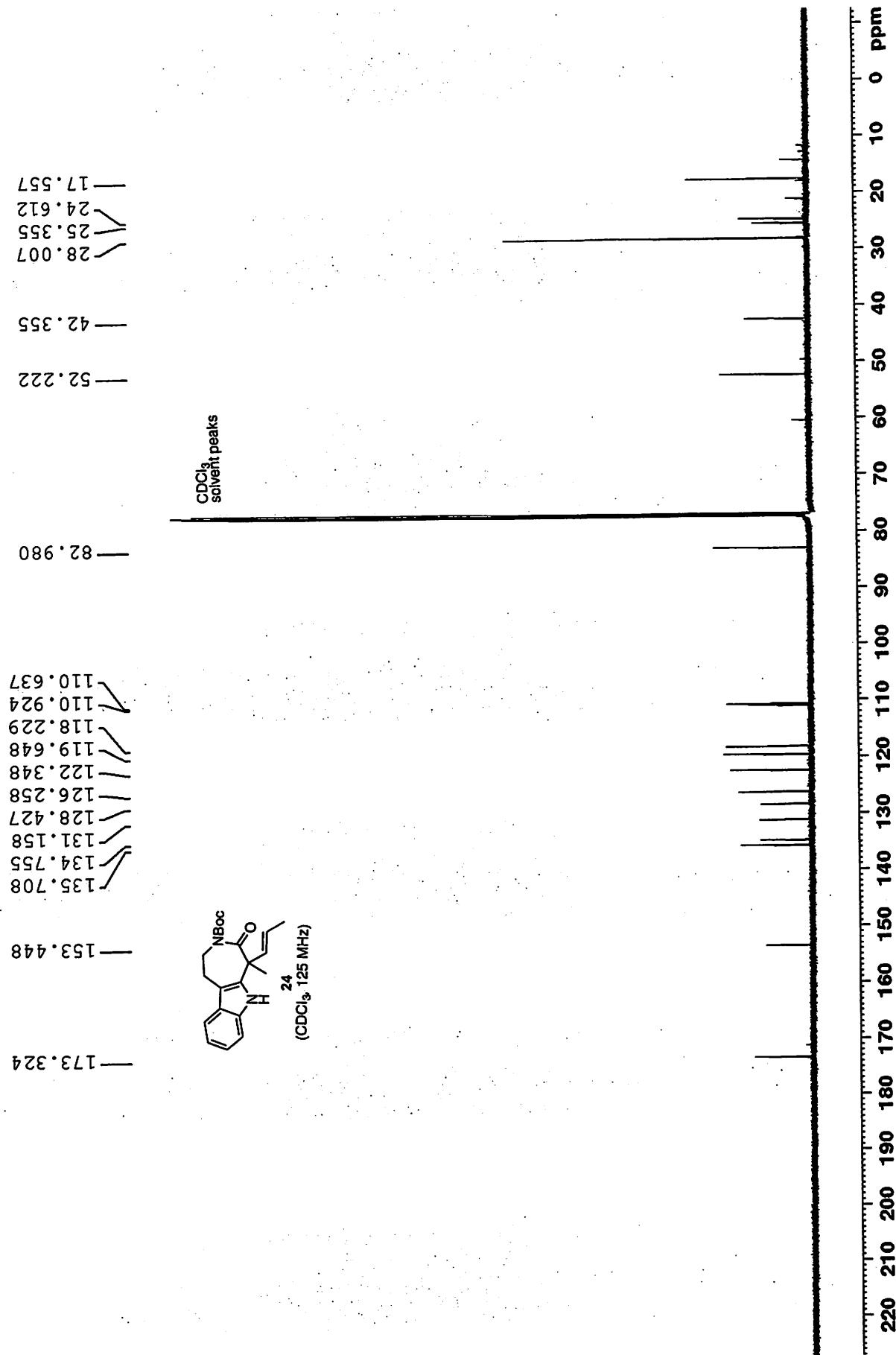


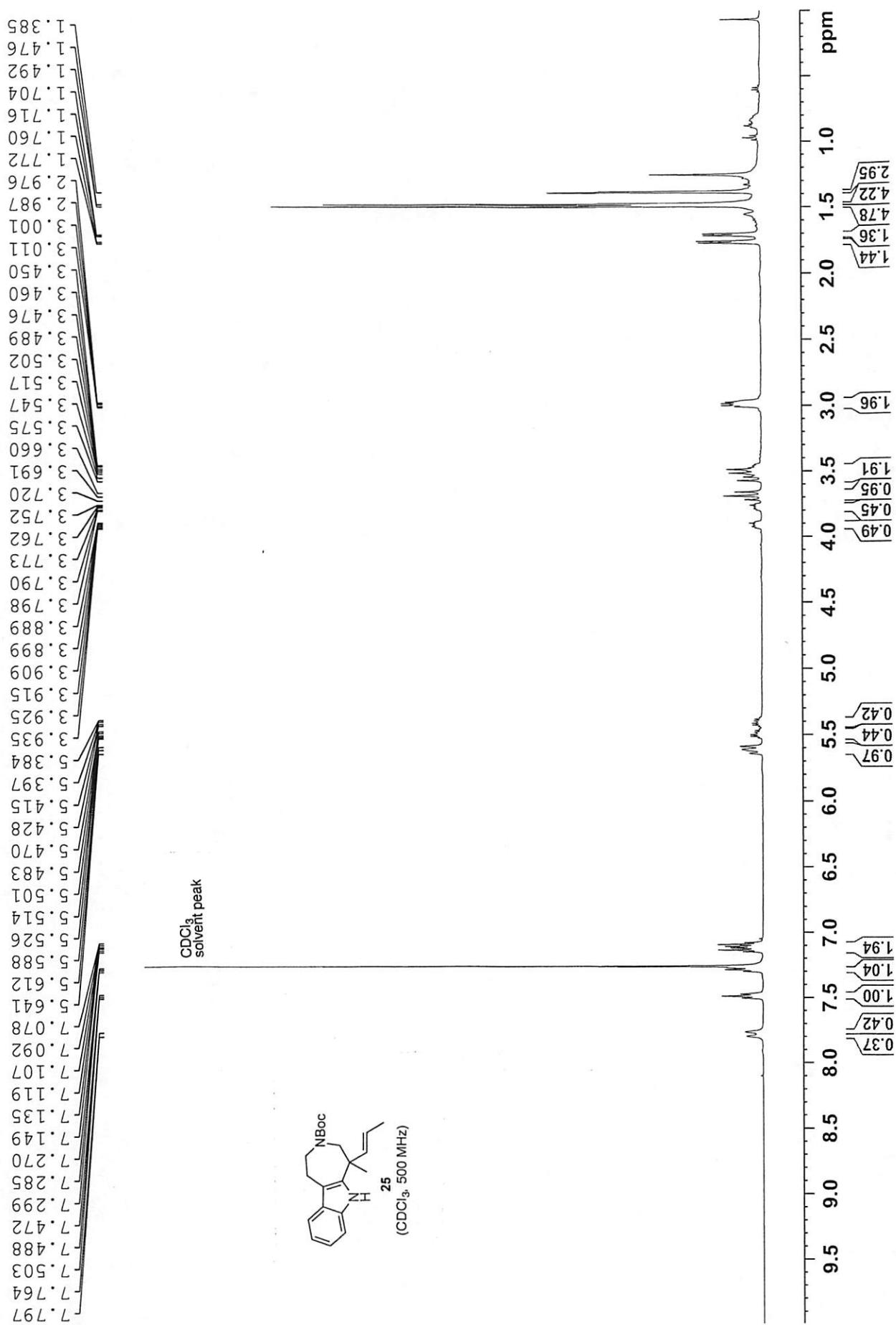


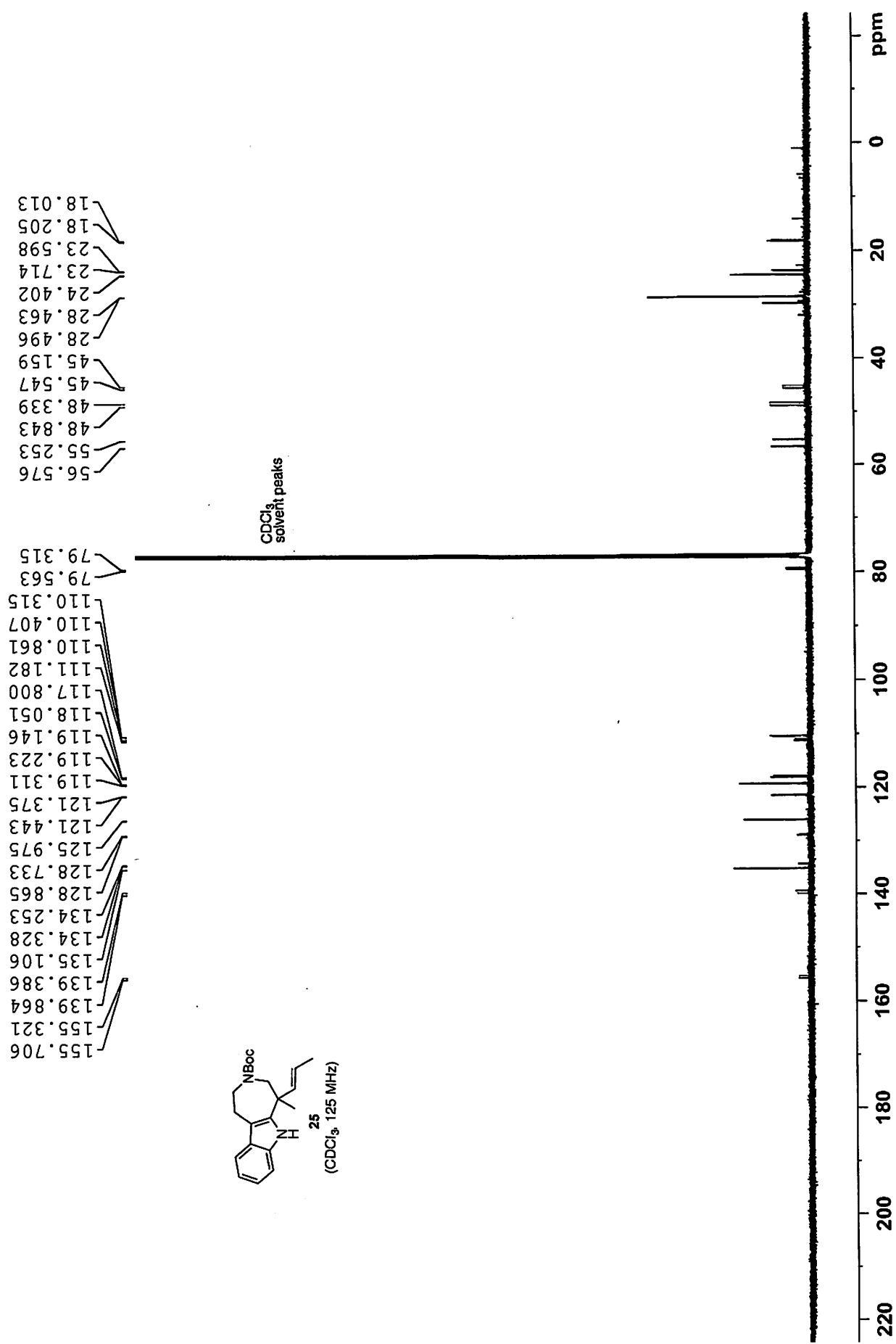






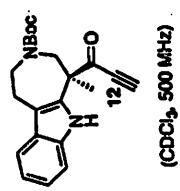




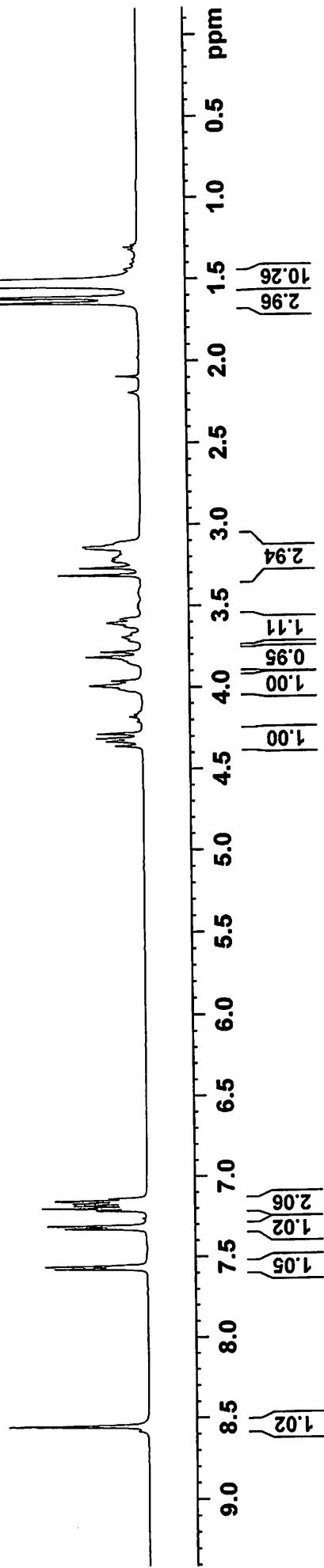


8.551

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3.988
3.960
3.848
3.812
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3.624
3.584
3.312
3.223
3.211
3.175
3.137
1.645
1.612
1.536
1.508



CDCl₃
solvent peak



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22.93
23.17
28.18
28.27

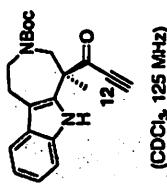
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82.76

110.76
110.85
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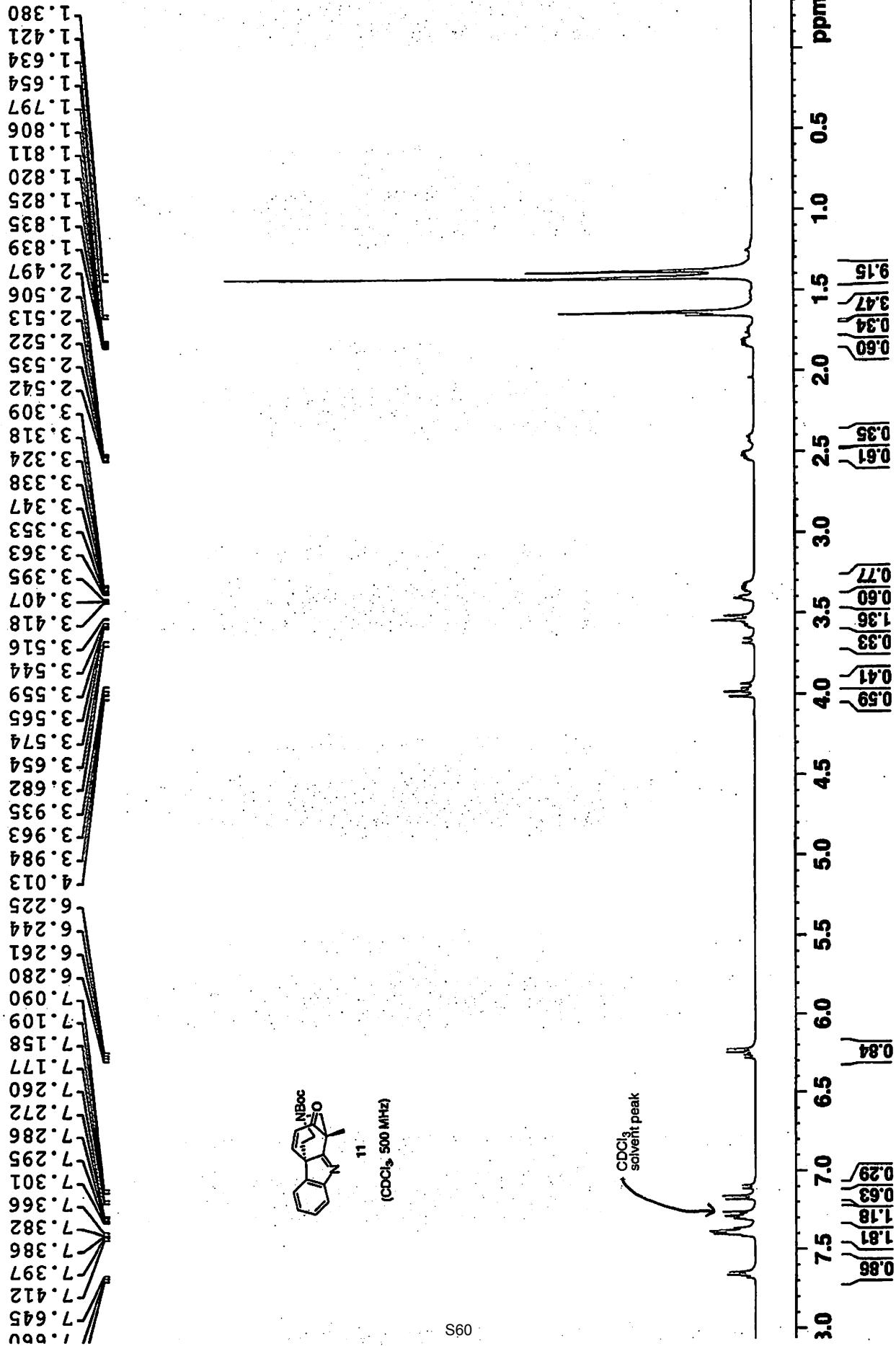
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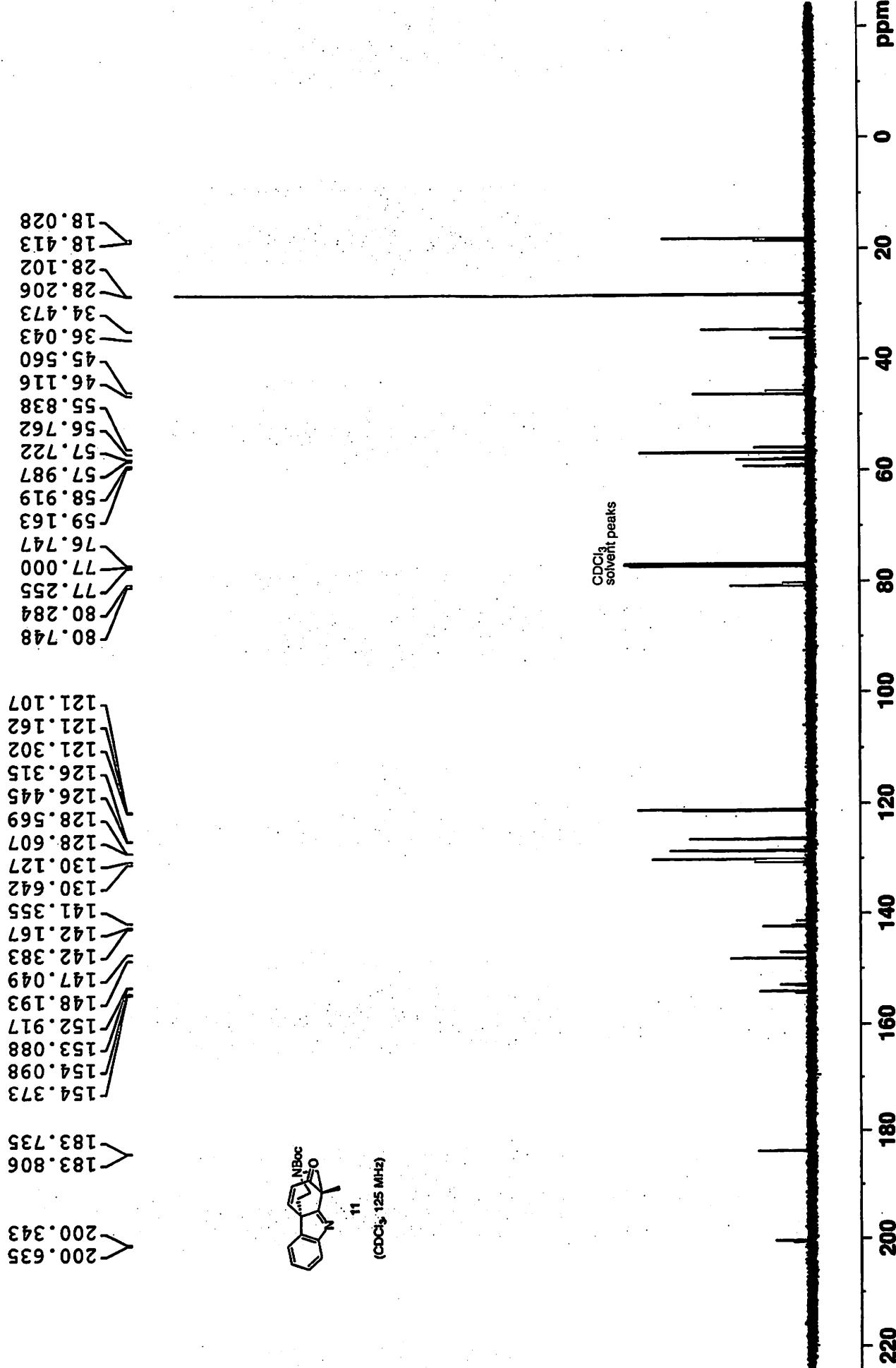
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188.34

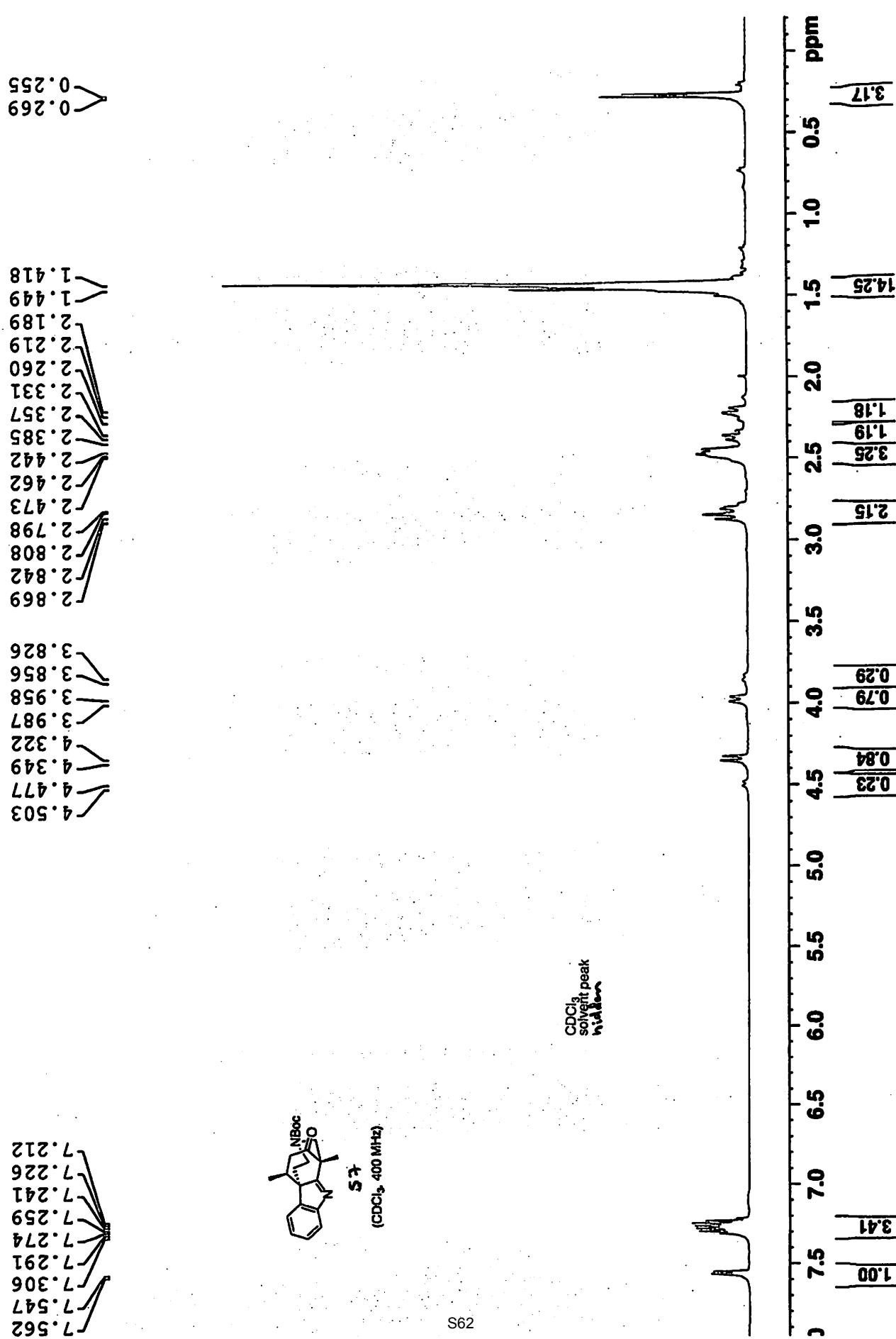


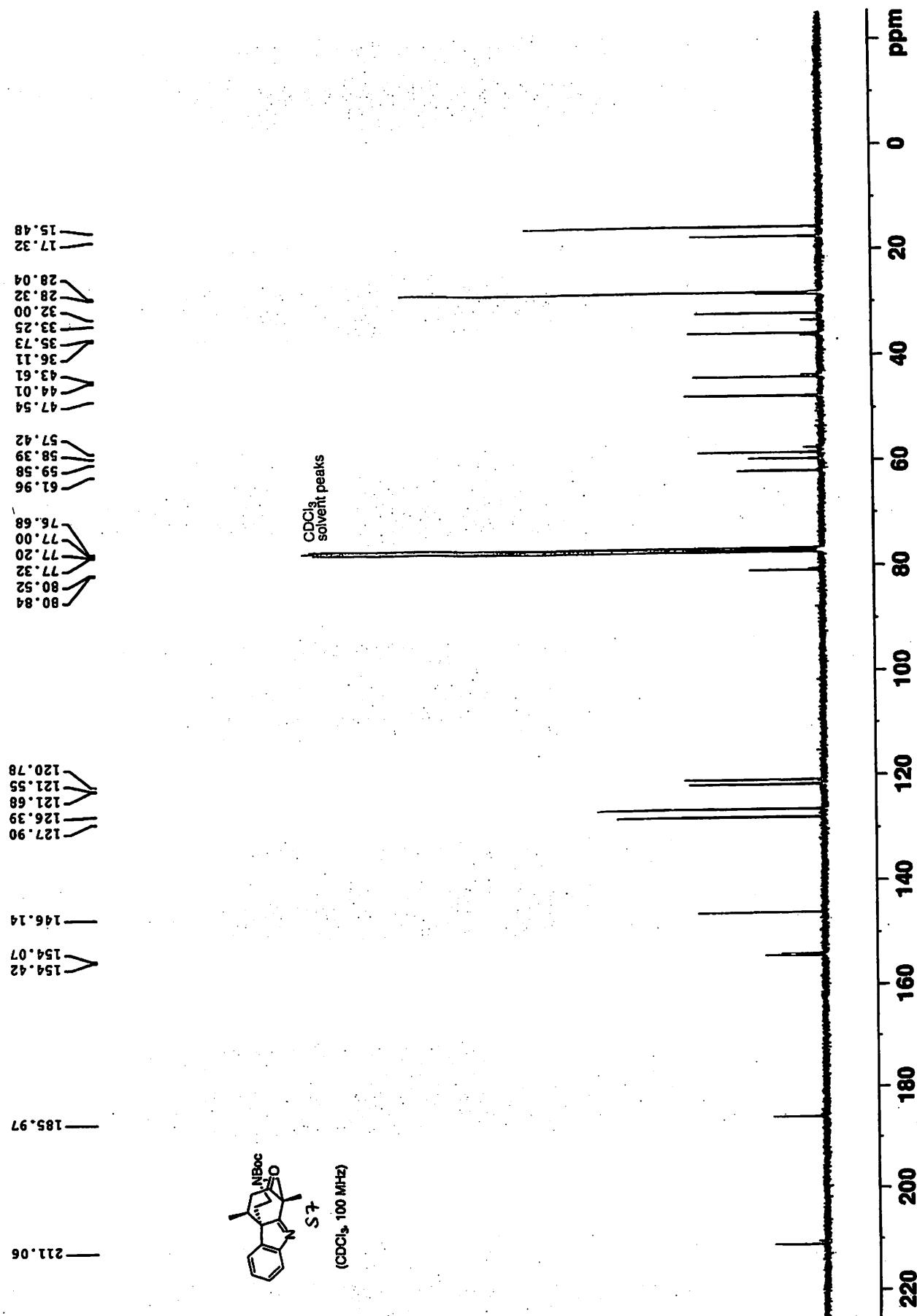
CDCl₃
solvent peaks

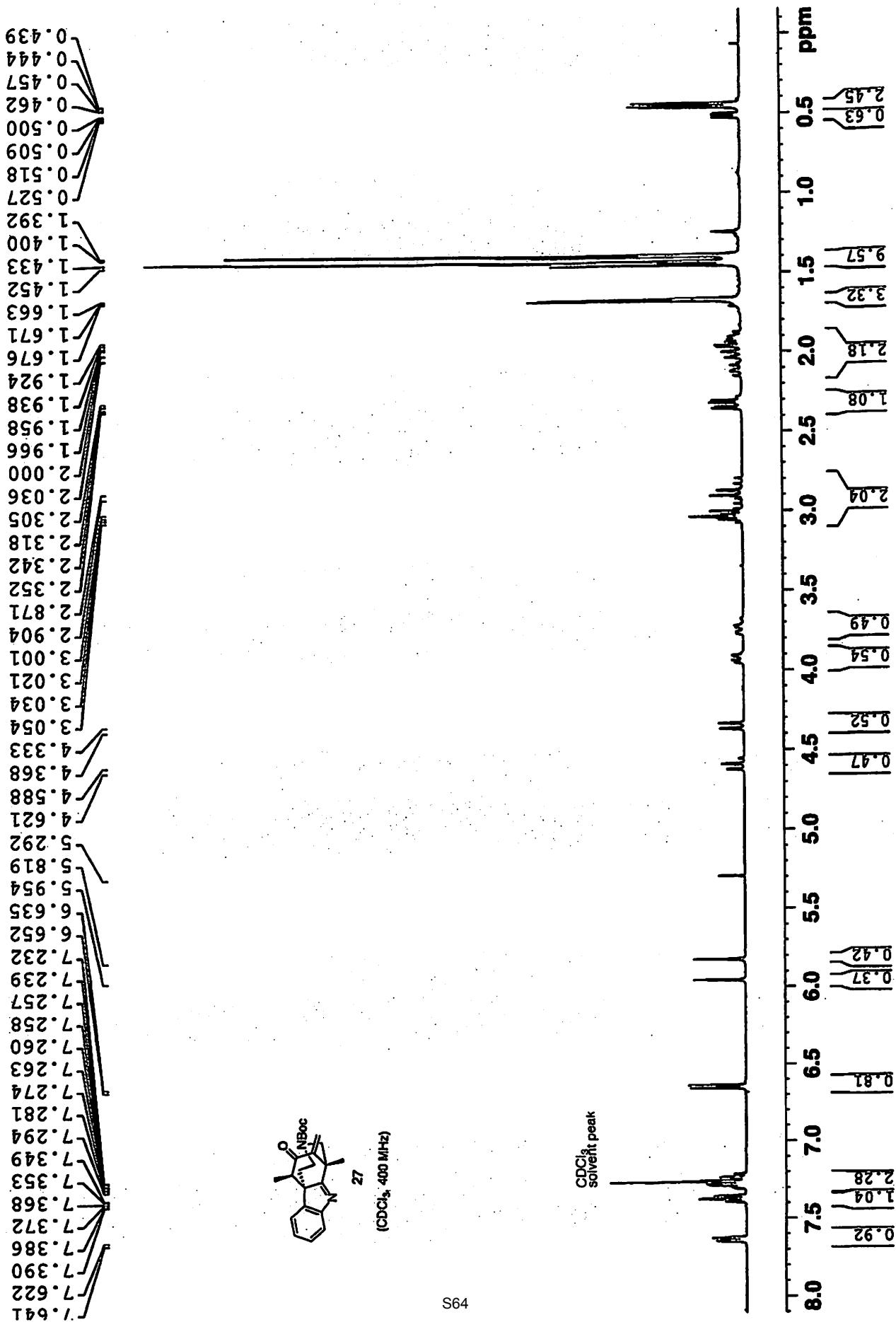
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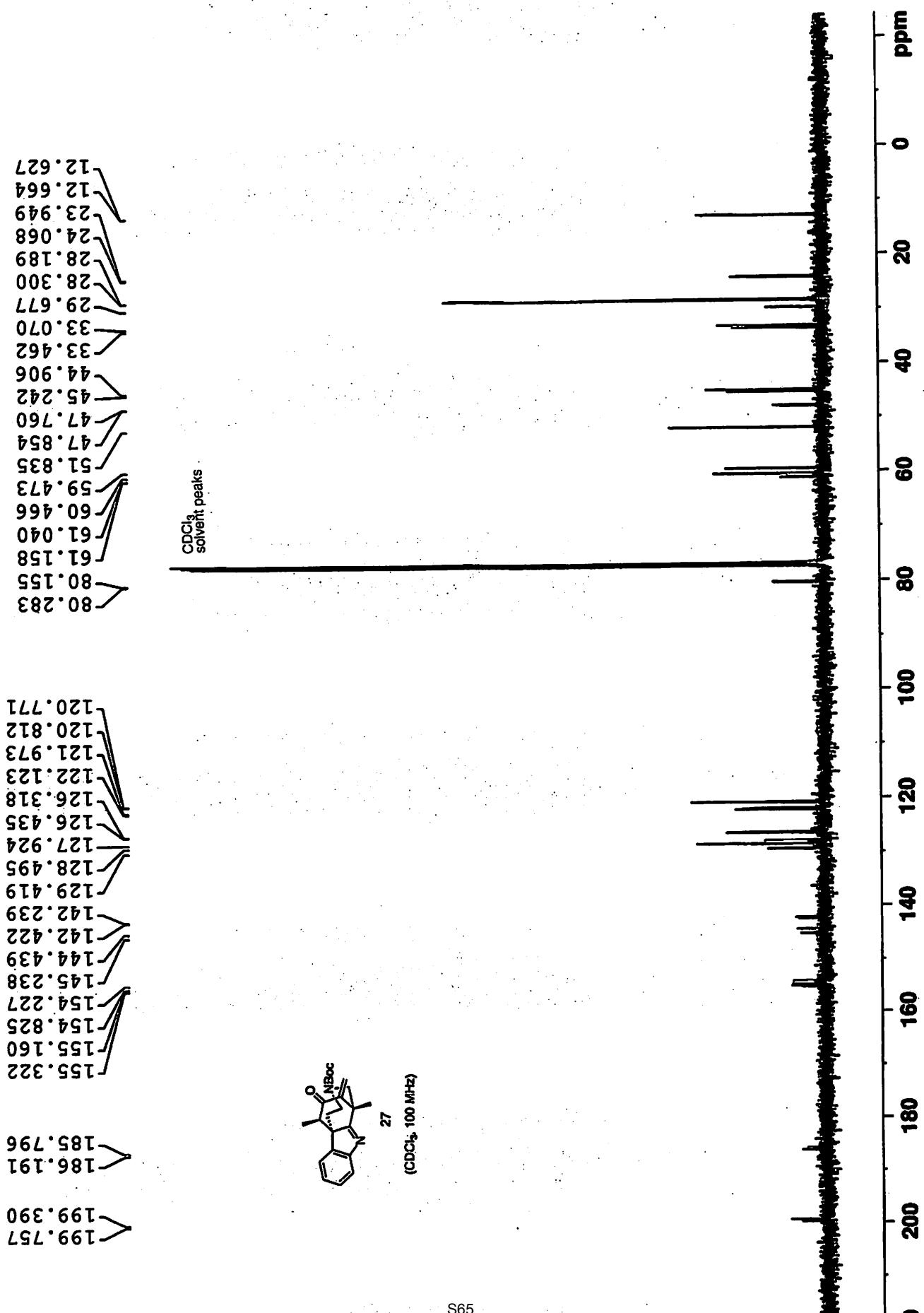


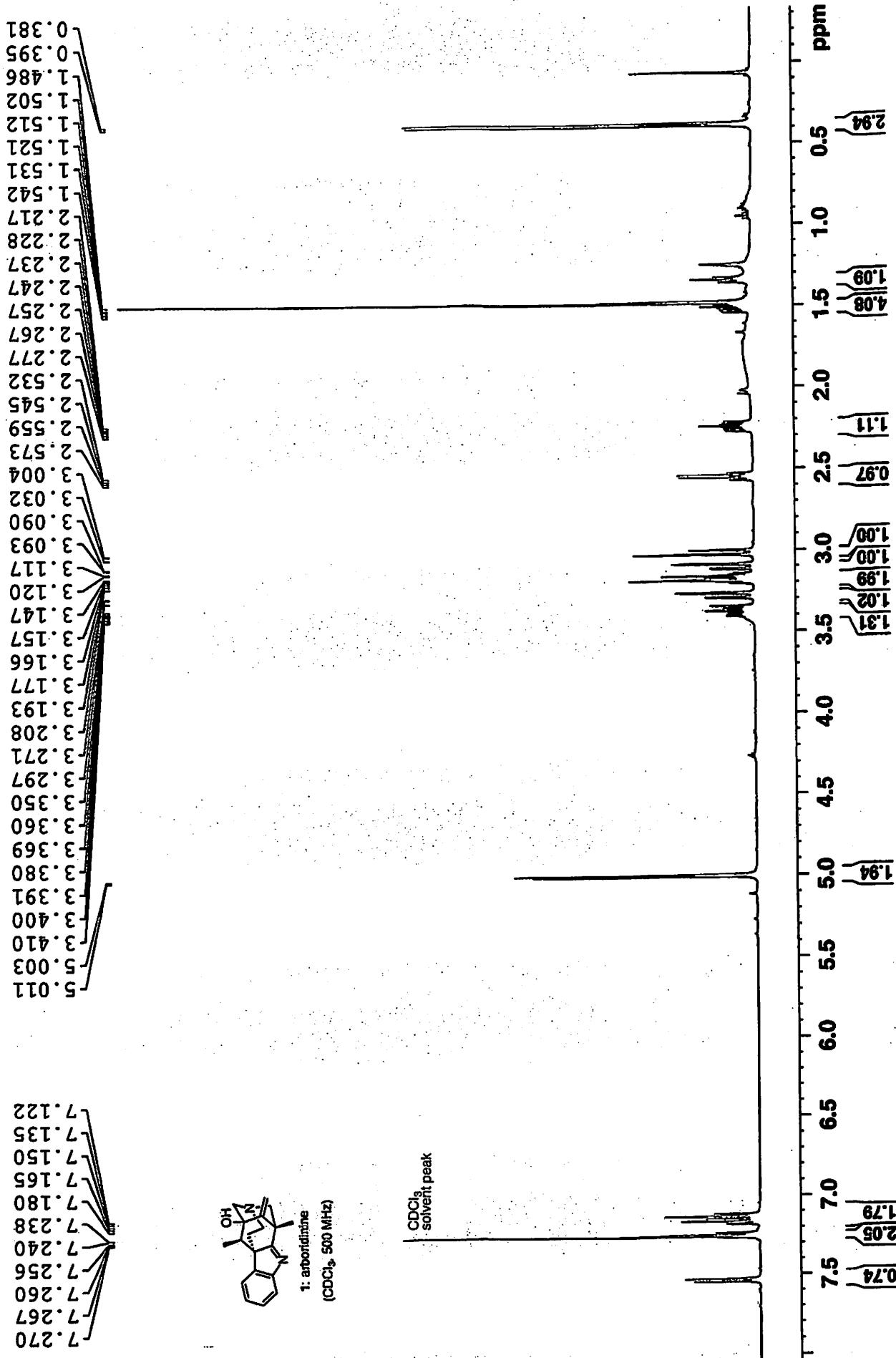


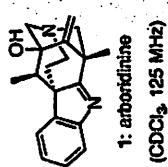
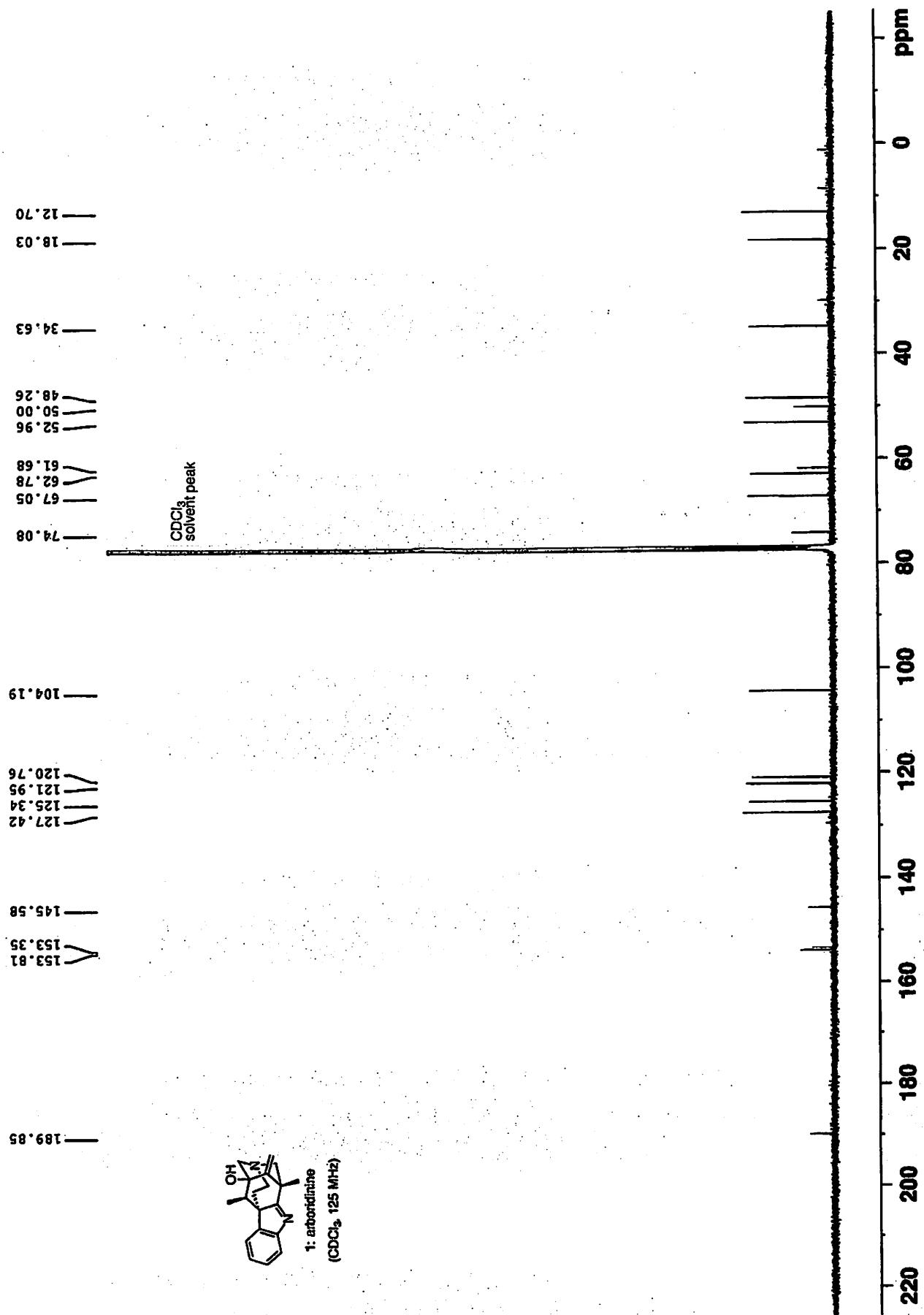


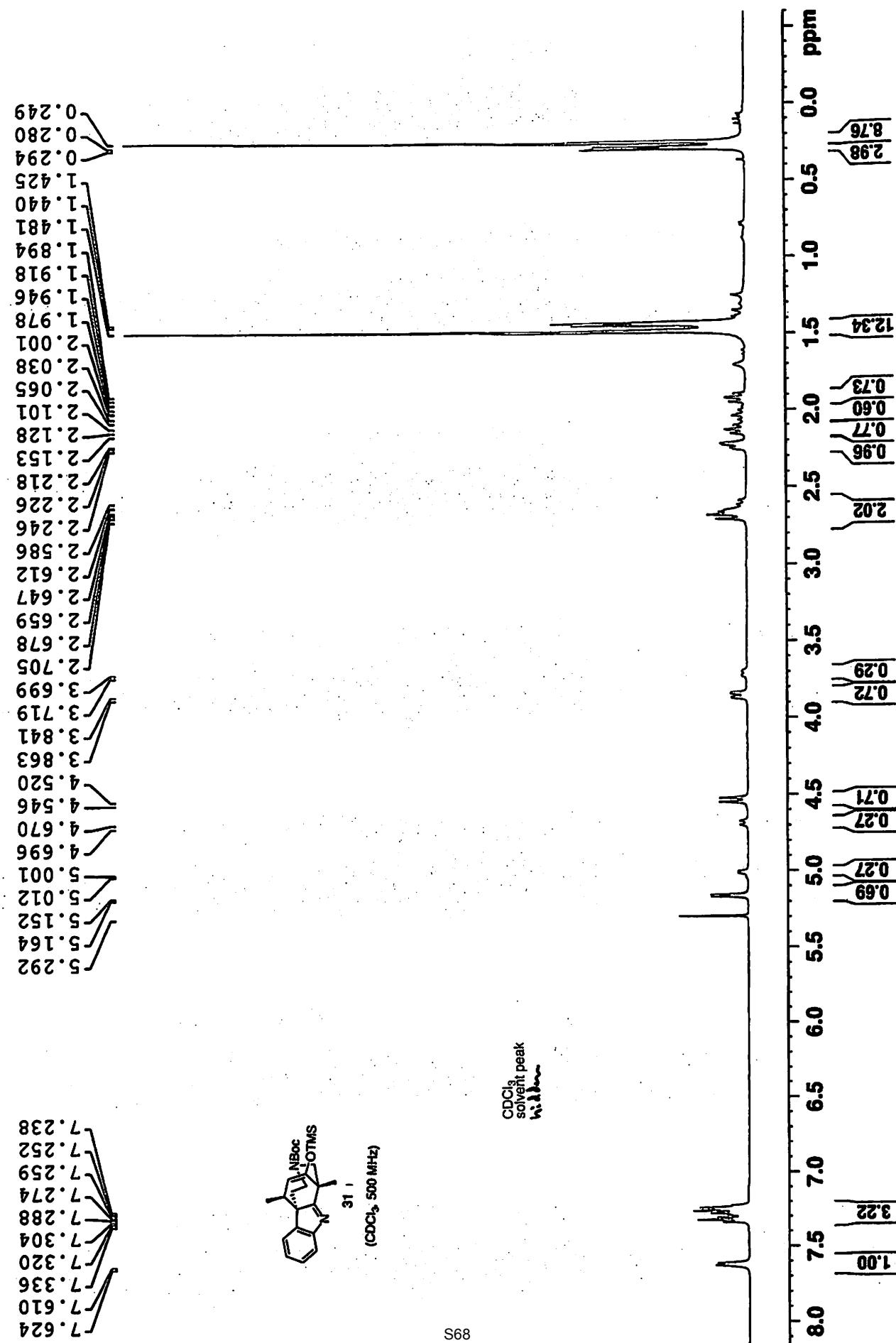


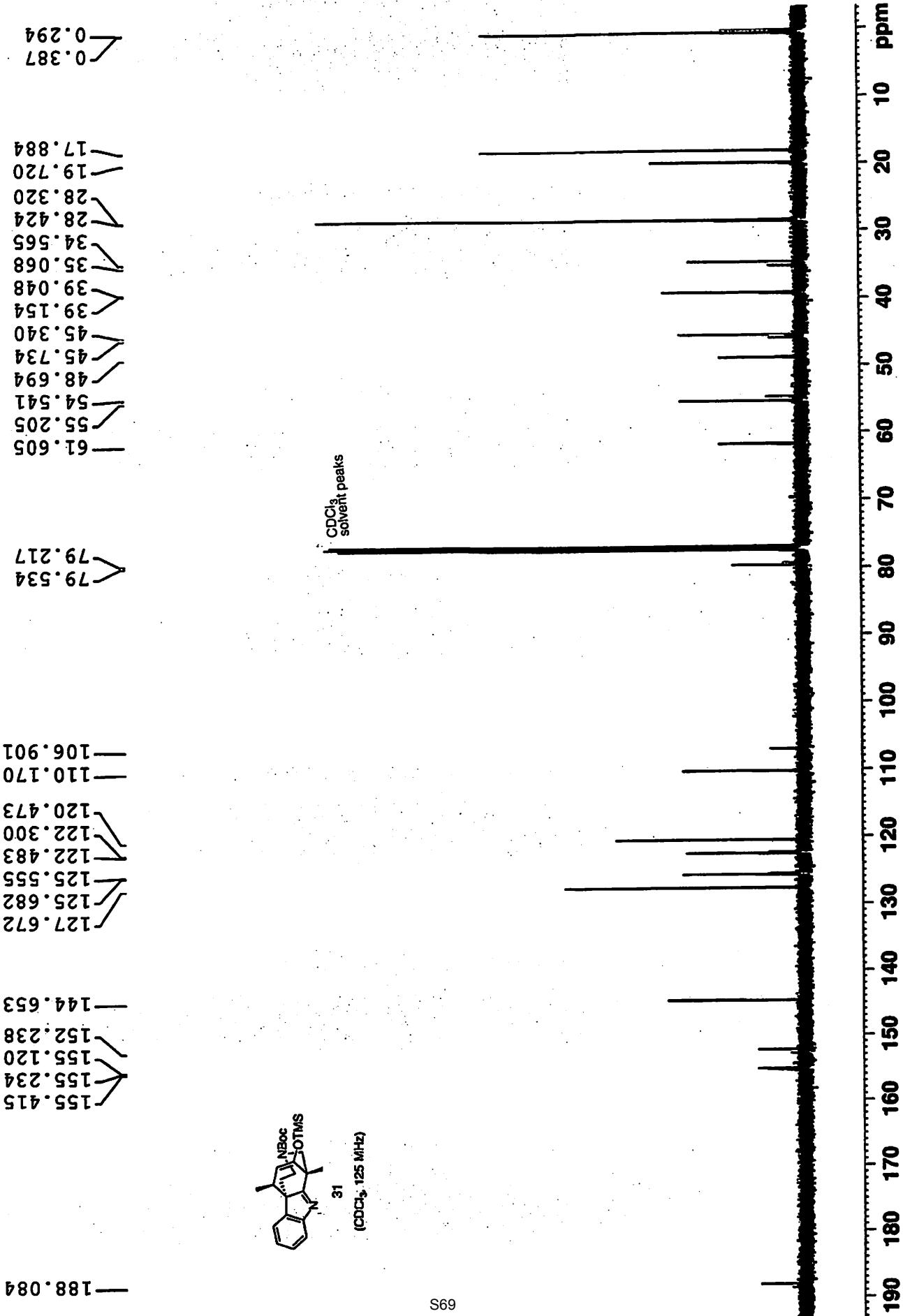


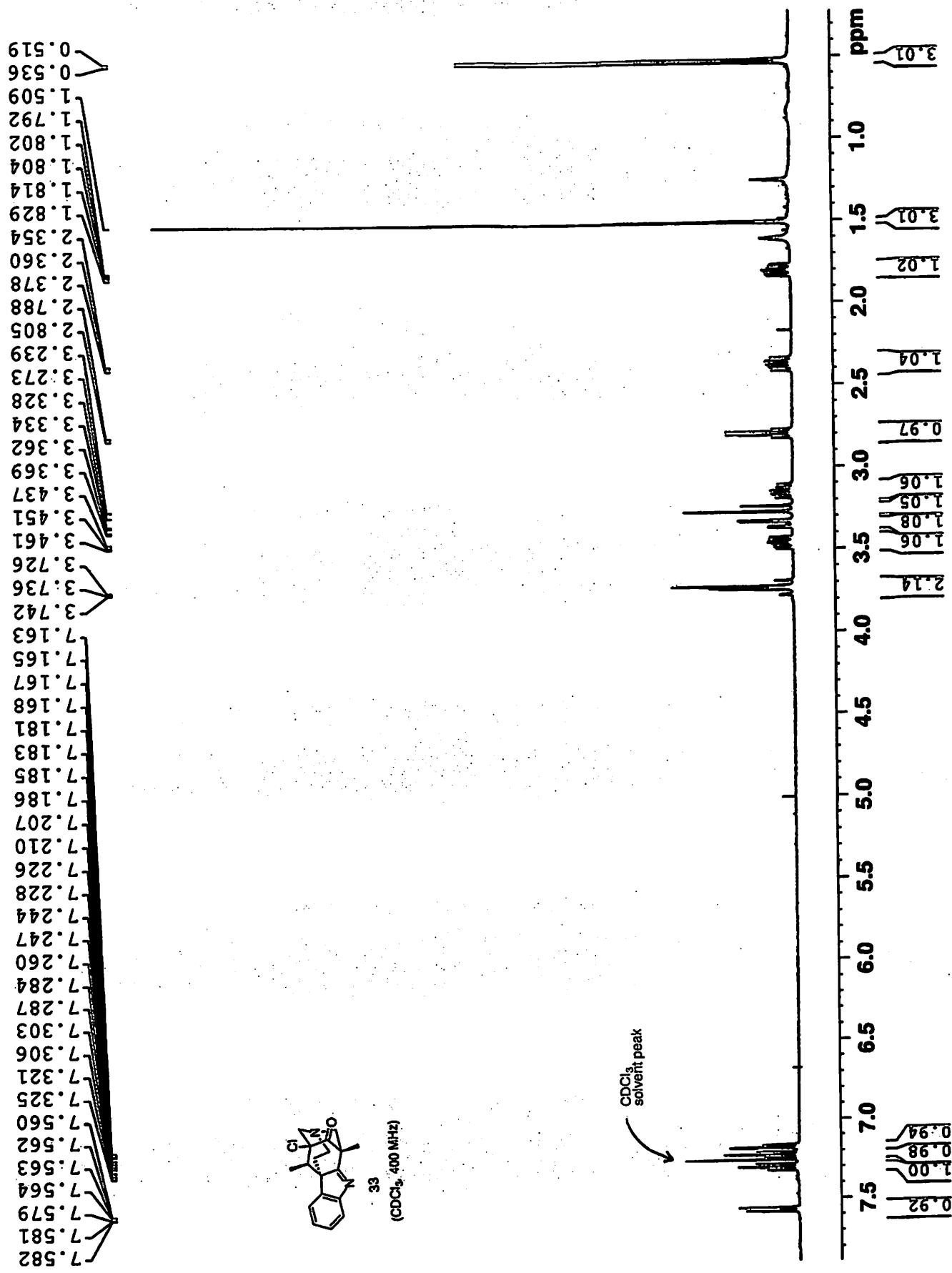


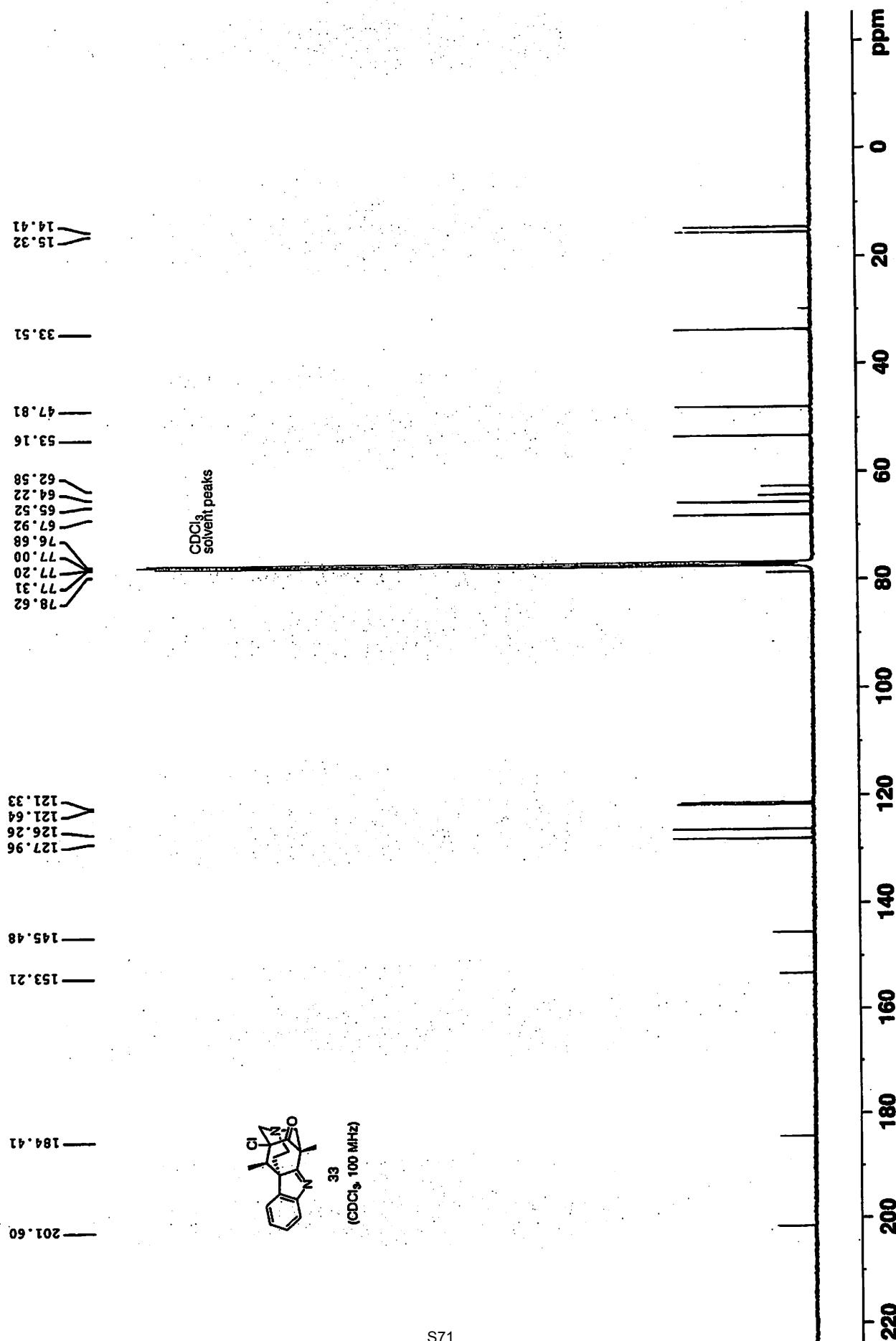


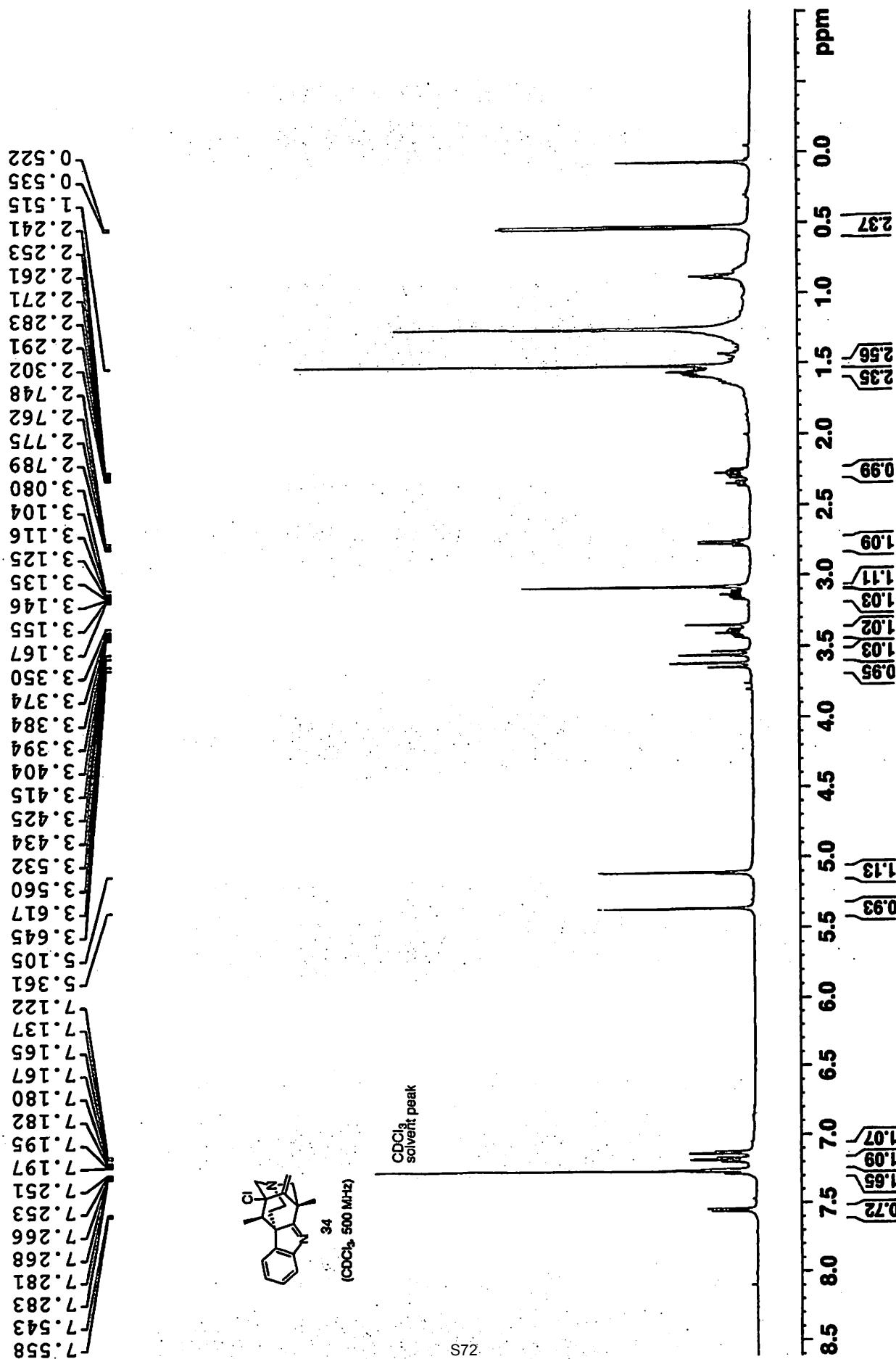


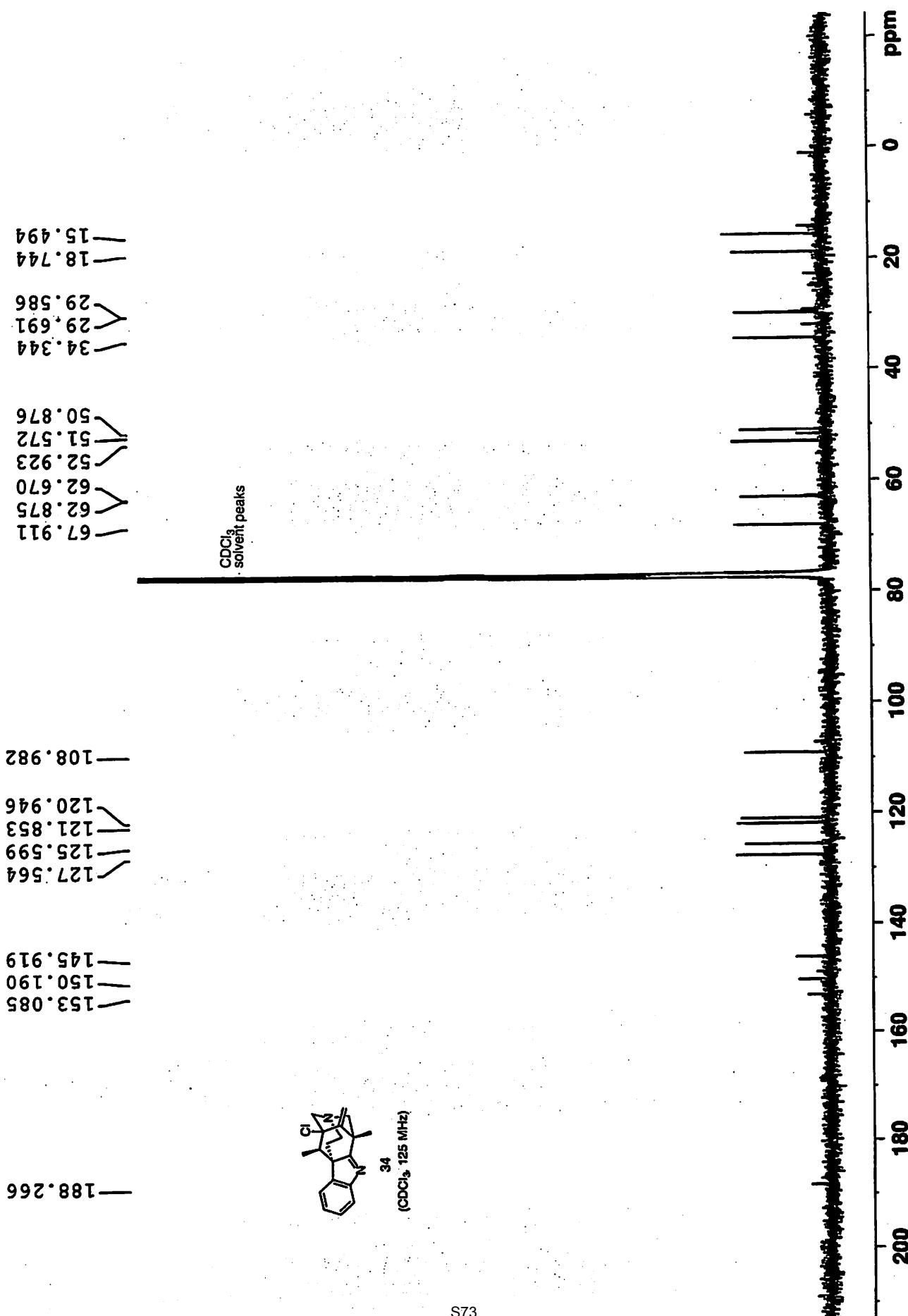


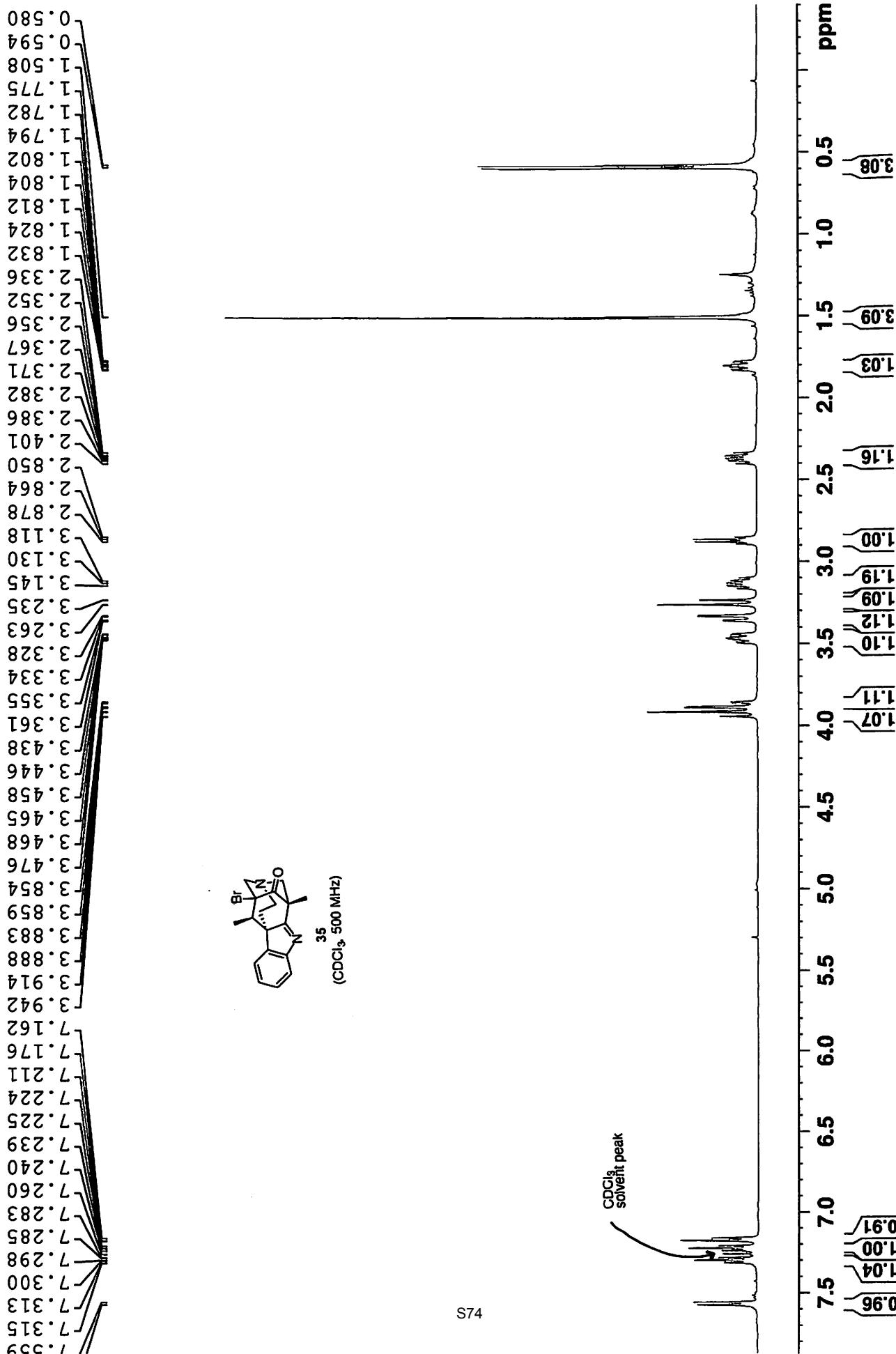


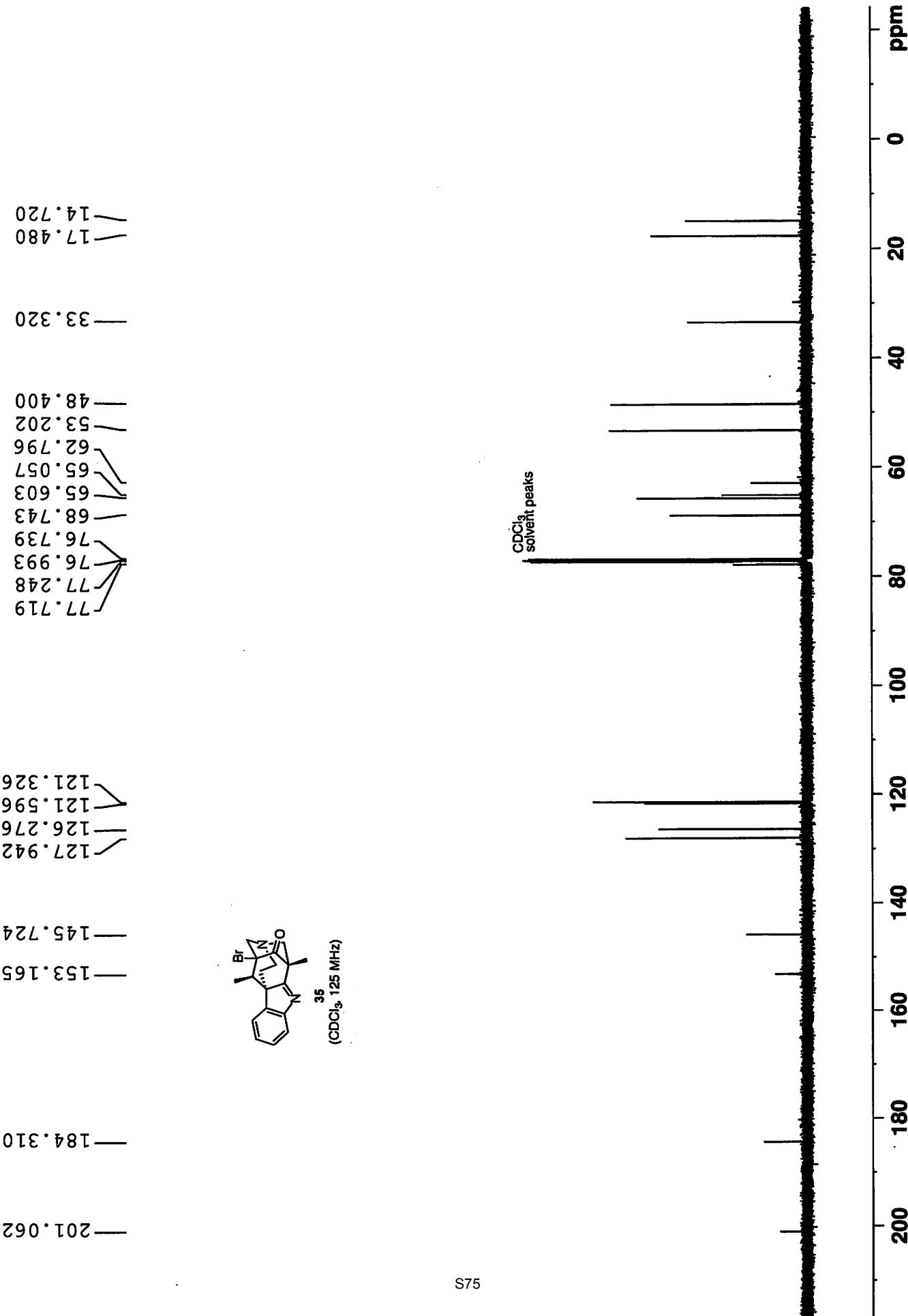


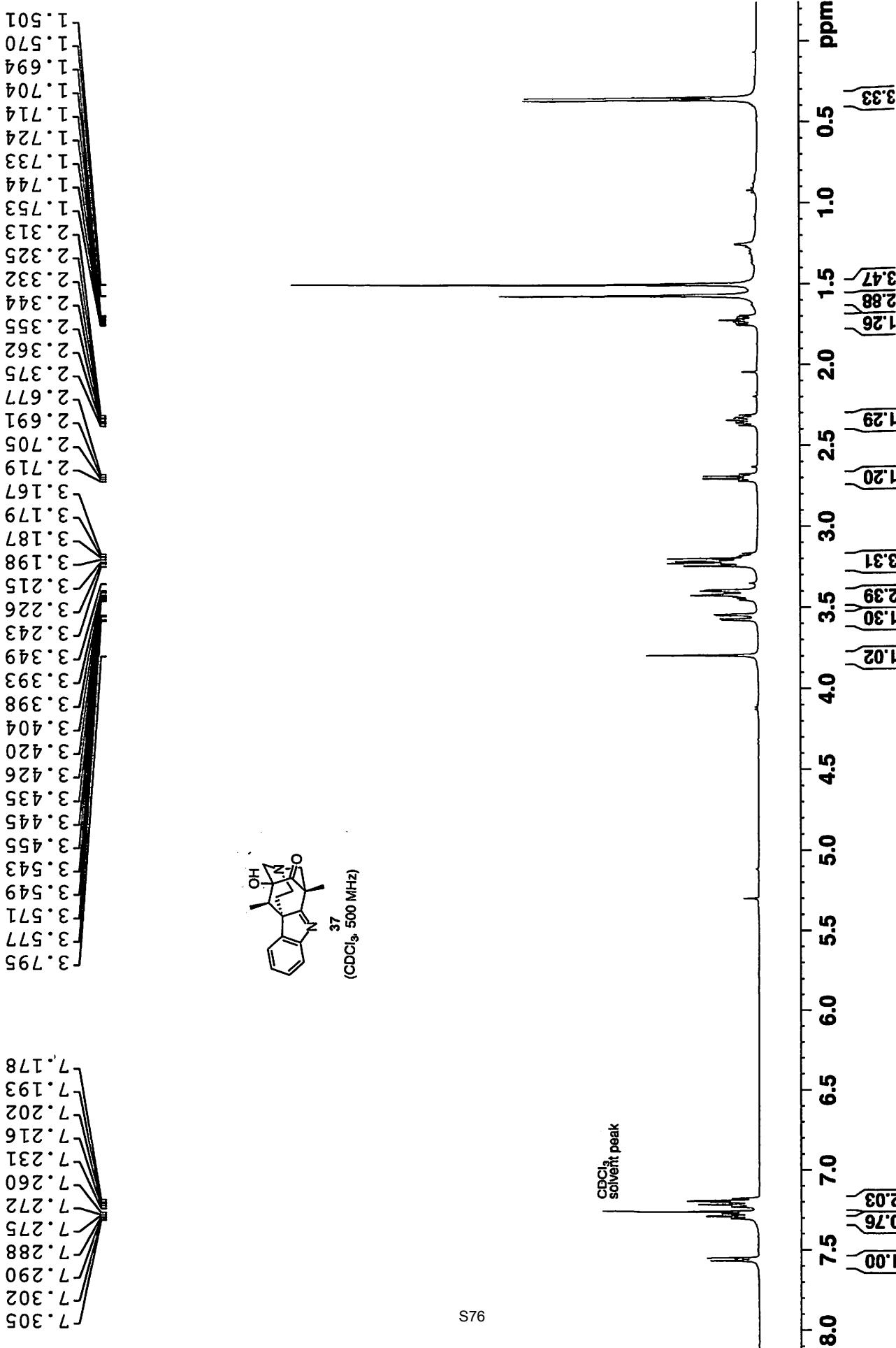


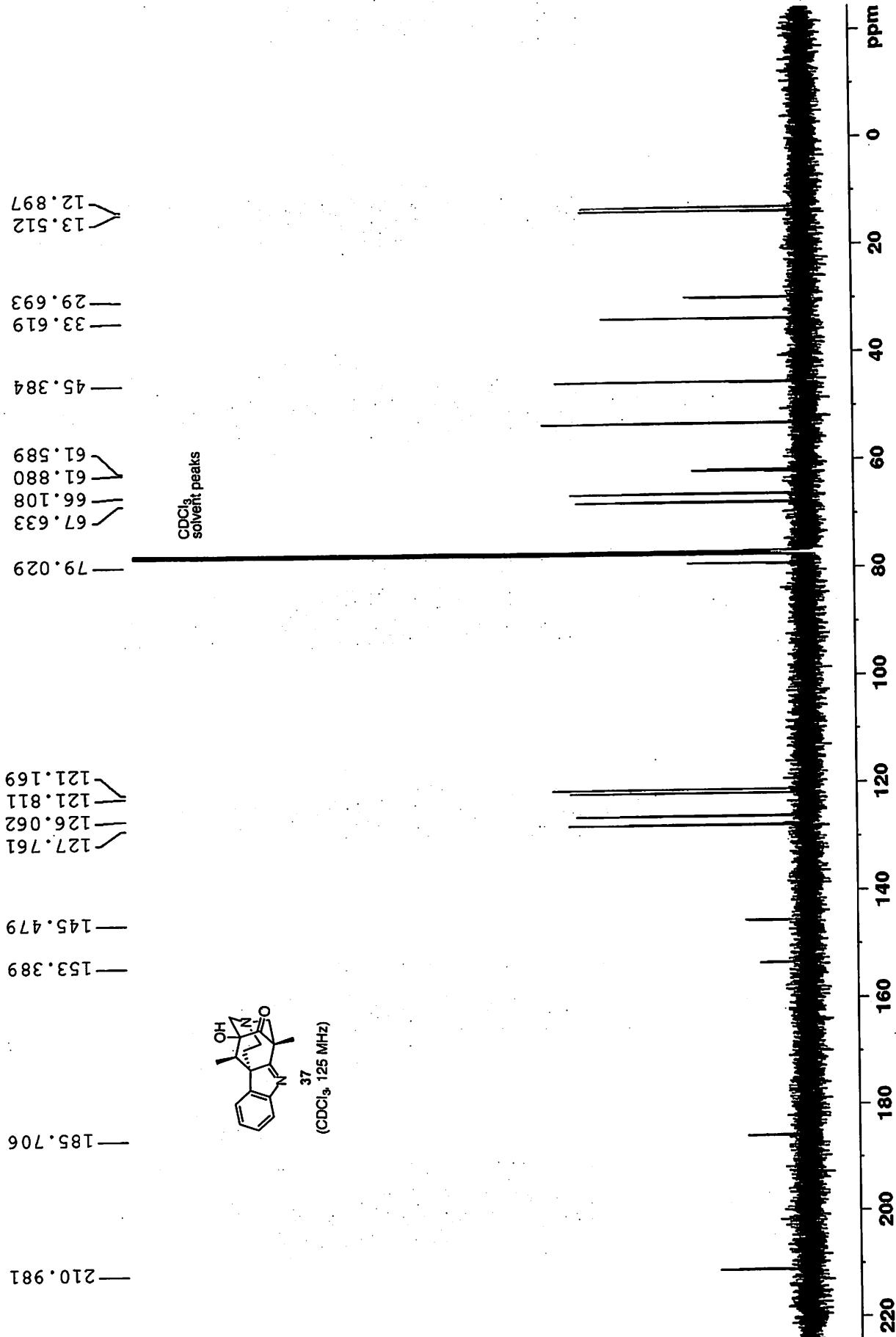


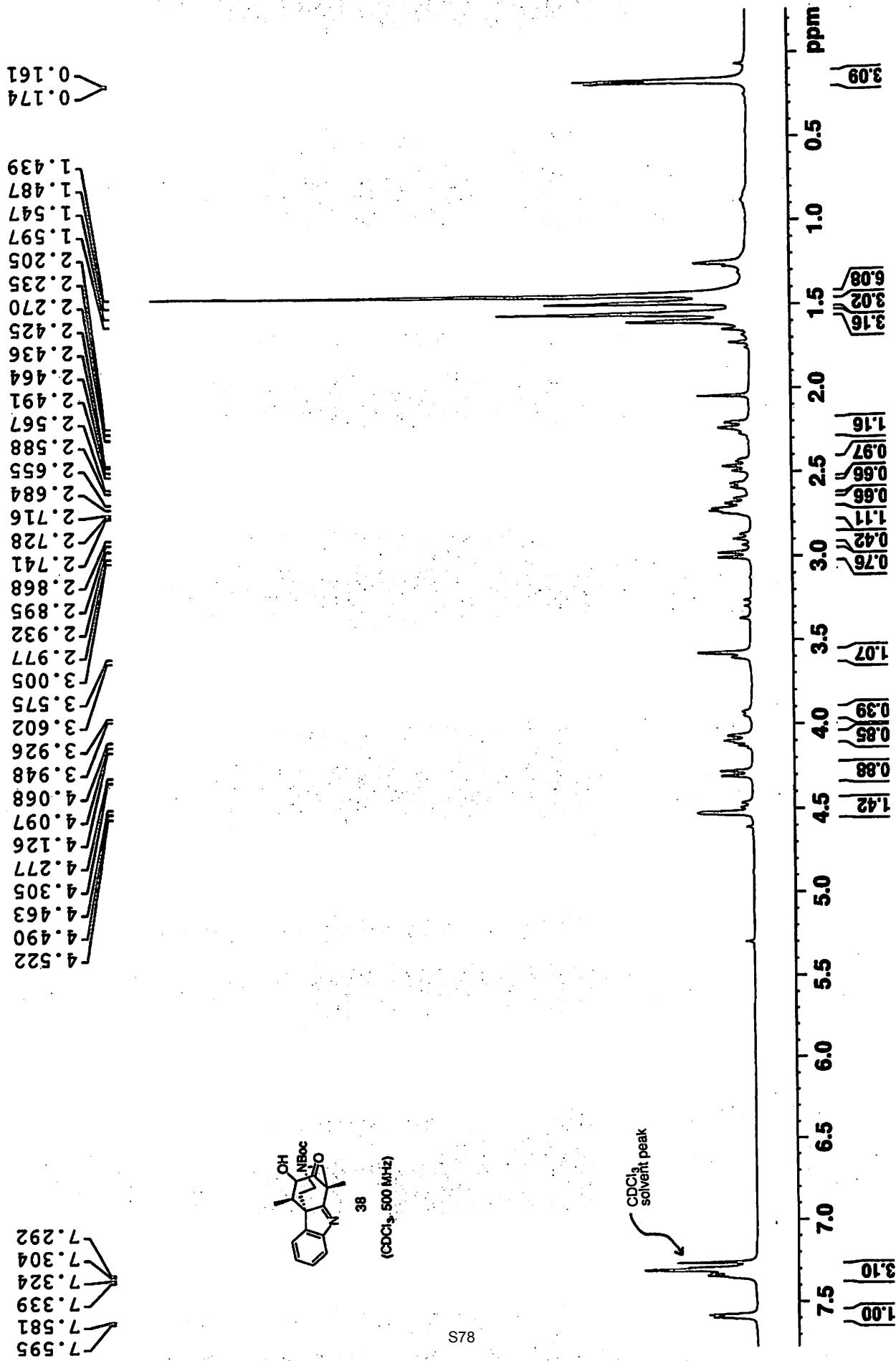


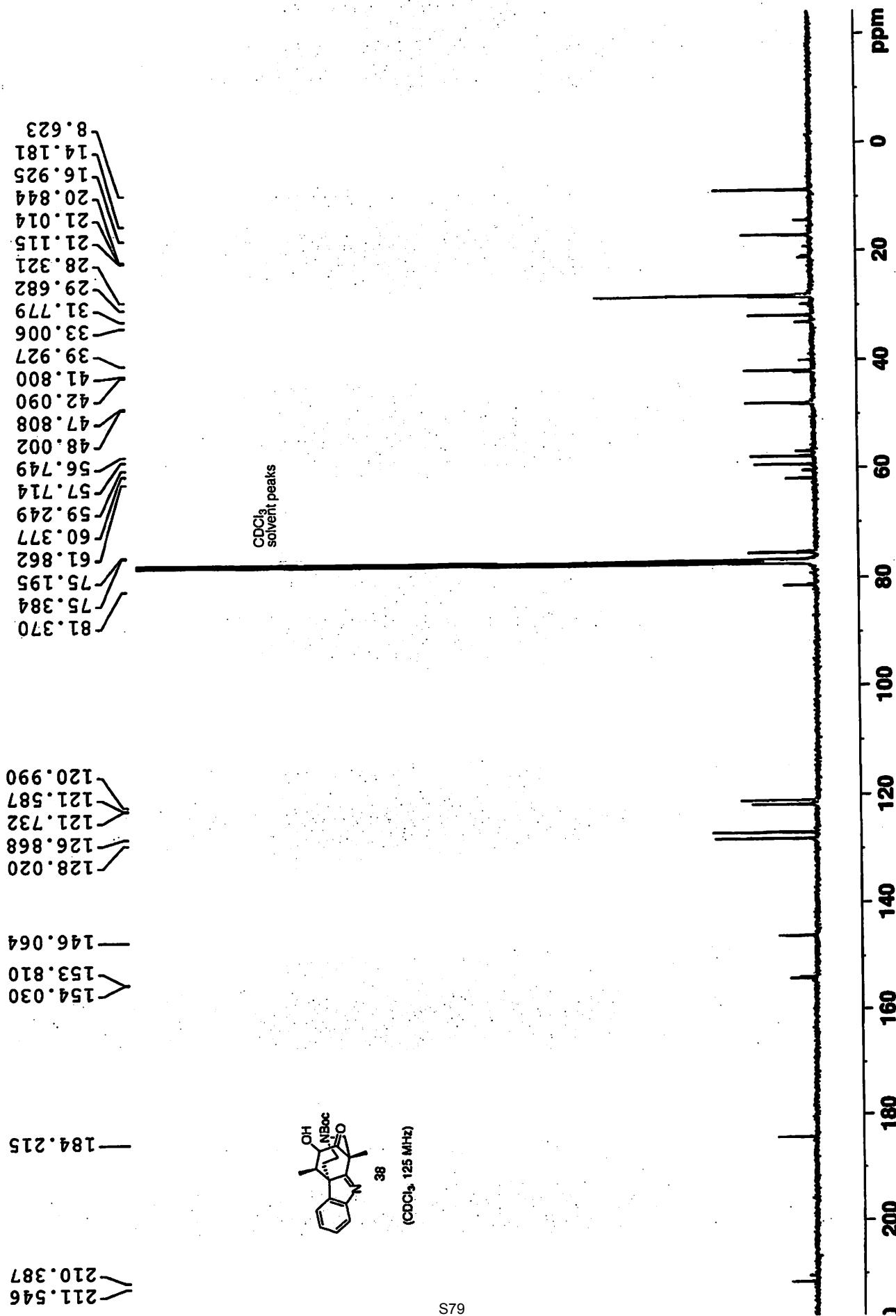


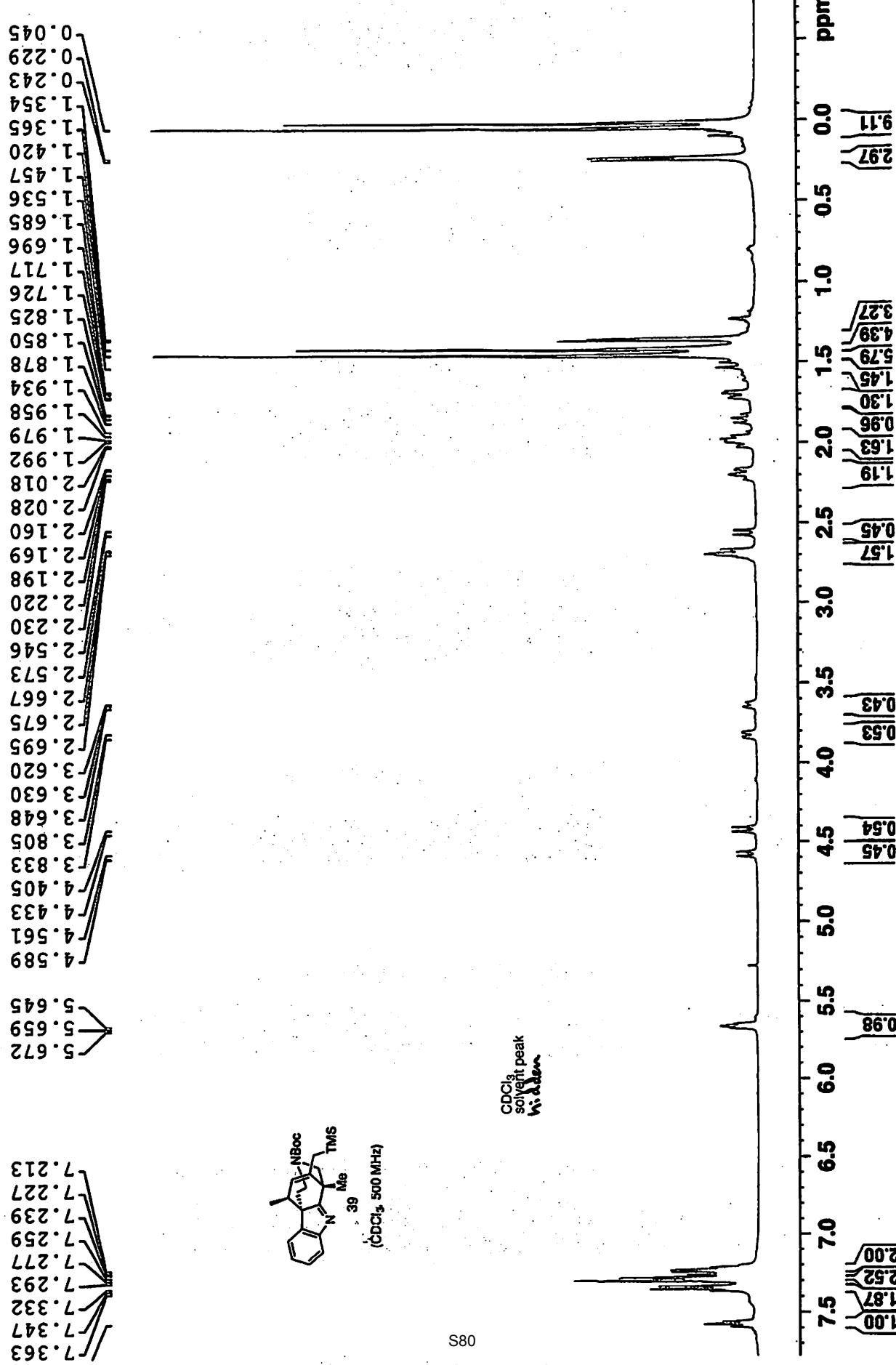


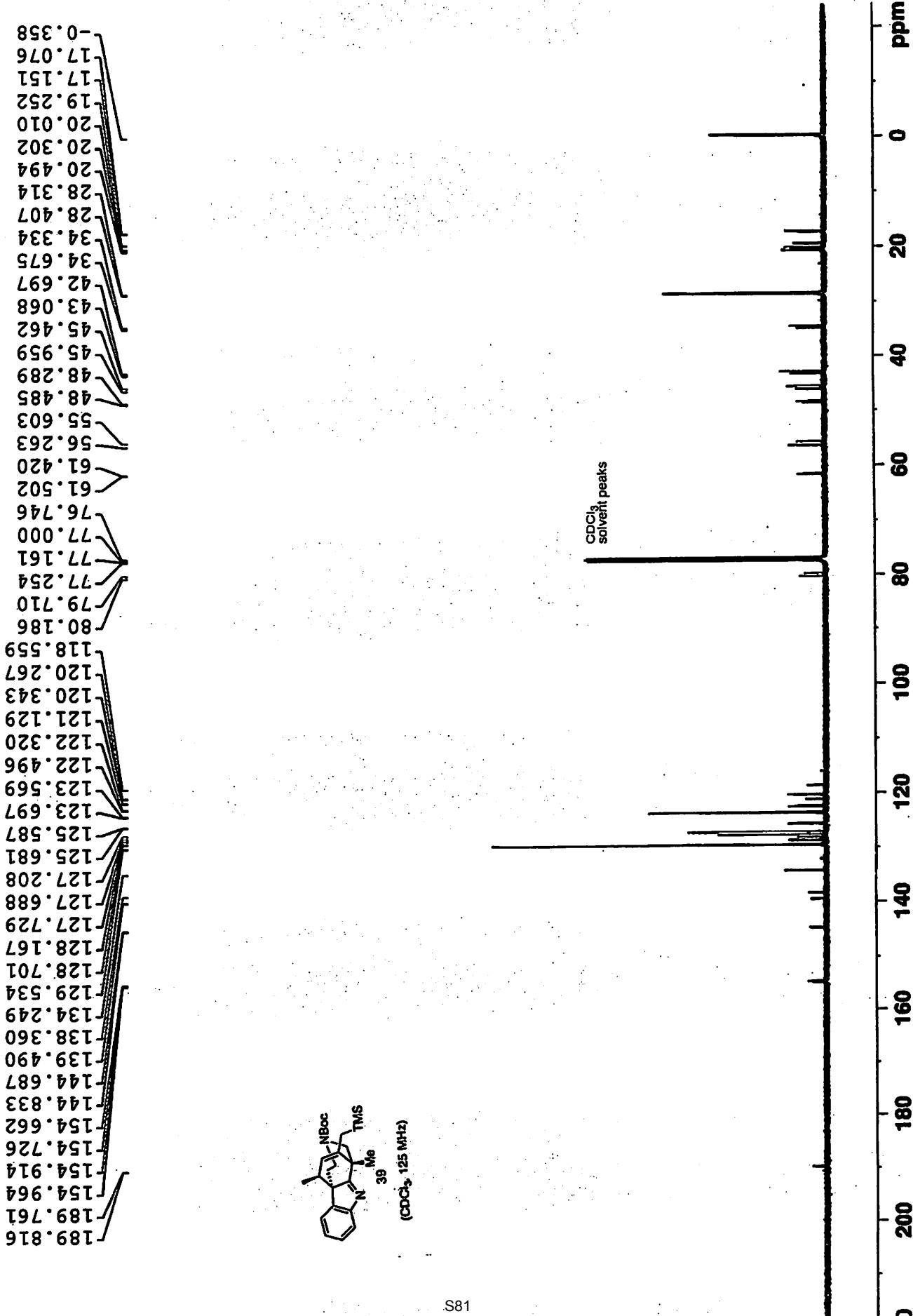


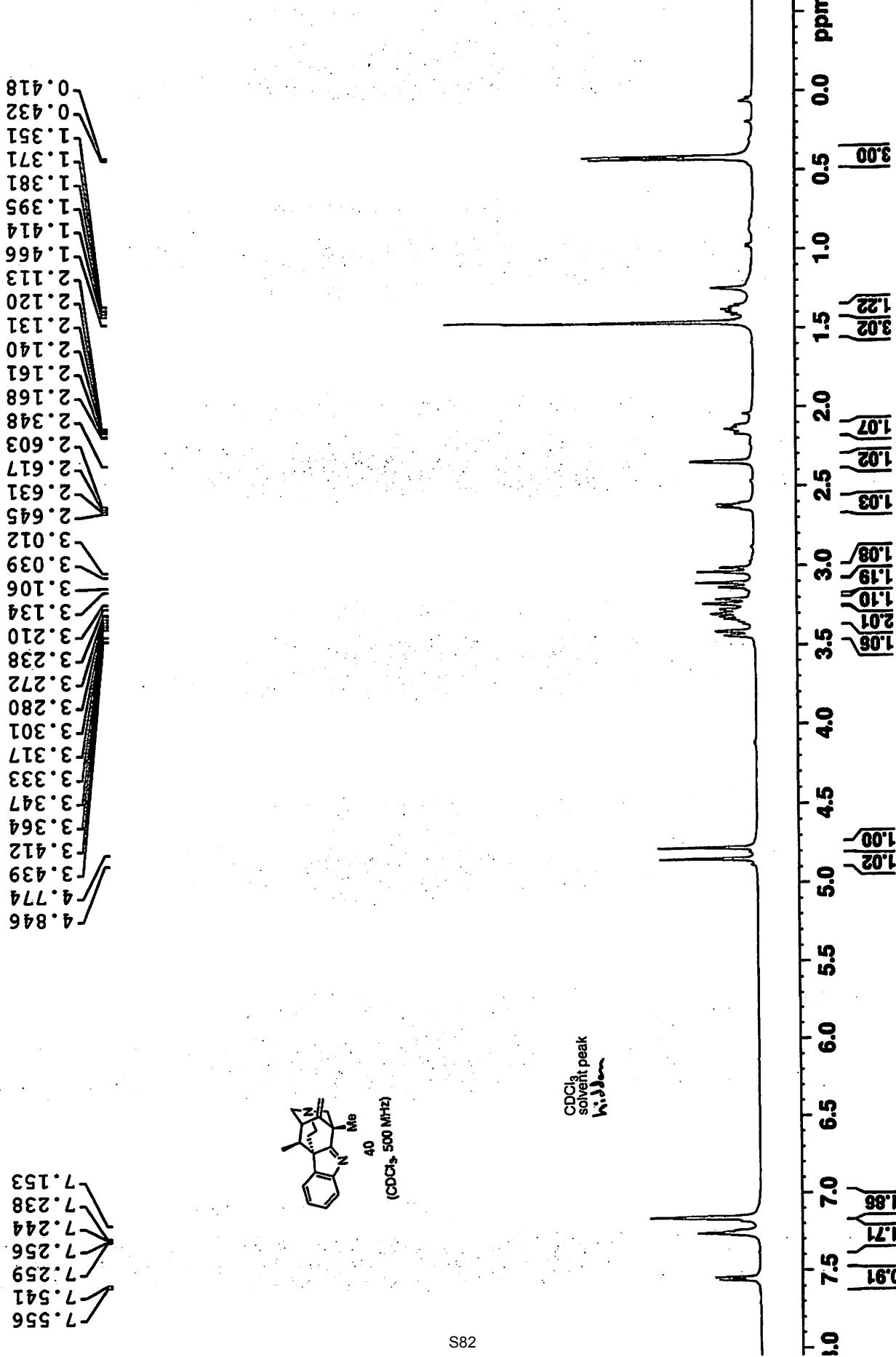


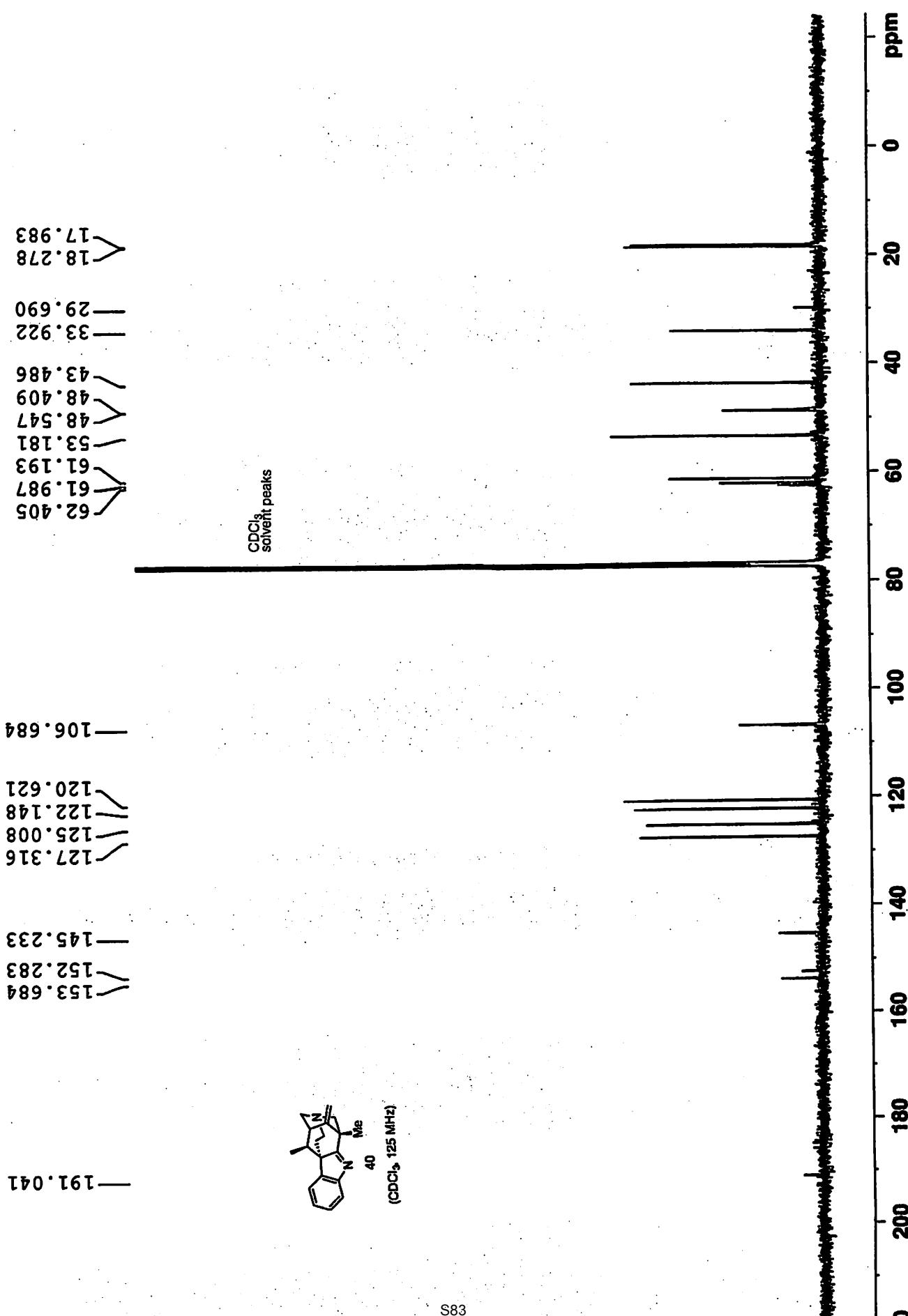




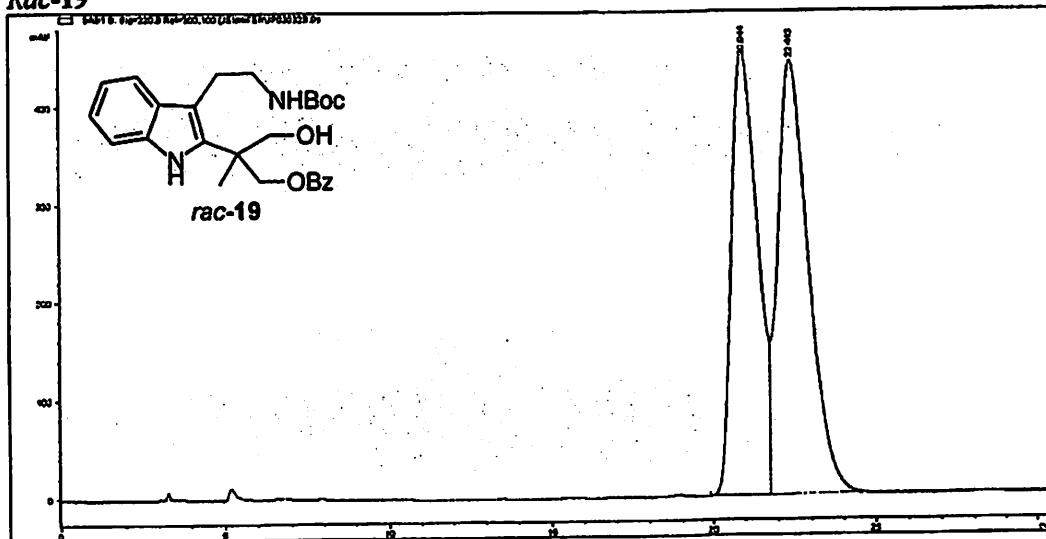








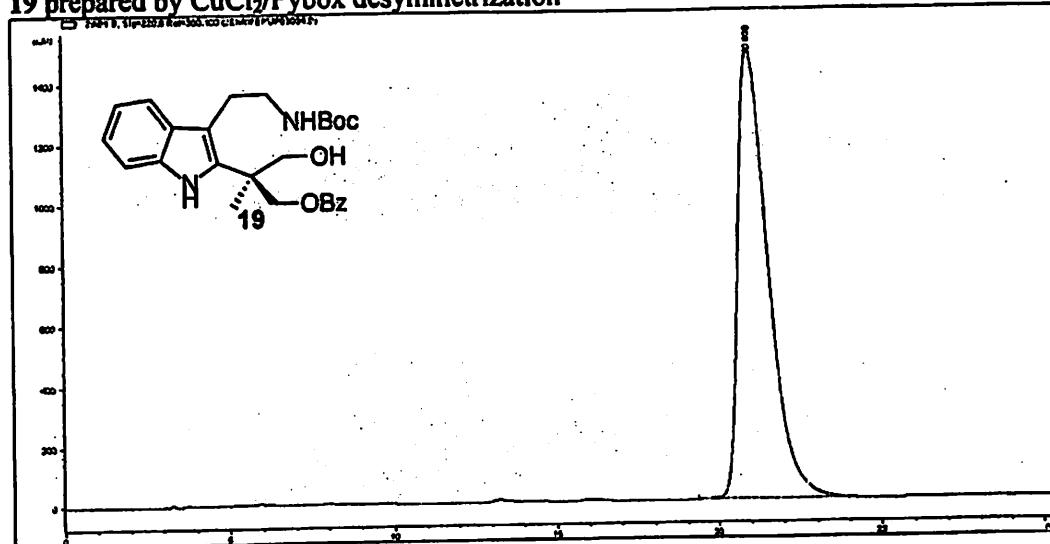
Rac-19



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.944	BV	0.0339	2.53097e4	458.57700	46.6677
2	22.415	VB	0.09624	2.89241e4	446.12915	53.3323
Totals :				5.42338e4	904.70615	

AD-H, 9:1 hexanes/i-PrOH, 1 mL/min, 220 nm.

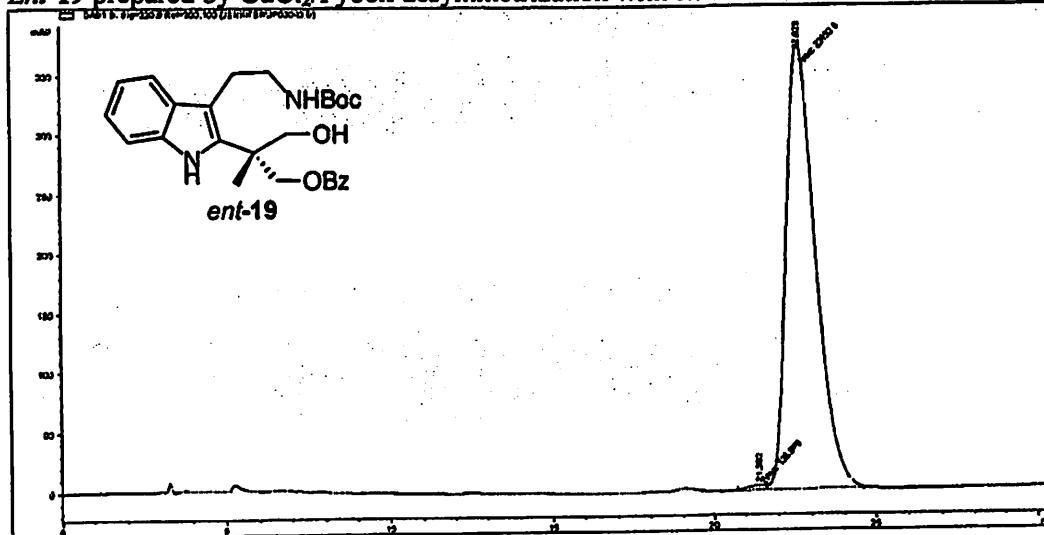
19 prepared by CuCl₂/Pybox desymmetrization



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.958	BB	0.0690	9.55816e4	1492.89136	100.0000
Totals :				9.55816e4	1492.89136	

AD-H, 9:1 hexanes/i-PrOH, 1 mL/min, 220 nm.

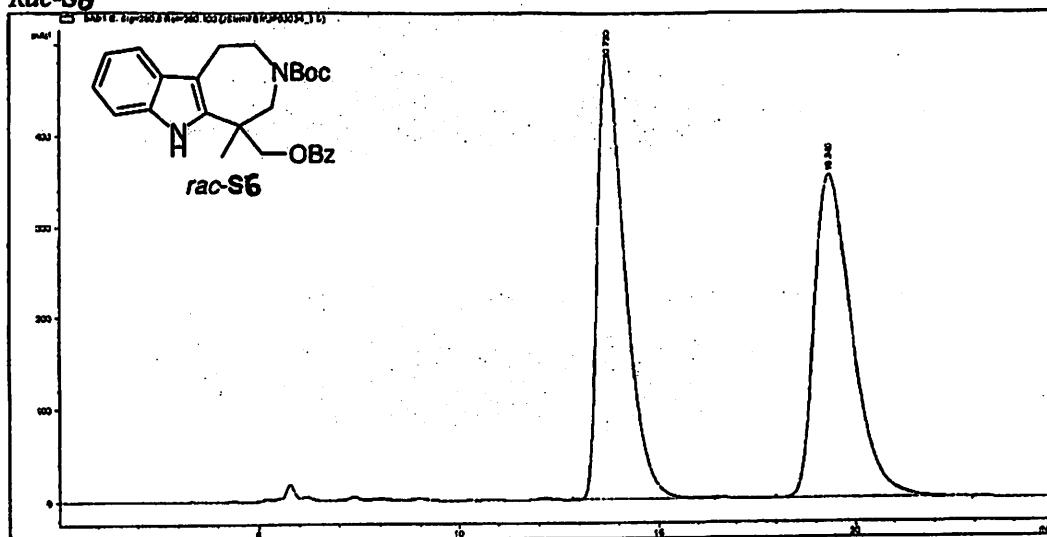
ent-19 prepared by CuCl₂/Pybox desymmetrization with *ent*-18



AD-H, 9:1 hexanes/i-PrOH,
1 mL/min, 220 nm.

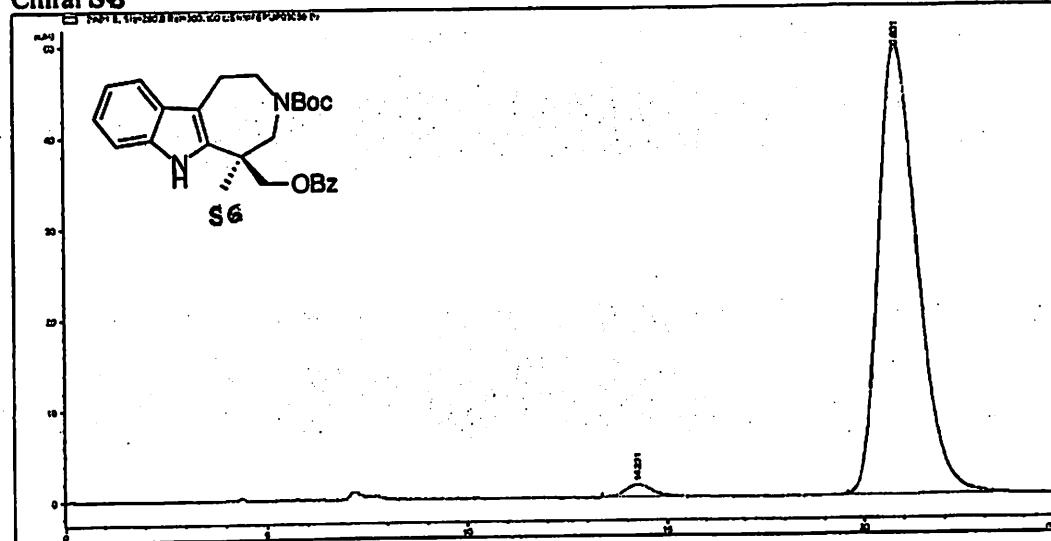
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.392	HF	0.6461	138.97646	3.58527	0.5980
2	22.628	TH	1.0236	2.31028e4	376.18427	99.4020
Totals :						379.76953

Rac-S6



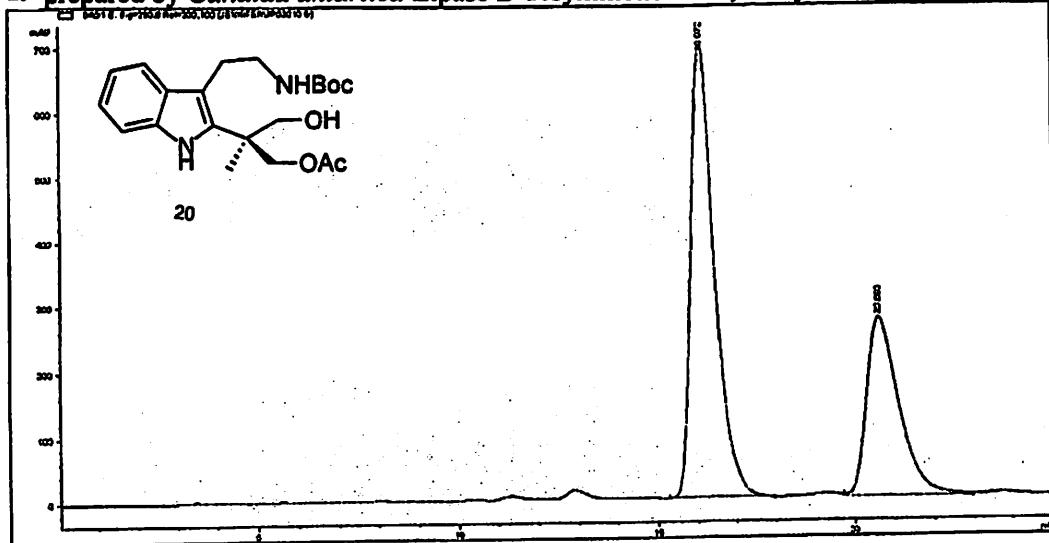
OD-H, 9:1 hexanes/i-PrOH, 1
mL/min, 280 nm.

Chiral S6

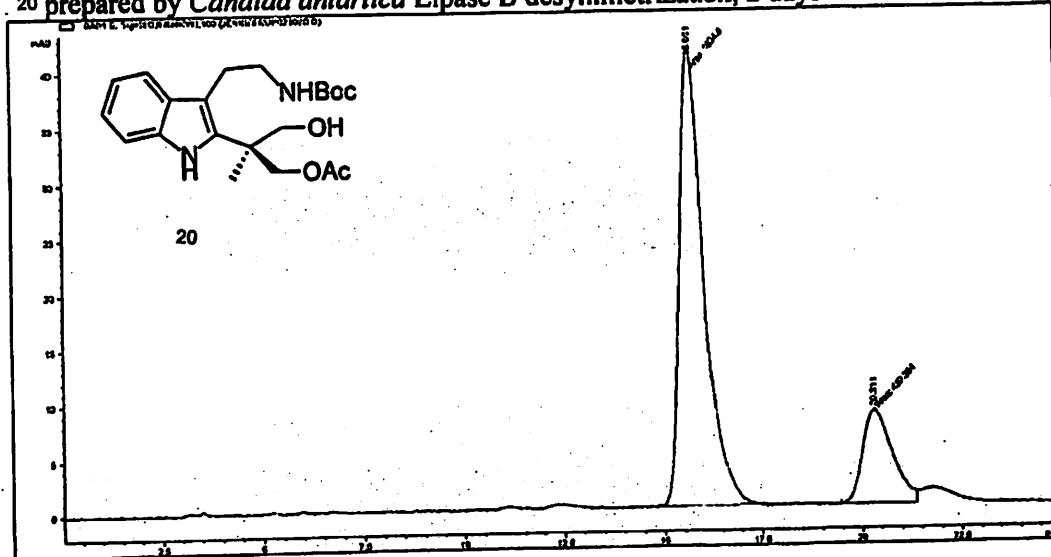


OD-H, 9:1 hexanes/i-PrOH, 1
mL/min, 280 nm.

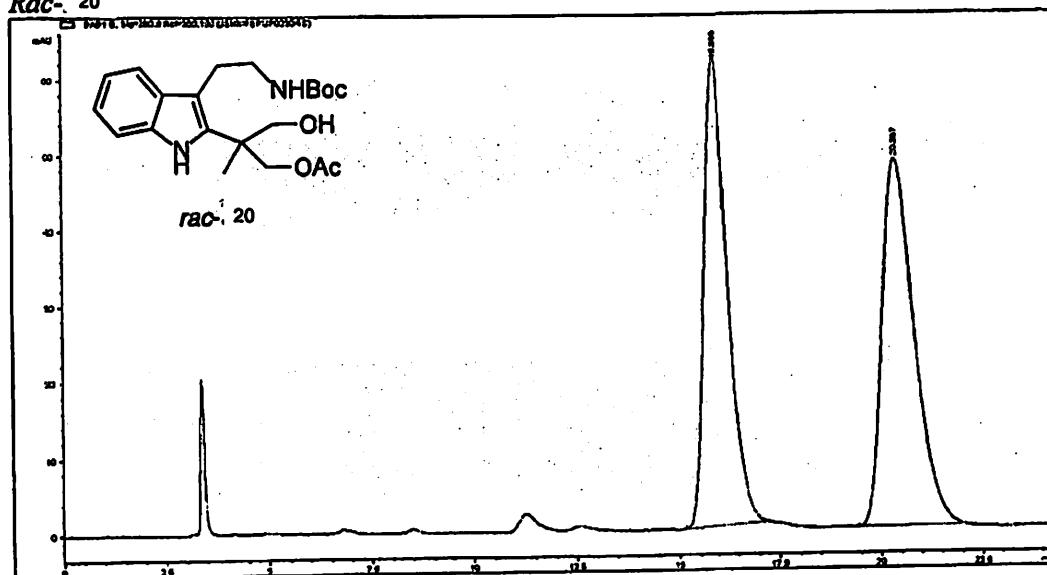
20 prepared by *Candida antartica* Lipase B desymmetrization, 9 days



20 prepared by *Candida antartica* Lipase B desymmetrization, 2 days

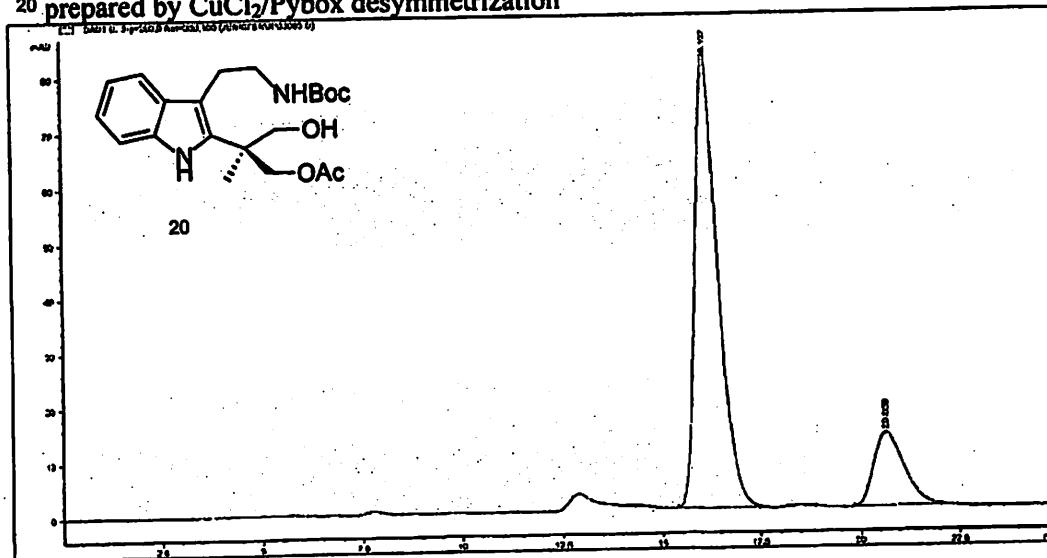


Rac- 20



AD-H, 9:1 hexanes/i-PrOH, 1 mL/min, 280 nm.

20 prepared by CuCl₂/Pybox desymmetrization



AD-H, 9:1 hexanes/i-PrOH, 1 mL/min, 280 nm.