

Total Synthesis of (±)-Cylindrospermopsin

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Supporting Material

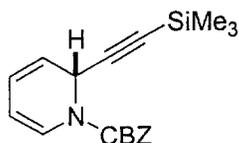
Methyl 2,6-dimethoxypyrimidine-4-carboxylate was prepared by Gershon's procedure.³⁸ A solution of orotic acid monohydrate (10.2 g, 58.6 mmol) in 80 mL of POCl₃ was refluxed at 120 °C overnight. The reaction was cooled, PCl₅ (25.5 g, 117 mmol) was added, and the solution was refluxed overnight, cooled and concentrated under reduced pressure giving crude 2,6-dichloropyrimidine-4-carbonyl chloride.

MeOH (50 mL) was added dropwise to the above residue at 0 °C over 2 h. The mixture was stirred at rt for 10 h and concentrated under reduced pressure. Flash chromatography of the residue on silica gel (3:1 hexane/EtOAc, then EtOAc) produced 1.87 g (18%) of 2,6-dimethoxypyrimidine-4-carboxylic acid preceded by 6.48 g (57%) of the desired ester as a white crystalline solid: mp 106.8-109.5 °C (lit.³⁸ mp 108-109 °C); ¹H NMR 7.06 (s, 1), 4.07 (s, 3), 4.03 (s, 3), 3.98 (s, 3); ¹³C NMR 172.5, 165.5, 164.2, 156.5, 102.9, 54.9, 54.1, 52.7; IR (KBr) 1727, 1600, 1550, 1269, 1204.

2,6-Dimethoxypyrimidine-4-methanol. To a solution of the methyl ester (6.48 g, 32.7 mmol) in 100 mL of THF was added a solution of LiBH₄ (2 M in THF, 18.0 mL, 36.0 mmol) and 140 mL of EtOH at rt. The reaction was stirred at rt for 2 h. 1 N HCl solution (7 mL) was added dropwise until the solution became clear. The volume of the mixture was reduced to 30 mL under reduced pressure and the residue was diluted with H₂O (100 mL). The organic compounds were then extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with H₂O (70 mL) and brine (70 mL), dried (Na₂SO₄), and concentrated to provide 5.18 g (93%) of 2,6-dimethoxypyrimidine-4-methanol as a white crystalline solid: mp 104.9-106.1 °C; ¹H NMR 6.43 (s,

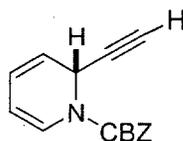
1), 4.60 (d, 2, $J = 5.6$), 3.98 (s, 3), 3.97 (s, 3), 3.96 (br s, OH); ^{13}C NMR 172.0, 171.0, 164.9, 97.1, 63.6, 54.6, 53.8; IR (KBr) 3396, 1604, 1571, 1473, 1357, 1207.

2,6-Dimethoxypyrimidine-4-carboxaldehyde (3). A solution of 2,6-dimethoxypyrimidine-4-methanol (5.18 g, 30.5 mmol) and Dess-Martin periodinane (13.6 g, 32.1 mmol) in 150 mL of CH_2Cl_2 was stirred at rt for 1 h. The mixture was washed with 10% $\text{Na}_2\text{S}_2\text{O}_3$ solution (60 mL) and saturated NaHCO_3 solution (40 mL), and the combined aqueous layer was extracted with CH_2Cl_2 (60 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried (Na_2SO_4) and concentrated. The residue was purified on silica gel (5:1 hexane/EtOAc) to give 4.62 g (90%) of **3** as a white crystalline solid: mp 105.0-106.2 °C (lit.³⁹ mp 107 °C); ^1H NMR 9.89 (s, 1), 6.90 (s, 1), 4.09 (s, 3), 4.04 (s, 3); ^{13}C NMR 192.1, 172.8, 166.3, 160.2, 99.5, 55.2, 54.5; IR (KBr) 1716, 1607, 1564, 1467, 1259, 1208. Anal. Calcd for $\text{C}_7\text{H}_8\text{N}_2\text{O}_3$: C, 50.00; H, 4.79; N, 16.65. Found: C, 50.26; H, 4.79; N, 16.38%.

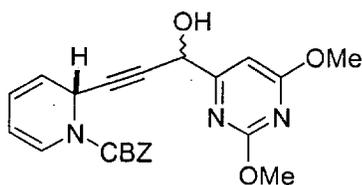


Phenylmethyl 2-Trimethylsilylethynyl-1(2H)-pyridinecarboxylate was prepared by a modification of the literature procedure using benzyl rather than methyl chloroformate.³⁷ A solution of trimethylsilylethynylmagnesium bromide in THF (30 mL) was prepared from ethynyltrimethylsilane (2.23 mL, 15.5 mmol) and EtMgBr (3 M in diethyl ether, 5.05 mL, 15.5 mmol) at 0 °C under nitrogen. To the above solution was added a solution of pyridine (1.00 mL, 12.2 mmol) in THF (20 mL), followed by the very slow addition of a solution of benzyl chloroformate (1.44 mL, 10.1 mmol) in THF (20 mL) over 1.5 h. The mixture was stirred at 0 °C for an additional 2 h and poured into a saturated NH_4Cl solution (100 mL), which was extracted with EtOAc (3×60 mL). The combined organic layers were washed with water (70 mL) and brine (70 mL), dried (Na_2SO_4), and concentrated. Flash chromatography of the residue on silica gel (15:1 hexane/EtOAc) gave 3.72 g (95%) of product as a 1:1 mixture of carbamate rotamers: ^1H NMR 7.43-7.30 (m, 5), 6.81 (d, 0.5×1 , $J = 7.5$), 6.72 (d, 0.5×1 , $J = 7.5$), 5.95 (dd, 1, $J = 7.5$,

5.7), 5.64-5.50 (m, 2), 5.38-5.19 (m, 3), 0.15 (s, 9); ^{13}C NMR (153.4, 152.7), (135.7, 135.6), (128.4, 128.2, 128.1, 128.0, 127.6, benzyl CH), (125.1, 124.4), (122.1, 121.8), (118.9, 118.2), (105.4, 105.0), (102.6, 102.2), (87.6, 87.6), (68.0, 67.8), (44.5, 43.9), (0.0, 0.0); IR (neat) 3340, 2169, 1719, 1391, 1250.

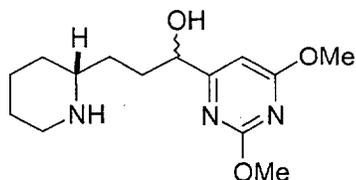


Phenylmethyl 2-ethynyl-1(2H)-pyridinecarboxylate. A solution of ethynylsilane (3.72 g, 12.0 mmol) and K_2CO_3 (2.00 g, 14.4 mmol) in MeOH (120 mL) was stirred vigorously at rt for 20 min and poured into a saturated NH_4Cl solution, which was extracted with EtOAc (3×50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure to provide 2.77 g (97%) of product as a pale yellow oil as a 6:4 mixture of carbamate rotamers: ^1H NMR 7.43-7.30 (m, 5), 6.84 (d, 0.4×1 , $J = 7.6$), 6.73 (d, 0.6×1 , $J = 8.0$), 5.98 (dd, 1, $J = 8.4$, 5.3), 5.68-5.51 (m, 2), 5.39 (dd, 0.4×1 , $J = 6.6$), 5.31 (dd, 0.6×1 , $J = 6.4$), 5.28-5.19 (m, 2), 2.35 (s, 1); ^{13}C NMR (153.2, 152.7), (135.4, 135.4), (128.4, 128.2, 128.1, 127.8, benzyl CH), (125.1, 124.4), (122.6, 122.2), (118.3, 117.8), (105.2, 105.2), (81.2, 81.0), (71.4, 71.4), (68.1, 68.0), (43.5, 43.1); IR (neat) 3285, 2112, 1713, 1392, 1326, 1301, 1254.



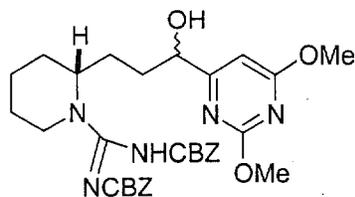
Phenylmethyl 2-[3-Hydroxy-3-[4,6-dimethoxy-2-pyrimidinyl]-1-propynyl]-1(2H)-pyridinecarboxylate (4). To a solution of alkyne (1.30 g, 5.44 mmol) in THF (50 mL) was added slowly an EtMgBr solution (1 M in THF, 5.90 mL, 5.90 mmol) at 0 °C under nitrogen over 1 h. The reaction solution was stirred at 0 °C for 30 min and a solution of **3** (762 mg, 4.54 mmol) in THF (20 mL) was then added dropwise to the above mixture. The reaction was stirred at 0 °C for 2 h and poured into a saturated NH_4Cl solution (70 mL), which was extracted with EtOAc (3×50

mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated. Flash chromatography of the residue on silica gel (5:1 hexane/EtOAc, then 3:1 hexane/EtOAc) provided 354 mg (27%) of recovered alkyne, followed by 1.15 g (62%) of **4** as a colorless oil which is a 6:4 mixture of carbamate rotamers: ^1H NMR 7.41-7.29 (m, 5), 6.82 (d, 0.4×1 , $J = 7.6$), 6.72 (d, 0.6×1 , $J = 7.6$), 6.55 (s, 0.6×1), 6.47 (br s, 0.4×1), 5.97 (dd, 1, $J = 9.2$, 5.5), 5.73-5.48 (m, 2), 5.37 (br dd, 0.4×1 , $J = 7.1$, 7.1), 5.29 (br dd, 0.6×1 , $J = 7.1$, 7.1), 5.28-5.20 (m, 2), 4.00 (s, 3), 3.98 (s, 3), 3.92 (br s, OH); ^{13}C NMR (172.3, 172.3), (168.3, 168.3), (164.9, 164.9), (153.3, 152.8), (135.6, 135.6), (128.5, 128.5), (128.2, 128.2), (127.9, 127.9), (125.2, 124.5), (122.7, 122.4), (118.3, 117.7), (105.4, 105.4), (98.2, 98.2), (83.6, 83.6), (80.9, 80.9), (68.2, 68.2), (63.1, 63.1), (54.9, 54.9), (54.1, 54.1), (43.9, 43.5); IR (neat) 3420, 3283, 1715, 1595, 1572, 1357.

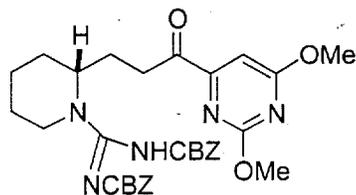


6-[1-Hydroxy-3-[2-piperidinyl]propyl]-2,4-dimethoxypyrimidine. A solution of **4** and 10% Pd/C (138 mg) in MeOH/THF (10:1, 50 mL) was stirred at rt under a hydrogen-filled balloon overnight. The solution was filtered and concentrated under reduced pressure to provide 743 mg (94%) of crude piperidine which was analyzed by ^1H and ^{13}C NMR spectroscopy in CD_3OD at pH 7. Flash chromatography on silica gel (20:20:1 EtOAc/MeOH/ Et_3N) gave 720 mg (92%) of piperidine as a colorless oil which was analyzed by NMR as a basic solution (pH 9) in CD_3OD : ^1H NMR (CD_3OD) (pH 7) 6.59 (s, 1), 4.50 (dd, 1, $J = 6.6$, 3.8), 3.96 (br s, 6), 3.33 (br d, 1, $J = 12.5$), 3.09 (m, 1), 2.95 (br dd, 1, $J = 12.5$, 12.5), 2.01-1.32 (m, 10); (pH 9) 6.58 (s, 1), 4.47 (dd, 1, $J = 7.6$, 4.0), 3.98 (s, 3), 3.97 (s, 3), 3.02 (br d, 1, $J = 11.8$), 2.60 (ddd, 1, $J = 11.8$, 11.8, 2.7), 2.49 (dddd, 1, $J = 12.8$, 6.4, 6.4, 3.8), 1.90 (dddd, 1, $J = 13.4$, 7.9, 7.9, 4.0), 1.80-1.36 (m, 8), 1.19-1.03 (m, 1); ^{13}C NMR (CD_3OD) (pH 7) (176.6, 176.6), (174.0, 174.0), (166.6, 166.6), (98.1, 98.1), (73.4, 73.4), (58.2, 58.2), (55.5, 55.5), (54.8, 54.8), (46.1, 46.1), (33.35, 33.30), (30.84, 30.76),

(29.85, 29.63), (23.43, 23.43), (23.27, 23.27); (pH 9) (177.4, 177.4), (174.5, 174.5), (166.6, 166.6), (98.12, 98.04), (74.26, 74.17), (57.98, 57.91), (55.4, 55.4), (54.7, 54.7), (47.60, 47.54), (34.7, 34.4), (33.67, 33.58), (33.3, 32.9), (26.7, 26.7), (25.65, 25.61); IR (neat) 3362, 1596, 1569, 1354.

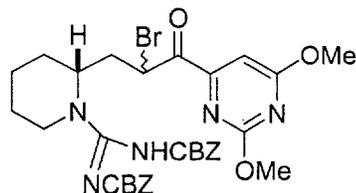


6-[1-Hydroxy-3-[2-N-[[[(phenylmethoxy)carbonyl]amino]][(phenylmethoxy) carbonylimino]methyl]piperidinyl]propyl]-2,4-dimethoxypyrimidine (2.128). To a solution of piperidine (743 mg, 2.64 mmol) in DMF (20 mL) was added *N,N'*-bis(benzyloxycarbonyl)-*S*-methylisothiourea⁵³⁻⁵⁴ (966 mg, 2.78 mmol), Et₃N (1.10 mL, 7.93 mmol) and HgCl₂ (788 mg, 2.91 mmol) sequentially. The mixture was stirred at rt for 2 h, diluted with EtOAc (50 mL), and filtered through celite. The filtrate was washed with H₂O (50 mL), and the aqueous layer was extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried (Na₂SO₄) and concentrated. The residue was purified on silica gel (1:1 hexane/EtOAc) to give 1.14 g (74%) of protected guanidine as a 1:1 mixture of diastereomers and a mixture of carbamate rotamers: ¹H NMR 10.5 (br s, NH), 7.45-7.23 (m, 10), 6.46 (br, 0.5 × 1), 6.41 (br s, 0.5 × 1), 5.24-5.06 (m, 4), 4.64 (br, 1), 4.46 (br, 1), 3.96 (br s, 6), 3.50 (br, 1), 3.18 (br, 1), 2.06-1.50 (m, 10); ¹³C NMR 172.1, 164.8, 163.2, 155.8, 151.8, 136.6, 135.1, 128.8, 128.6, 128.5, 128.3, 128.1, 127.8, 97.3, 72.2, 68.2, 68.0, 67.2, 54.7, 53.9, 52.4, 44.3, 32.7, 28.3, 25.6, 18.5; IR (neat) 3435, 1795, 1753, 1596, 1354.



6-[1-Oxo-3-[2-N-[[[(phenylmethoxy)carbonyl]amino]][(phenylmethoxy) carbonylimino]methyl]piperidinyl]propyl]-2,4-dimethoxypyrimidine (5). To a solution of protected

guanidine (207 mg, 0.356 mmol) in CH₂Cl₂ (30 mL) was added Dess-Martin periodinane (156 mg, 0.374 mmol). The reaction was stirred at rt for 30 min and washed with 10% Na₂S₂O₃ solution (25 mL) and saturated NaHCO₃ solution (25 mL). The aqueous layer was extracted with CH₂Cl₂ (2 × 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried (Na₂SO₄), and concentrated. The residue was purified on silica gel (3:1 hexane/EtOAc) to provide 149 mg (72%) of **5** as a mixture of carbamate rotamers: ¹H NMR 10.5 (br s, NH), 7.38-7.23 (m, 10), 6.92 (s, 1), 5.18-4.99 (m, 4), 3.98 (s, 3), 3.92 (s, 3), 3.50 (br, 1), 3.20 (br, 2), 3.25 (dddd, 1, *J* = 13.0, 8.8, 8.4, 5.5), 1.94-1.50 (m, 8); ¹³C NMR 200.1, 172.9, 165.5, 163.3, 161.1, 155.9, 151.7, 136.6, 135.2, 128.6-127.6 (benzyl CH), 99.3, 67.8, 67.2, 54.9, 54.3, 52.0, 44.1, 34.5, 28.5, 25.8, 23.7, 18.6; IR (neat) 1752, 1707, 1634, 1594, 1567, 1350.



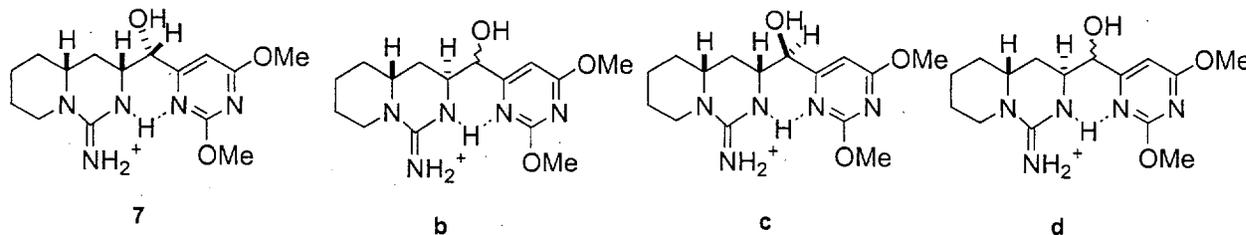
6-[2-Bromo-1-oxo-3-[2-*N*-[[[(phenylmethoxy)carbonyl]amino]

[(phenylmethoxy)carbonyl-imino]methyl]piperidinyl]propyl]-2,4-dimethoxypyrimidine (6).

A suspension of CuBr₂⁴⁰ (114 mg, 0.515 mmol) in EtOAc (30 mL) was stirred vigorously at 40 °C under nitrogen for 20 min. A solution of **5** (149 mg, 0.257 mmol) in EtOAc (10 mL) was then added by syringe. The mixture was stirred at 40 °C for 15 min, diluted with EtOAc (20 mL), and filtered through celite. The filtrate was washed with water (30 mL). The water layer was extracted with EtOAc (2 × 20 mL), and the combined organic layers were washed with water (30 mL) and brine (30 mL), dried (Na₂SO₄), and concentrated to give 190 mg of a 7:1 mixture of **6** and a cyclized byproduct which decomposed on attempted purification.

Partial data for **6**: ¹H NMR 7.40-7.20 (m, 10), 7.02 (s, 1), 6.09 (dd, 1, *J* = 7.4, 5.5), 5.10-4.97 (m, 4), 4.47 (ddd, 1, *J* = 14.0, 4.3, 4.3), 4.023 (s, 3), 4.019 (s, 3), 3.55 (dddd, 1, *J* = 10.6, 6.4, 5.5, 5.5), 3.26 (ddd, 1, *J* = 14.0, 14.0, 2.5), 2.76 (ddd, 1, *J* = 13.8, 7.4, 6.4), 2.28 (ddd, 1, *J* = 13.8, 5.5, 5.5), 1.80-1.40 (m, 6).

Partial data for the byproduct: $^1\text{H NMR}$ 7.40-7.20 (m, 10), 7.01 (s, 1), 6.29 (dd, 1, $J = 5.6$, 2.3).



(*R*^{*})-6-[Hydroxy[3*R*,4*aR*-hexahydro-1-imino-3*H*-pyrido[1,2*c*] pyrimidin-3-yl]methyl]-2,4-dimethoxypyrimidine (**7**), 6-[Hydroxy[3*R*^{*},4*aS*-hexahydro-1-imino-3*H*-pyrido[1,2*c*] pyrimidin-3-yl]methyl]-2,4-dimethoxypyrimidine (**b**), (*R*^{*})-6-[Hydroxy[3*S*,4*aS*-hexahydro-1-imino-3*H*-pyrido[1,2*c*] pyrimidin-3-yl]methyl]-2,4-dimethoxypyrimidine (**c**), and 6-[Hydroxy[3*R*^{*},4*aS*-hexahydro-1-imino-3*H*-pyrido[1,2*c*]pyrimidin-3-yl]methyl]-2,4-dimethoxypyrimidine (**d**). A suspension of crude **6** and 10% Pd/C (25 mg) in methanol (30 mL) was stirred at rt under a hydrogen-filled balloon for 2 h, and filtered through celite. The filtrate was evaporated under reduced pressure, and the residue was purified on silica gel (80:20:1 CH₂Cl₂/MeOH/HCO₂H) to give 77 mg (81% from **5**) of a difficulty separable 17:3:1:0.1 mixture of **7**, **b**, **c**, and **d**. Careful flash chromatography on silica gel (90:10:1 CH₂Cl₂/MeOH/HCO₂H) gave 35 mg (45%) of a 8:1 mixture of **7** and **b**, followed by 12 mg (16%) of a 7.5:3.5:1 mixture of **7**, **b** and **c**, 23 mg (30%) of a 2:3:7:1 mixture of **7**, **b**, **c**, and **d**. Rechromatography of the fraction richest in **7** gave 2 mg (3%) of pure **7**, and 30 mg (39%) of an 8:1 mixture of **7** and **b**. Similarly, rechromatography of the fraction richest in **b** gave 5 mg (6.5%) of a 4:2:1 mixture of **7**, **b**, and **c**, followed by 2 mg (4%) of a 5:1 mixture of **7** and **b**, and 1 mg (1.3%) of a 1.2:1 mixture of **7** and **b**. Rechromatography of the fraction richest in **c** gave 4 mg (5%) of a 1:9:1.5 mixture of **b**, **c**, and **d**. The chemical shifts are pH sensitive. The downfield absorptions of isomers **7** and **b** overlap at pH 6.5, but are distinguishable in the $^1\text{H NMR}$ spectrum of the guanidinium salts at pH \approx 1, which was obtained by adding one drop of conc HCl to the CD₃OD solution.

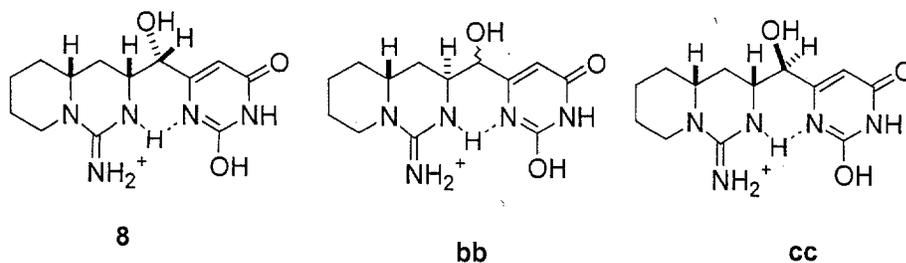
The data for **7**: $^1\text{H NMR}$ (CD₃OD) (pH 6.5) 8.50 (br s, HCO₂⁻), 6.67 (s, 1), 4.61 (d, 1, $J = 4.4$), 3.993 (s, 3), 3.991 (s, 3), 3.89 (br d, 1, $J = 12.8$), 3.84 (ddd, 1, $J = 11.6, 4.4, 3.6$), 3.31 (dddd,

1, $J = 11.4, 11.4, 4.3, 3.1$), 2.95 (ddd, 1, $J = 12.8, 12.8, 3.1$), 1.94 (ddd, 1, $J = 13.4, 4.3, 3.6$), 1.89 (m, 1), 1.81 (m, 2), 1.65 (ddd, 1, $J = 13.4, 11.6, 11.4$), 1.59-1.22 (m, 3); (pH 1) 8.08 (s, HCO₂H), 6.99 (s, 1), 4.97 (d, 1, $J = 4.4$), 4.30 (s, 3), 4.24 (s, 3), 3.91 (br d, 1, $J = 12.8$), 3.81 (ddd, 1, $J = 11.6, 4.4, 3.6$), 3.38 (dddd, 1, $J = 11.4, 11.4, 4.3, 3.1$), 2.96 (ddd, 1, $J = 12.8, 12.8, 3.1$), 2.06 (ddd, 1, $J = 13.4, 4.3, 3.6$), 1.90-1.30 (m, 7); ¹³C NMR (CD₃OD) 174.2, 172.7, 166.7, 156.2, 99.9, 73.9, 55.6, 55.4, 54.8, 53.7, 47.0, 33.8, 31.2, 26.0, 24.0; IR (neat) 3306, 3144, 1649, 1587, 1457, 1356.

Partial data for **b** were determined from the 1.2:1 mixture of **7** and **b**: ¹H NMR (CD₃OD) (pH 6.5) 6.67 (s, 1), 4.57 (d, 1, $J = 5.5$), 3.99 (s, 6), 3.94 (br d, 1, $J = 12.8$), 3.83 (m, 1), 3.51 (dddd, 1, $J = 10.8, 8.1, 5.6, 2.7$), 3.00 (ddd, 1, $J = 12.8, 12.8, 2.2$), 2.07 (ddd, 1, $J = 14.0, 5.6, 5.6$); (pH 1) 8.08 (s, HCO₂H), 6.98 (s, 1), 4.85 (d, 1, $J = 7.6$), 4.30 (s, 3), 4.24 (s, 3), 3.96 (br d, 1, $J = 13.2$), 3.65 (ddd, 1, $J = 7.6, 5.2, 3.5$), 3.61-3.53 (m, 1), 3.10 (ddd, 1, $J = 13.2, 13.2, 3.6$), 2.36 (ddd, 1, $J = 14.8, 4.8, 3.5$), 1.90-1.30 (m, 7); ¹³C NMR 174.2, 173.1, 166.7, 155.2, 99.9, 75.0, 55.6, 55.4, 54.3, 51.7, 47.9, 33.8, 29.3, 26.4, 24.7.

The data for **c** were determined from the 1:9:1.5 mixture of **b**, **c**, and **d**: ¹H NMR (CD₃OD) (pH 6.5) 8.19 (br s, HCO₂), 6.67 (s, 1), 4.38 (br d, $J = 6.4$), 4.00 (s, 3), 3.99 (s, 3), 3.89 (br d, 1, $J = 12.8$), 3.74 (ddd, 1, $J = 11.6, 6.4, 3.4$), 3.31 (m, 1), 2.95 (ddd, 1, $J = 12.8, 12.8, 2.9$), 2.01 (ddd, 1, $J = 13.4, 4.6, 3.4$), 1.93 (br d, 1, $J = 11.3$), 1.85-1.80 (m, 2), 1.74 (ddd, 1, $J = 13.4, 11.6, 11.6$), 1.59-1.42 (m, 2), 1.35-1.14 (m, 1); ¹³C NMR (125 MHz) (CD₃OD) 174.3, 172.5, 166.9, 156.2, 100.2, 75.4, 55.6, 55.4, 54.8, 53.6, 47.0, 33.8, 33.6, 26.0, 24.1; IR (neat) 3310, 3145, 1587, 1457, 1356.

Partial data for **d** were determined from the 1:9:1.5 mixture of **b**, **c**, and **d**: ¹H NMR (CD₃OD) 4.47 (d, 1, $J = 5.2$), 3.972 (s, 3), 3.965 (s, 3).



(*R*^{*})-6-[Hydroxy[3*R*,4*aR*-hexahydro-1-imino-3*H*-pyrido[1,2*c*] pyrimidin-3-yl]methyl]-2,4-(1*H*,3*H*)-pyrimidinedione (**8**), 6-[Hydroxy[3*R*^{*},4*aS*-hexahydro-1-imino-3*H*-pyrido[1,2*c*] pyrimidin-3-yl]methyl]-(1*H*,3*H*)-pyrimidinedione (**bb**), and (*R*^{*})-6-[Hydroxy[3*S*,4*aS*-hexahydro-1-imino-3*H*-pyrido[1,2*c*] pyrimidin-3-yl]methyl]-2,4-(1*H*,3*H*)-pyrimidinedione (**cc**). A solution of a 10:1.5:1 mixture of **7**, **b**, and **c** (20 mg, 0.440 mmol) in conc HCl (2 mL) was refluxed at 100 °C for 6 h. The mixture was evaporated under reduced pressure to give 17 mg (95%) of a 10:1.5:1 mixture of **8**, **bb**, **cc**. A similar reaction with a 1:9:1.5 mixture of **b**, **c**, and **d** gave 95% of a 1:9:1.5 mixture of **bb**, **cc**, and **dd**.

The data for **8**: ¹H NMR (D₂O) 5.83 (s, 1), 4.70 (d, 1, *J* = 4.0), 3.80 (br d, 1, *J* = 12.8), 3.74 (ddd, 1, *J* = 11.3, 4.0, 4.0), 3.35 (dddd, 1, *J* = 11.0, 11.0, 4.6, 2.8), 2.94 (ddd, 1, *J* = 12.8, 12.8, 2.5), 2.06 (ddd, 1, *J* = 13.4, 4.6, 4.0), 1.92-1.75 (m, 3), 1.66 (ddd, 1, *J* = 13.4, 11.3, 11.0), 1.53-1.23 (m, 3); ¹³C NMR (D₂O) (CH₃)₃SiCH₂CH₂CH₂SO₃⁻Na⁺ was used as an external reference) 169.4, 158.0, 157.1, 155.3, 101.5, 71.7, 56.0, 53.7, 48.3, 34.6, 31.5, 26.7, 24.8; IR (neat) 3310, 3154, 1669, 1622, 1441, 1363, 1024; HRMS-FAB MeOH/NBA M⁺ Calcd for C₁₃H₂₀N₅O₃⁺ 294.1566, found 294.1556.

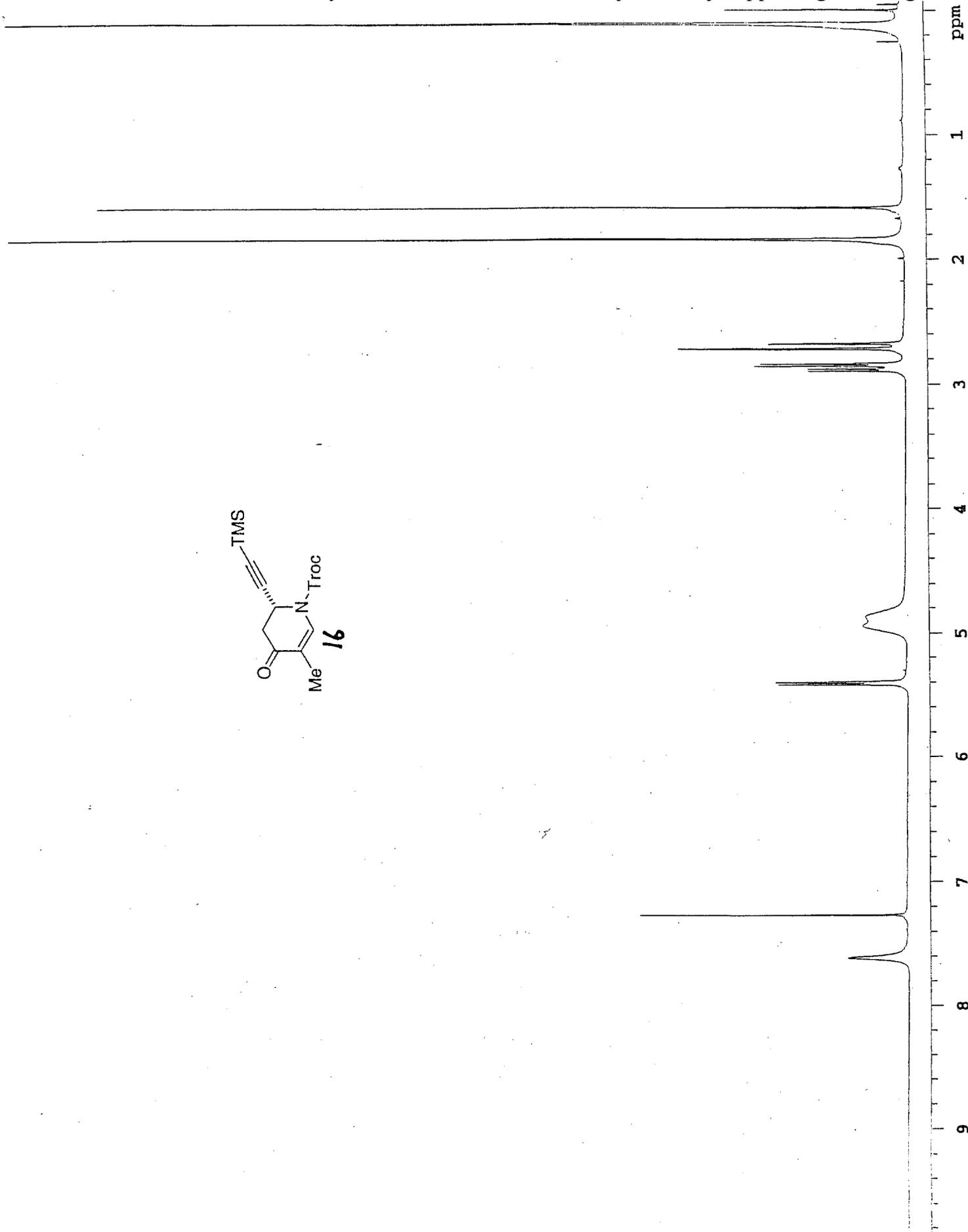
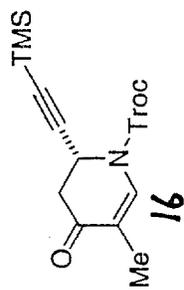
Partial data for **bb**: ¹H NMR (D₂O) 5.79 (s, 1), 4.56 (d, 1, *J* = 7.3), 3.64 (ddd, 1, *J* = 7.3, 4.8, 4.8), 3.35 (dddd, 1, *J* = 10.9, 10.9, 4.1, 4.0);

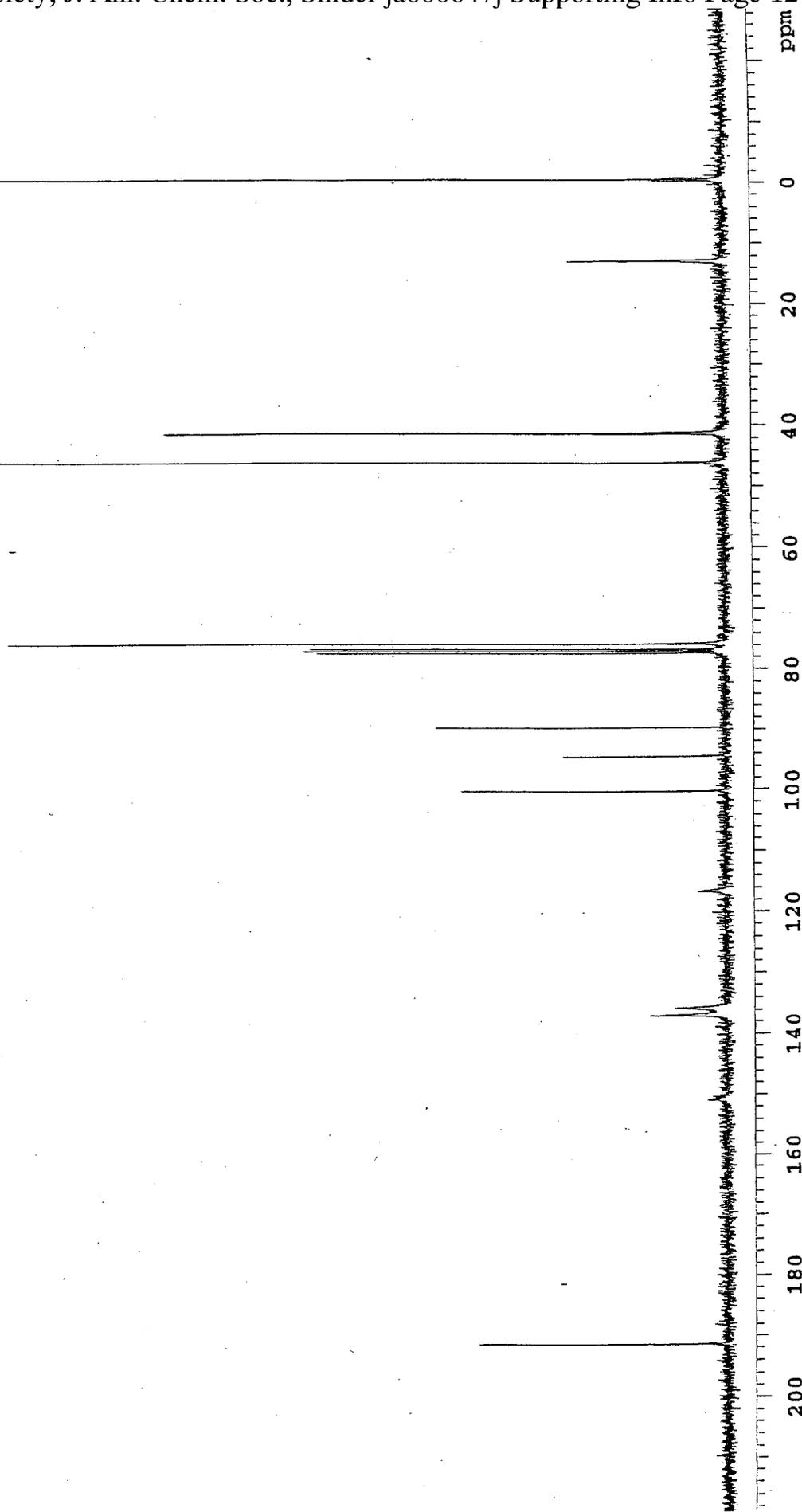
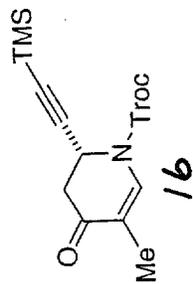
The data for **cc**: ¹H NMR (D₂O) 5.84 (s, 1), 4.44 (d, 1, *J* = 6.8), 3.81 (br d, 1, *J* = 12.8), 3.66 (ddd, 1, *J* = 11.3, 6.8, 3.6), 3.37 (dddd, 1, *J* = 10.8, 10.8, 3.0, 3.0), 2.96 (ddd, 1, *J* = 12.8, 12.8, 2.6), 2.08 (ddd, 1, *J* = 13.6, 3.6, 3.0), 1.92-1.74 (m, 3), 1.68 (ddd, 1, *J* = 13.6, 11.3, 10.8), 1.58-1.22 (m, 3); ¹³C NMR (D₂O) (CH₃)₃SiCH₂CH₂CH₂SO₃⁻Na⁺ was used as an external reference) 169.5, 157.9, 157.0, 155.5, 101.9, 73.9, 56.1, 53.6, 48.3, 34.6, 34.0, 26

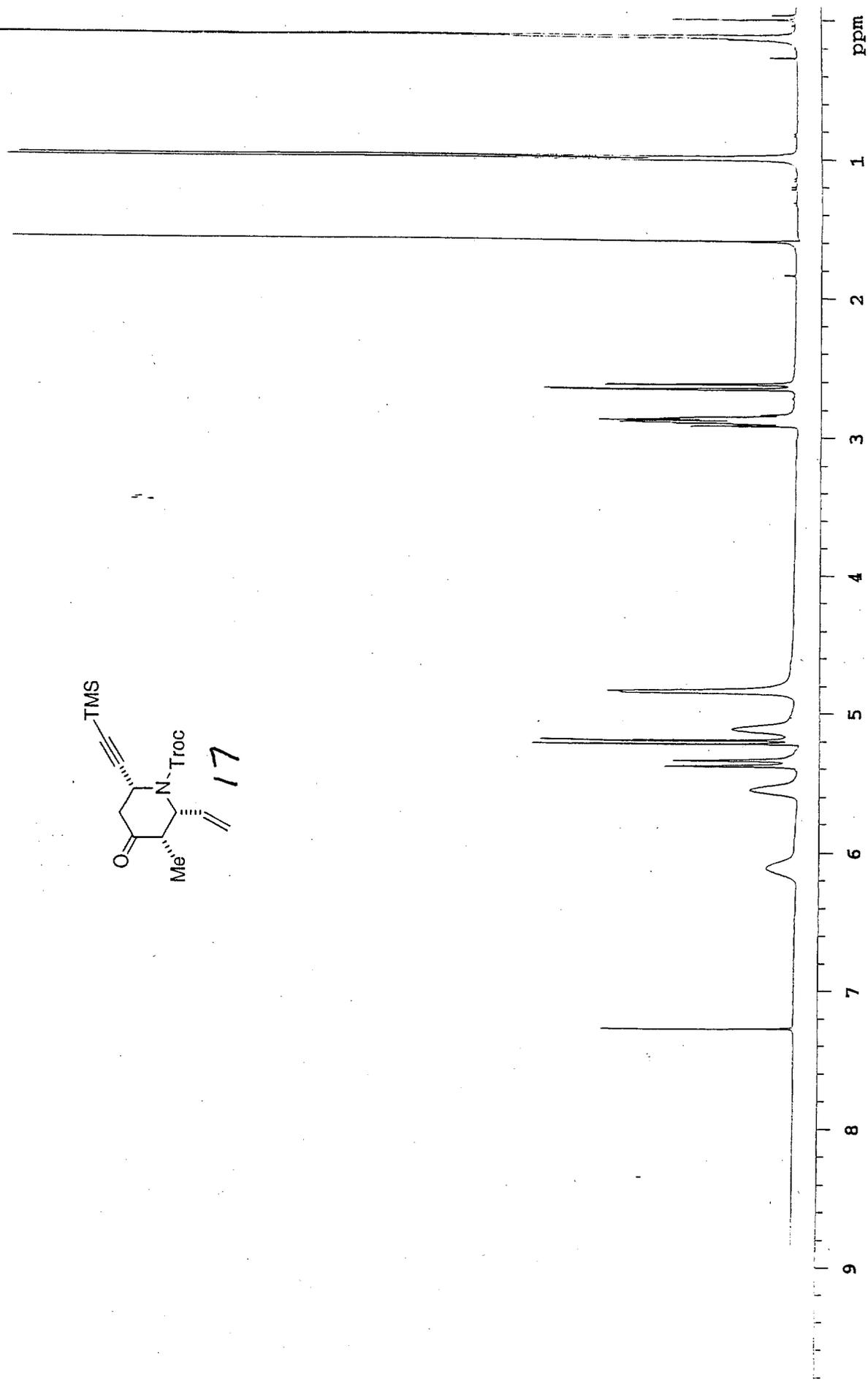
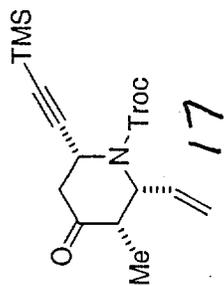
4-Methoxy-3-methylpyridine N-oxide (15). A solution of **14**⁴⁶ (14.2 g, 0.092 mol) and K₂CO₃ (15 g) in MeOH (100 mL) was refluxed for 2 h. The precipitated solid was removed by filtration. The filtrate was concentrated and the residue was taken up in CH₃CN (150 mL) with the formation of some precipitate. The solution was filtered and concentrated to give 12.5 g of crude **15** as a brown oil.

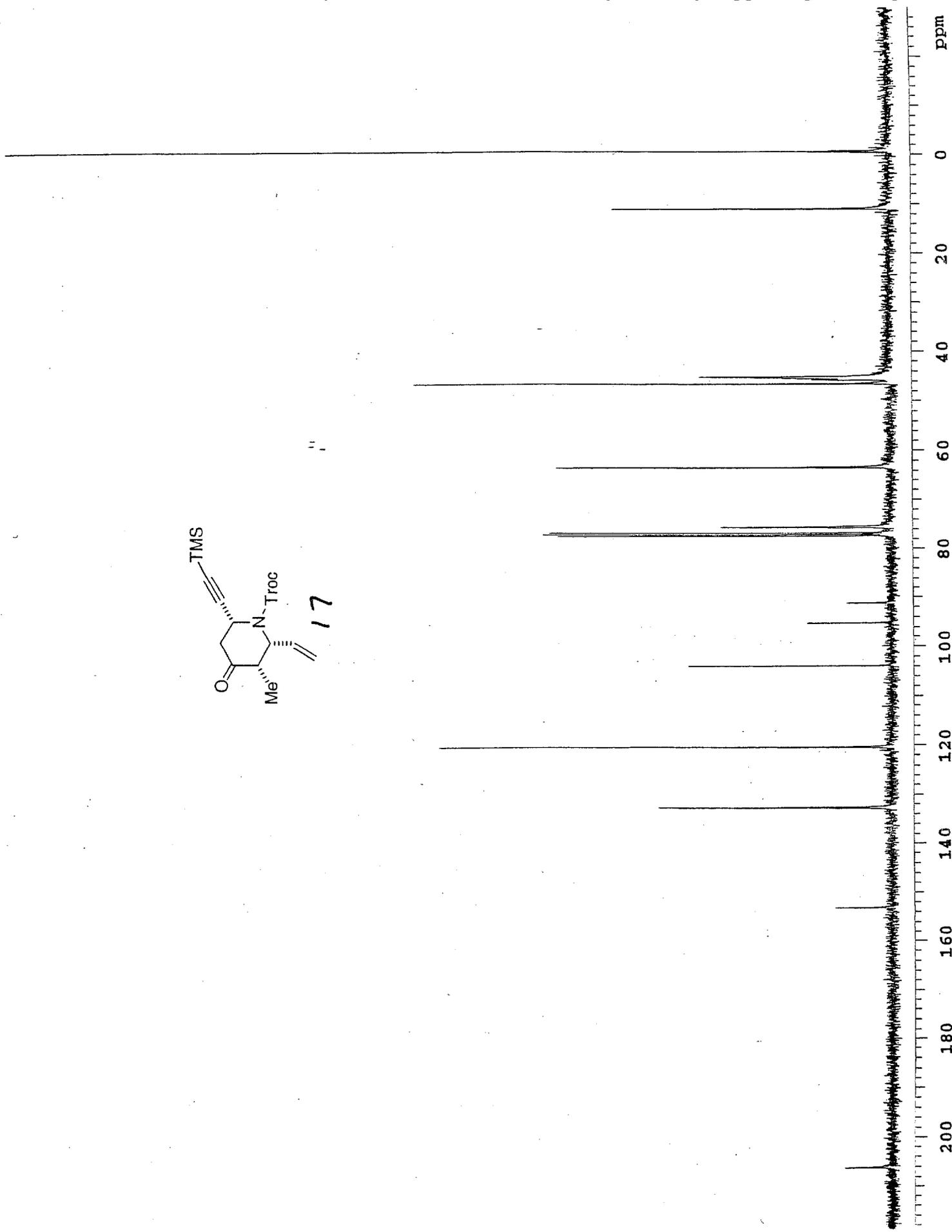
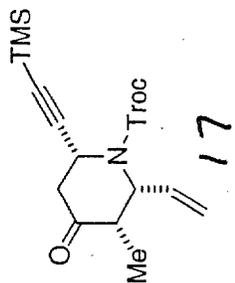
4-Methoxy-3-methylpyridine (12). A solution of crude **15** (12.5 g), 10% Pd/C (2.0 g), and AcOH (8 mL) in EtOH (70 mL) was shaken in under H₂ (45 psi) for 2 d. The Pd catalyst was filtered off. Fresh 10% Pd/C (2.0 g) was added and the solution was hydrogenated again for 2 d. This process was repeated two or three more times until the NMR spectrum indicated that the reaction was complete. The solution was filtered and concentrated. The residue was treated with 1 N NaOH until the pH of the solution reached 10. The solution was extracted with EtOAc, which was concentrated to provide 10.2 g (83%) of **12**: ¹H NMR 8.35 (d, 1, *J* = 5.5), 8.25 (s, 1), 6.72 (d, 1, *J* = 5.5), 3.87 (s, 3), 2.17 (s, 3); ¹³C NMR 162.6, 149.4, 148.1, 120.9, 104.4, 53.8, 11.7; IR (neat) 1592, 1578, 1502, 1286.

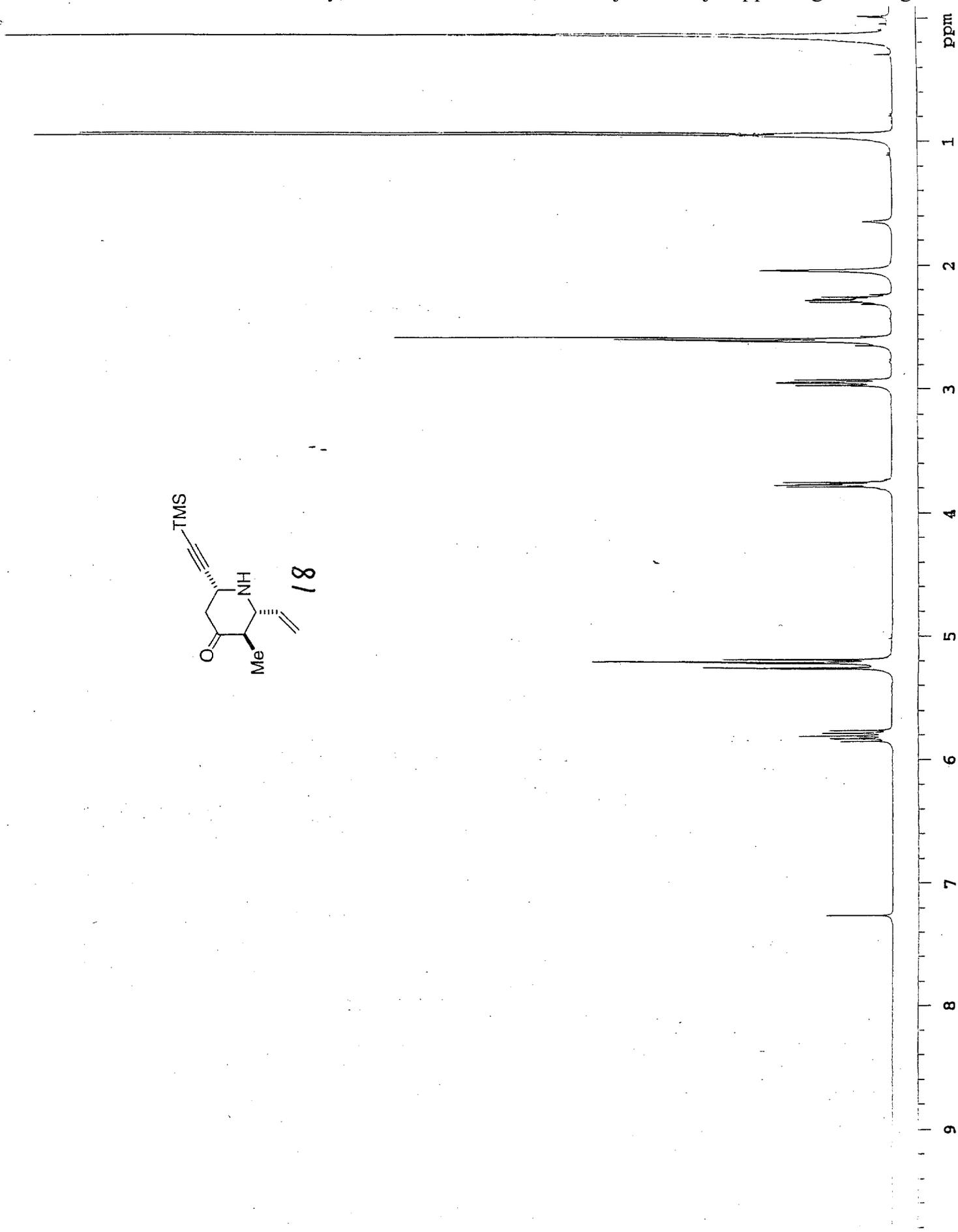
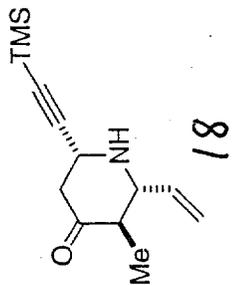
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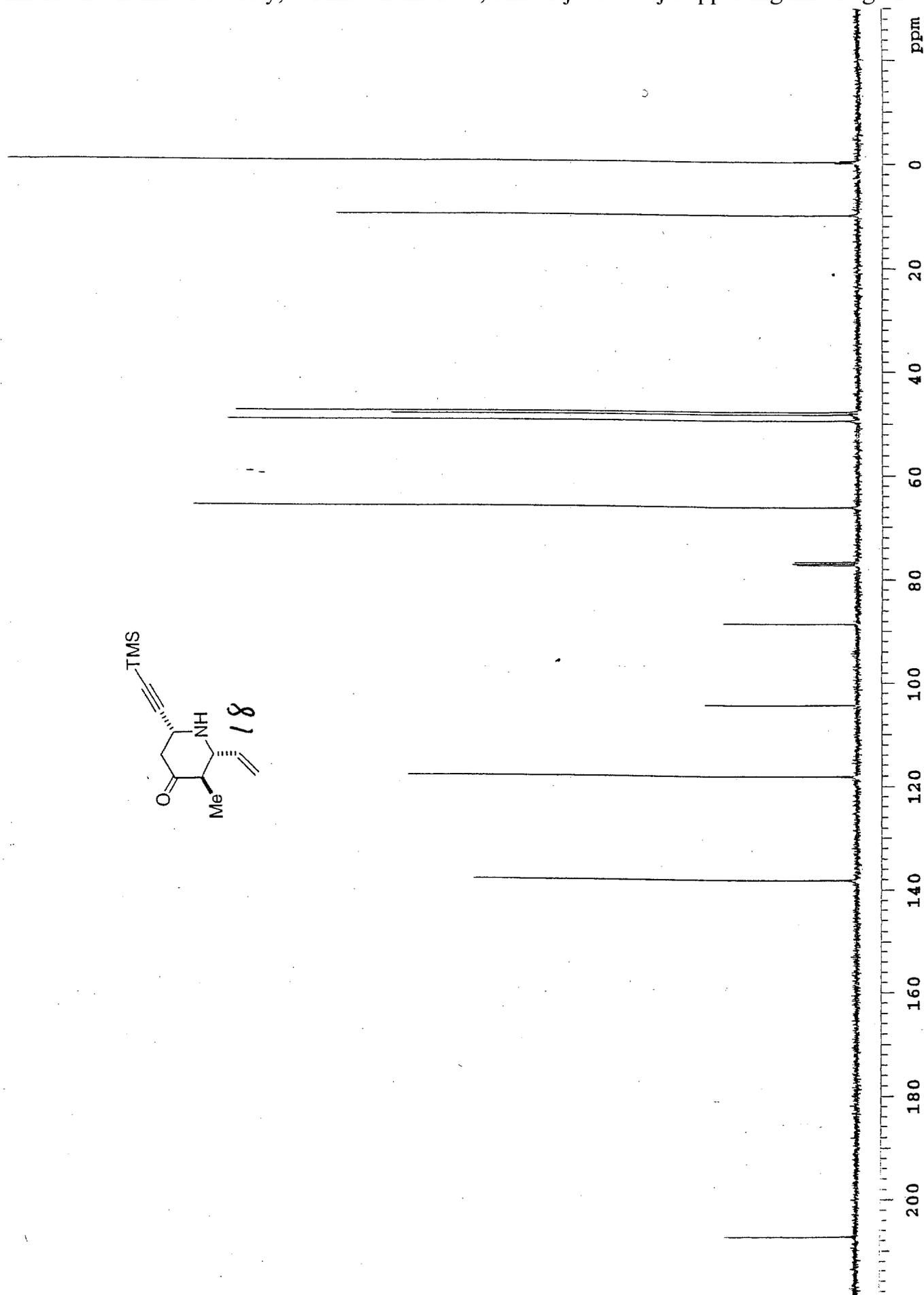
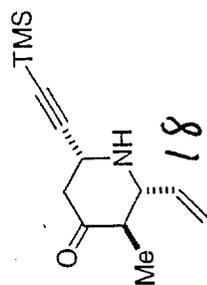


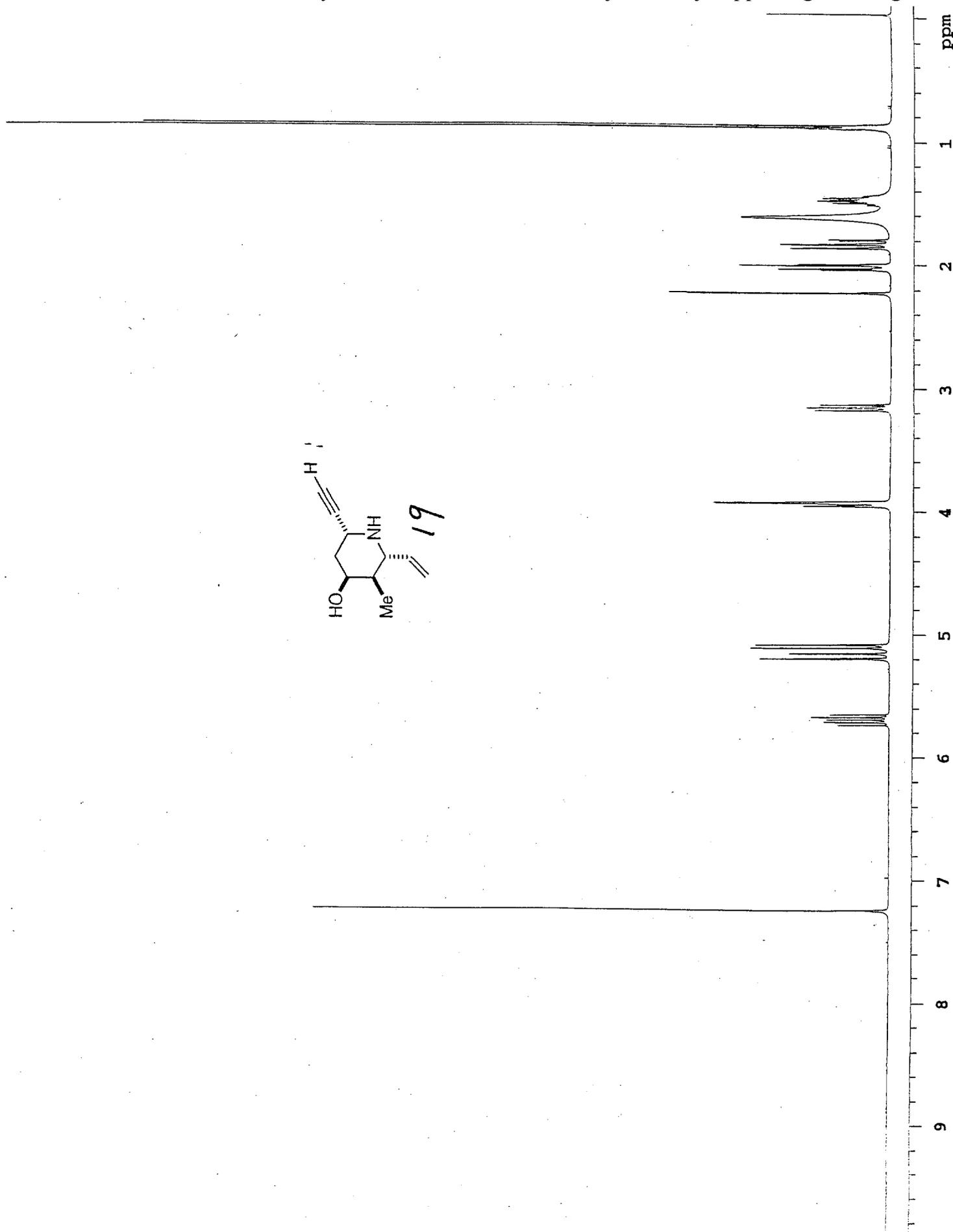
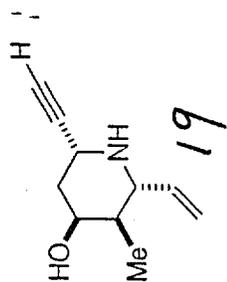


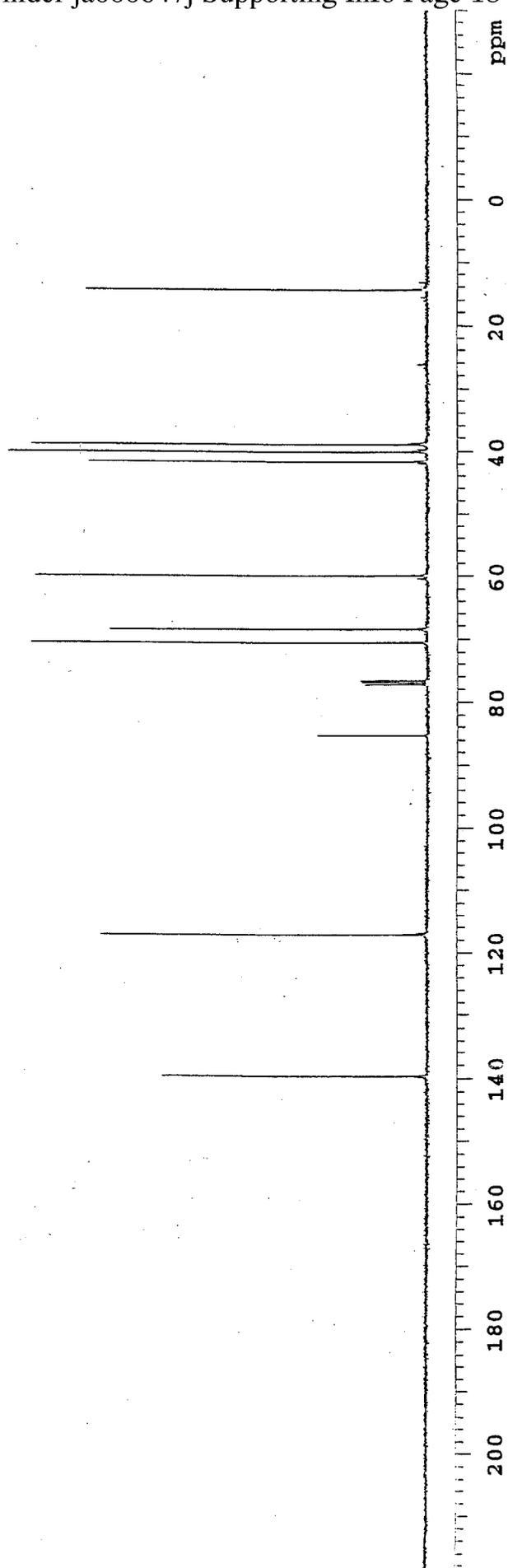
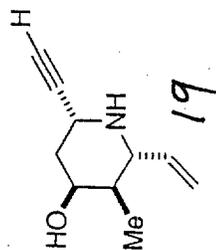


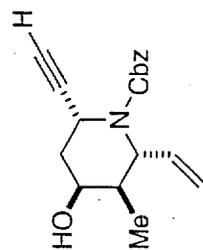




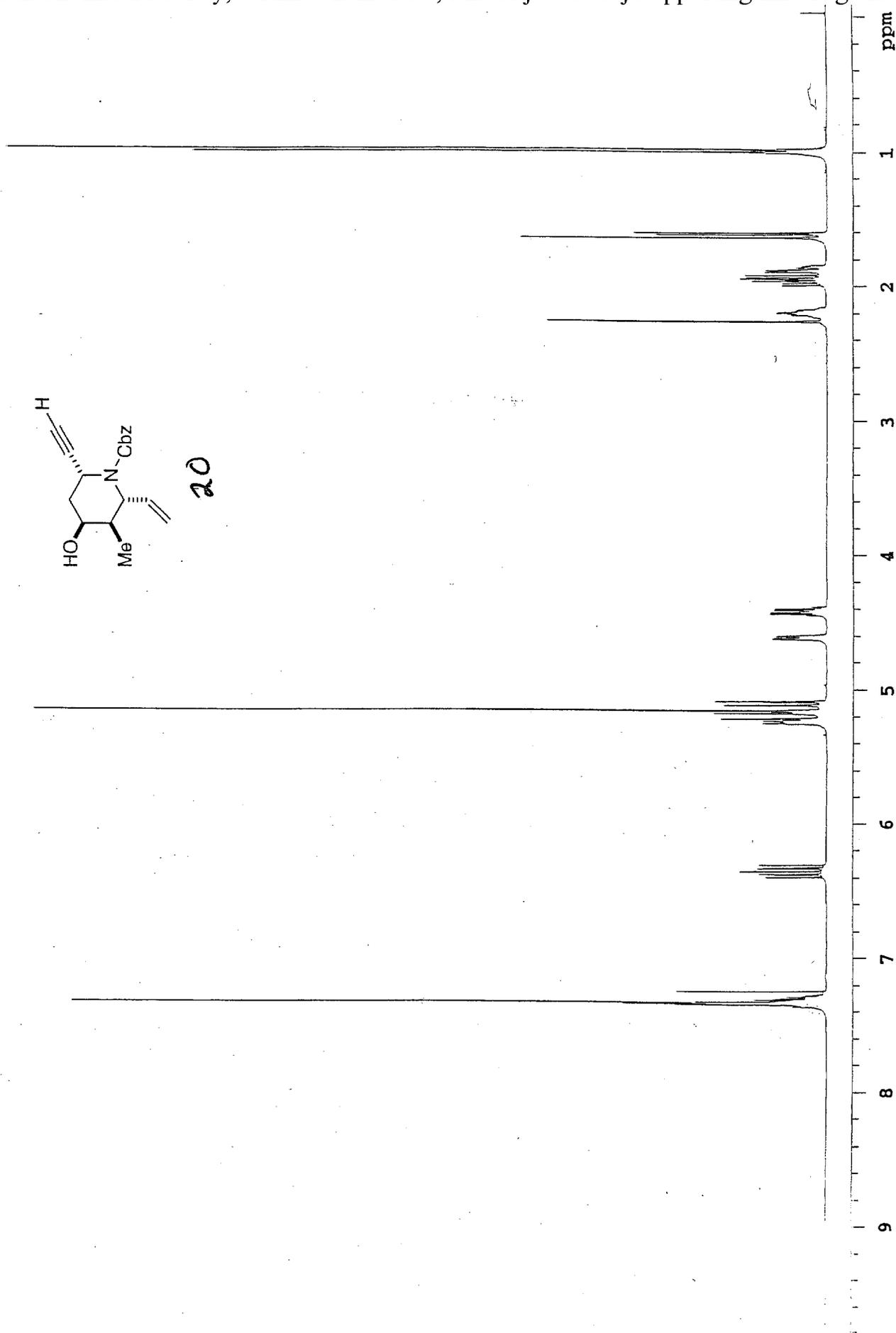


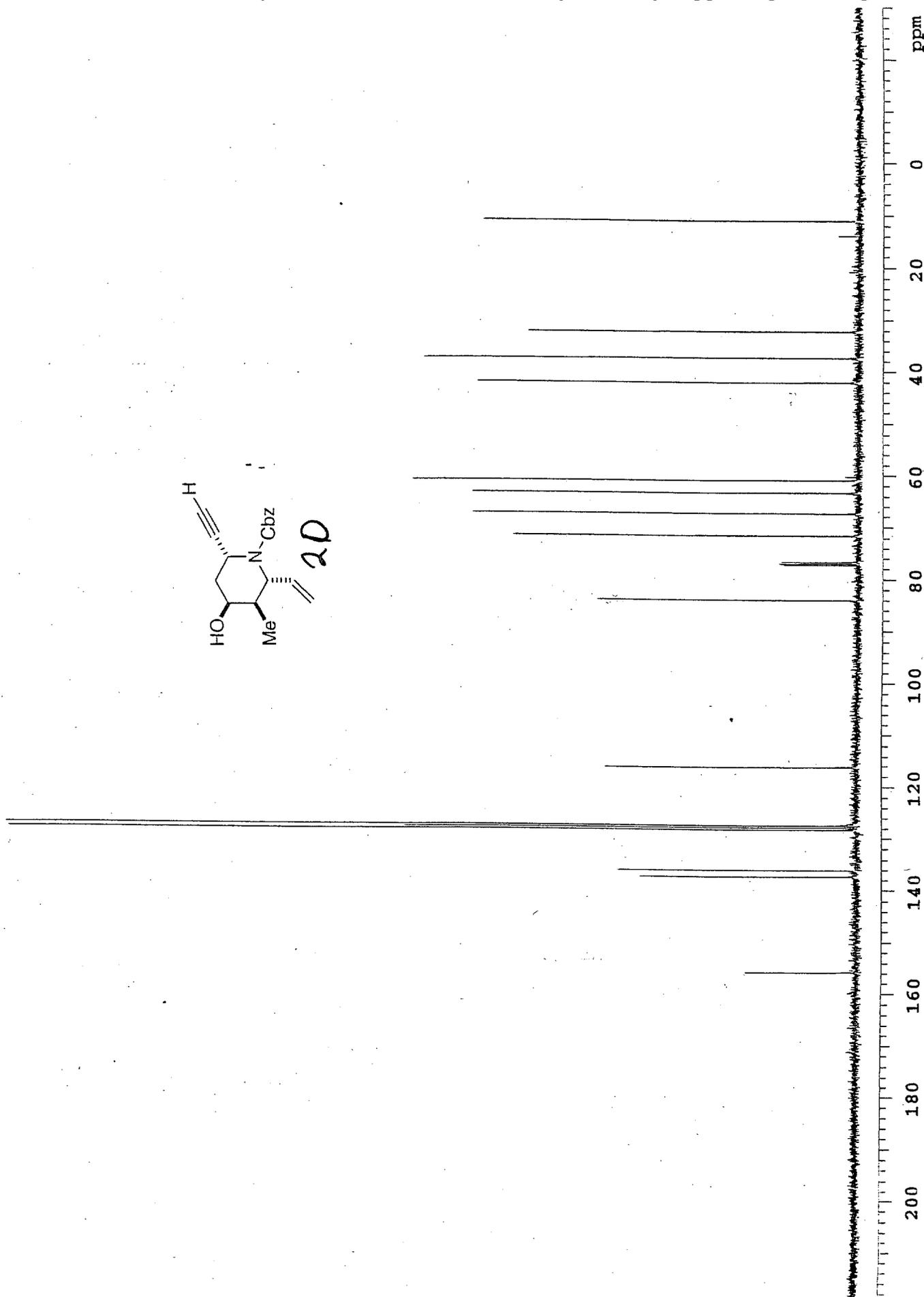
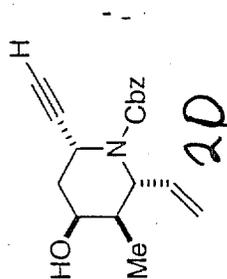


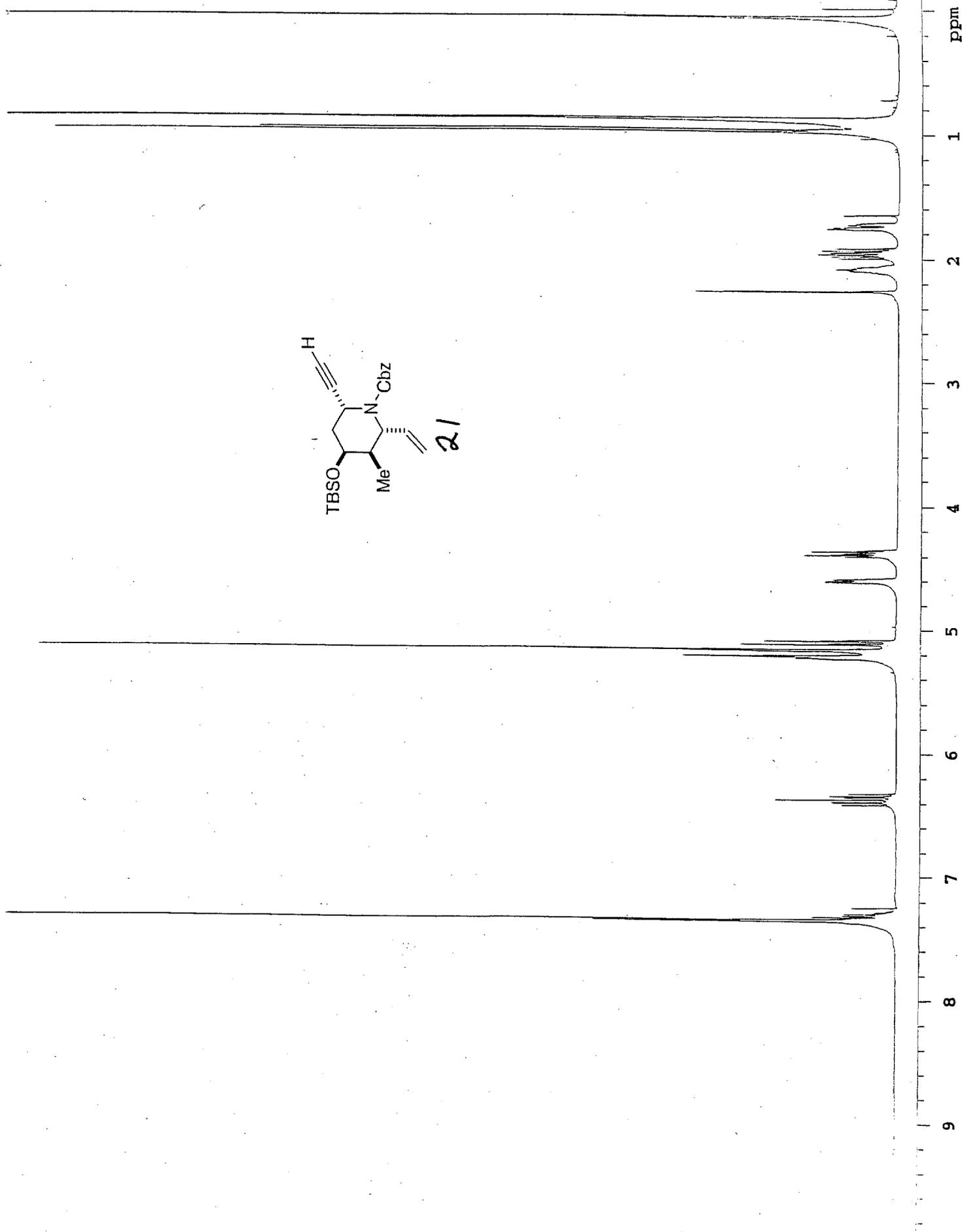
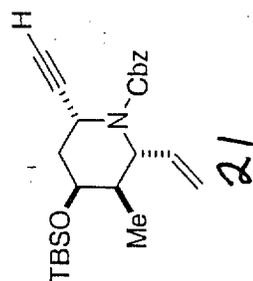


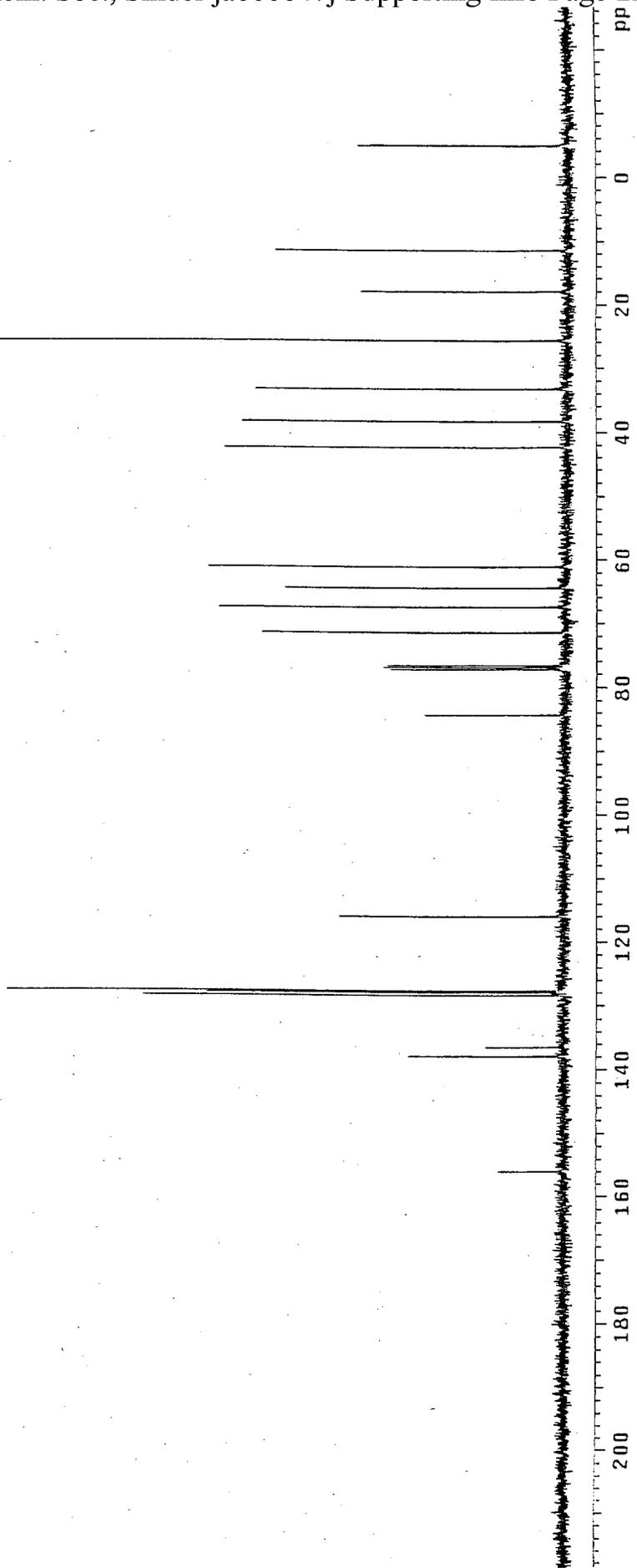
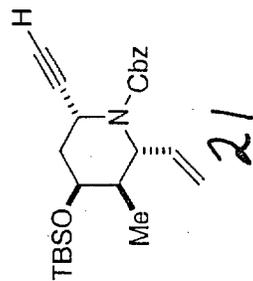


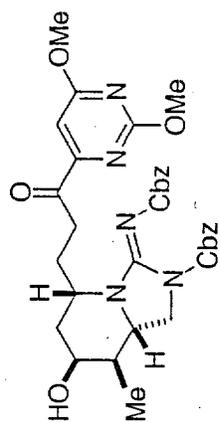
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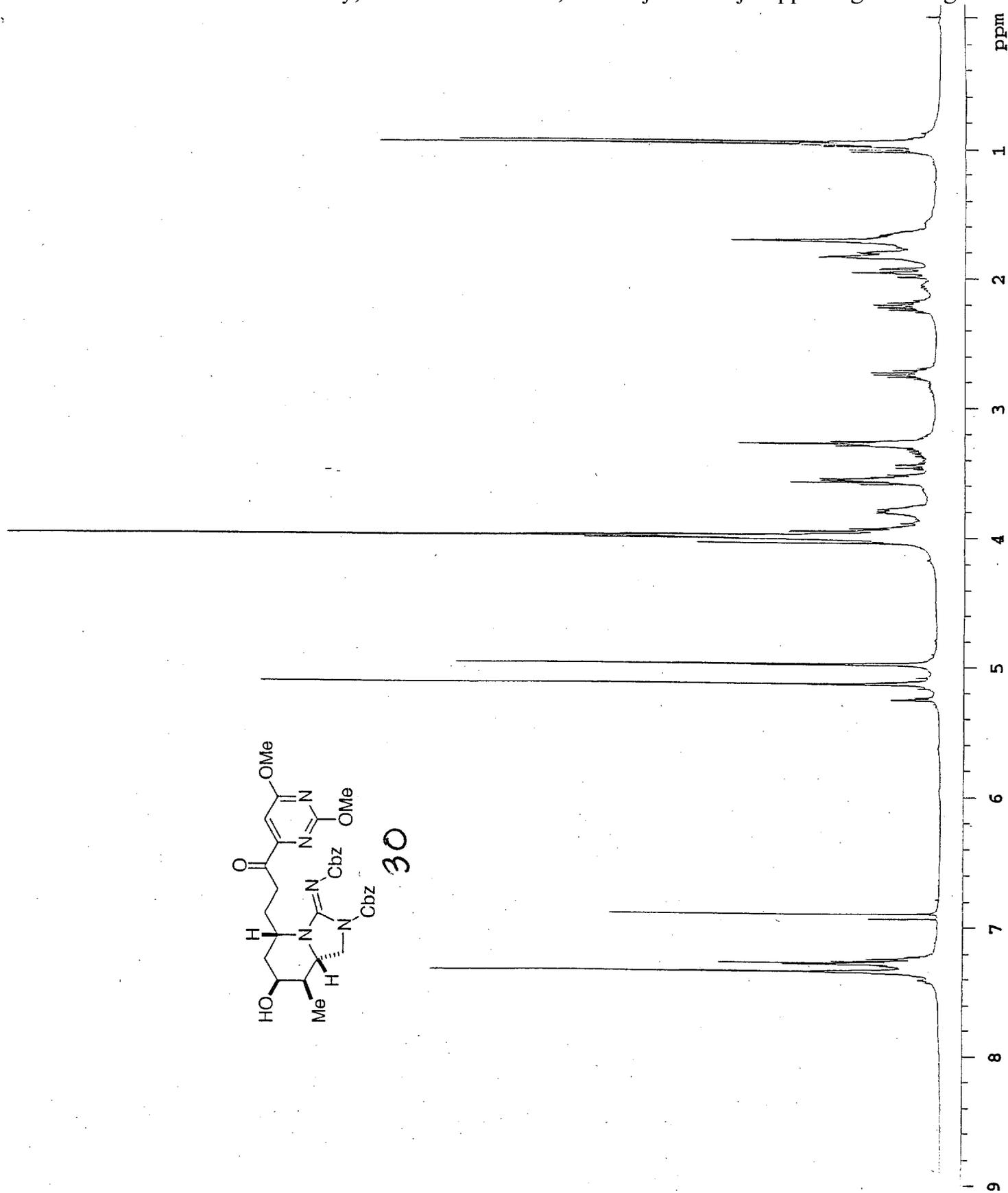


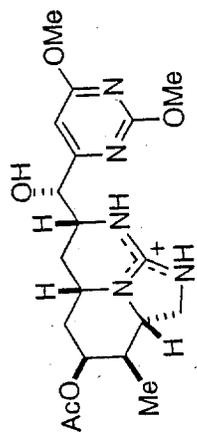




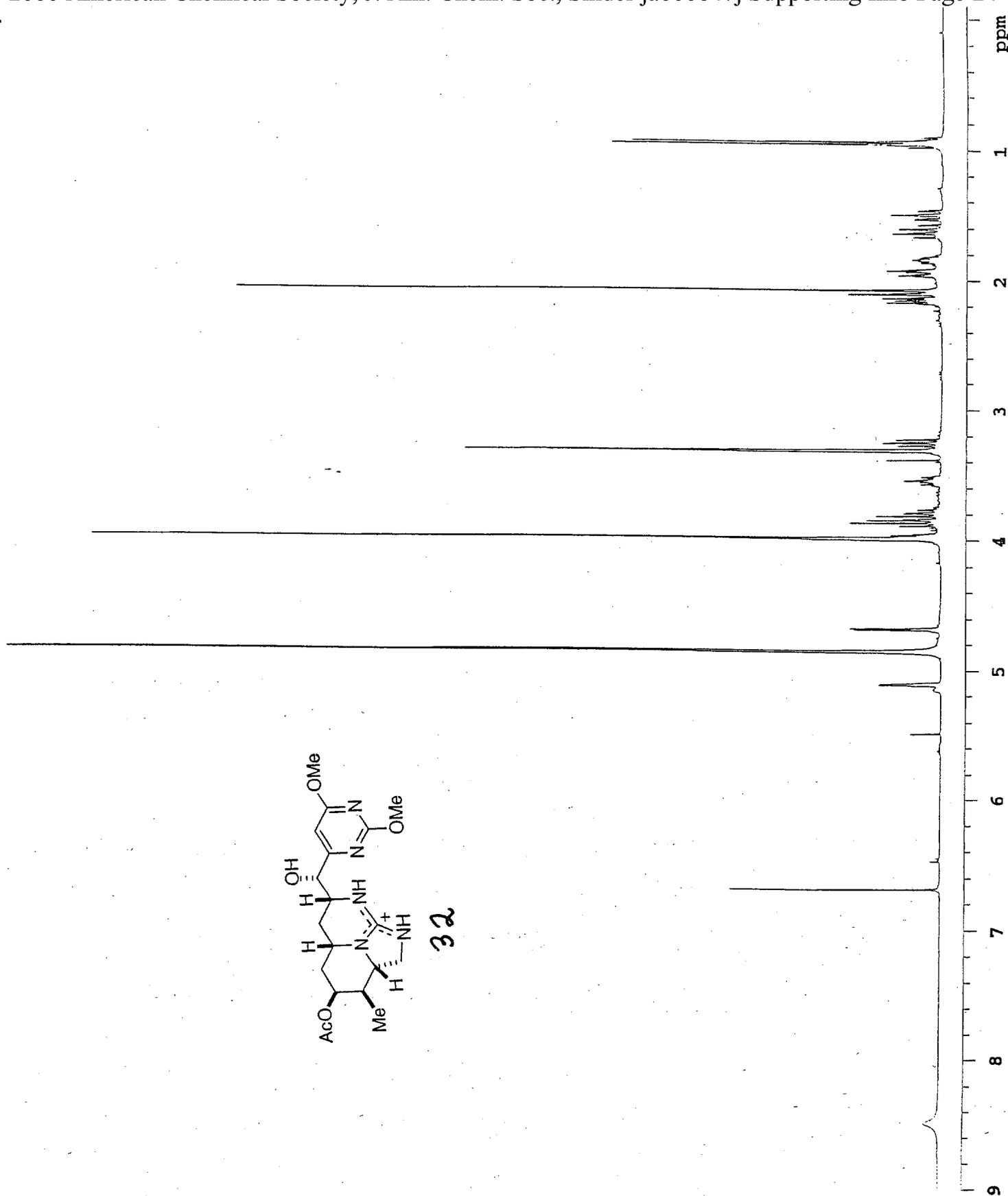


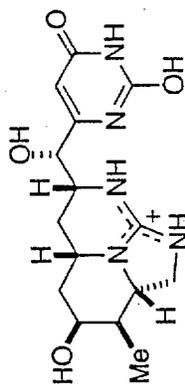
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