



Supporting Information

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Total Synthesis of (-)-Decarbamoyloxysaxitoxin

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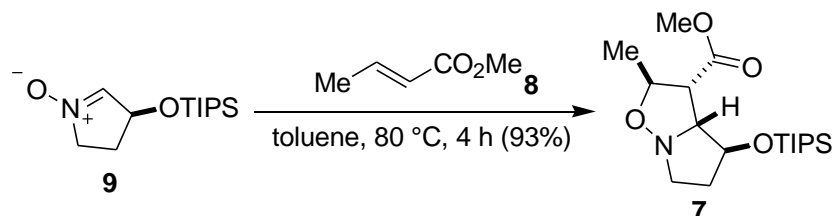
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General

Flash chromatography was performed on Silica gel 60 (spherical, particle size 0.040 ~ 0.100 μm ; Kanto). Optical rotations were measured on a JASCO DIP 1000 polarimeter, using the sodium D line. ^1H and ^{13}C NMR spectra were recorded on JEOL JNM-ECX 400. The spectra are referenced internally according to residual solvent signals of CDCl_3 (^1H NMR; $\delta = 7.26$ ppm, ^{13}C NMR; $\delta = 77.0$ ppm), CD_3OD (^1H NMR; $\delta = 3.30$ ppm, ^{13}C NMR; $\delta = 49.0$ ppm) and D_2O (^1H NMR; $\delta = 4.79$ ppm). Data for ^1H NMR are recorded as follows: chemical shift (δ , ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; br, broad), integration, coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (δ , ppm). Mass spectra were recorded on JEOL JMS-T100X spectrometer with ESI-MS mode using methanol as solvent.

Experimental Procedures

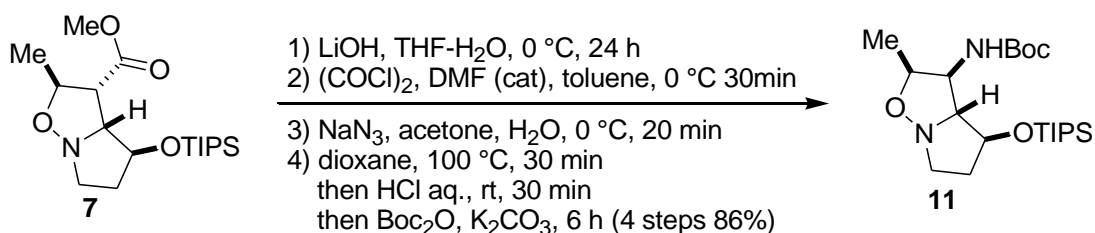
Isoxazolidine 7



To a solution of nitronium **9** (1.09 g, 4.25 mmol) toluene (20 mL) was added methyl crotonate (**8**) (900 μ L, 8.49 mmol) at room temperature. Then the reaction mixture was heated to 80 °C. After stirring for 4 h, the reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography (hexane/EtOAc; 15:1 to 10:1) to give isoxazolidine **7** (1.41 g, 93%) as a clear oil.

Spectral data for **7**: $[\alpha]_D^{22} = -8.57$ (*c* 1.16, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 4.29 (dt, *J* = 2.3, 5.1 Hz, 1H), 4.20 (dq, *J* = 6.0, 9.1 Hz, 1H), 3.89 (dd, *J* = 1.4, 9.2 Hz, 1H), 3.71 (s, 3H), 3.43 (ddd, *J* = 4.1, 7.3, 12.8 Hz, 1H), 3.27 (ddd, *J* = 6.4, 10.0, 12.8 Hz, 1H), 3.17 (t, *J* = 9.6 Hz, 1H), 2.01 (m, 1H), 1.76 (m, 1H), 1.25 (d, *J* = 6.0 Hz, 3H), 1.02 (s, 21H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 170.7, 76.8, 75.6, 74.7, 56.9, 56.5, 51.9, 35.6, 17.9, 17.8, 12.1; HRMS (ESI, $\text{M}+\text{Na}^+$) calcd for $\text{C}_{18}\text{H}_{35}\text{NO}_4\text{SiNa}$ 380.2233 found 380.2202

Amine 11



1) To a solution of isoxazolidine **7** (562 mg, 1.57 mmol) in mixed solvent of THF and H₂O (3/1) (8 mL) was added LiOH hydrate (132 mg, 3.14 mmol) at 0 °C. Stirring for 24 h at this temperature, the reaction was quenched by slow addition of aqueous 10% HCl until pH of the reaction mixture was set to 3 ~ 5 checking by pH-test paper. The resulting mixture was then extracted with EtOAc three times and washed with brine.

The combined organic layer was dried over MgSO₄, filtered and concentrated in vacuo to give crude carboxylic acid (549 g).

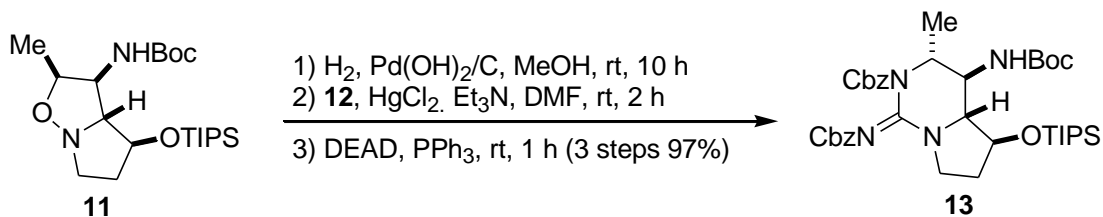
2) To a solution of crude carboxylic acid in toluene (16 mL) was added oxalyl chloride (275 μ L, 3.14 mmol) and catalytic amount of DMF (3 drops) at 0 °C under nitrogen atmosphere. After 1 h, the reaction mixture was concentrated to give crude acid chloride (598 mg).

3) To a solution of crude acid chloride in acetone (16 mL) was added NaN₃ (510 mg, 7.85 mmol) dissolved in H₂O (2 mL) at 0 °C. Stirring for 1 h at this temperature, the reaction mixture was extracted with hexane twice and the combined organic layer was dried over MgSO₄. The resulting solution was concentrated *in vacuo* to give crude azide carboxylate (581 mg).

4) The crude azide carboxylate was dissolved in 1,4-dioxane (16 mL) at room temperature and the solution was heated to 100 °C and stirring for 30 min. The reaction mixture was cooled to room temperature and the corresponding isocyanate was hydrolyzed with aqueous 10% HCl (3 mL). After additional 30 min, the reaction mixture was then added K₂CO₃ (3.0 g) and Boc₂O (445 mg, 2.04 mmol). Additional stirring for 6 h, the reaction mixture was diluted with EtOAc and extracted with EtOAc twice. The combined organic layer was dried over MgSO₄, filtered and concentrated *in vacuo* to give dark brown oil. The crude mixture was purified by silica gel column chromatography (hexane/EtOAc; 15:1 to 10:1) to give *N*-Boc amine **11** (561 mg, 4 steps 86%) as clear yellow oil.

Spectral data for **11**: $[\alpha]_D^{20} = -8.4$ (*c* 0.99, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.03 (bd, *J* = 9.6 Hz, 1H), 4.27 (m, 2H), 4.00 (dq, *J* = 4.6, 6.0 Hz, 1H), 3.35 (m, 2H), 3.19 (ddd, *J* = 4.6, 6.7, 11.9 Hz, 1H), 2.04 (m, 1H), 1.73 (m, 1H), 1.42 (s, 9H), 1.16 (d, *J* = 6.0 Hz, 3H), 1.04 (m, 21H); ¹³C NMR (100 MHz, CDCl₃) δ 155.6, 81.0, 79.6, 77.3, 74.8, 61.1, 55.7, 34.5, 28.2, 17.9, 13.1, 12.0; HRMS (ESI, M+Na⁺) calcd for C₂₁H₄₂N₃O₄SiNa 437.2812 found 437.2811

Cyclic guanidine **13**



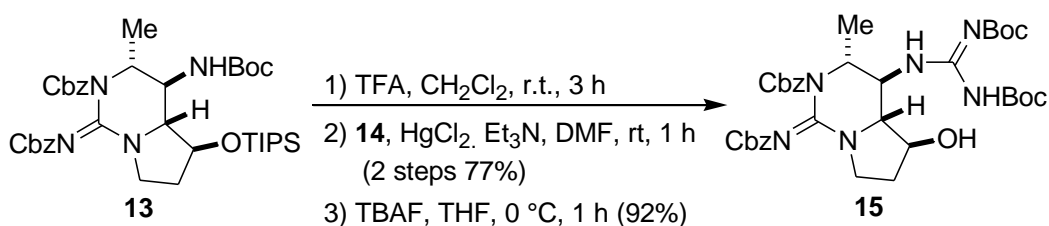
1) To a solution of amine **11** (1.07 g, 2.58 mmol) in MeOH (25 mL) was added $\text{Pd}(\text{OH})_2/\text{C}$ (catalytic amount), and the reaction mixture was stirred at room temperature under an atmosphere of hydrogen (balloon). After 10 h, the reaction mixture was filtered through a pad of celite, and the filtrates were concentrated to give crude secondary amine (1.24 g).

2) To a solution of the crude secondary amine (1.24 g) in DMF (10 mL) was added Et_3N (1.08 mL, 7.23 mmol), thiopseudourea **12** (1.06 g, 2.83 mmol) and Mercury (II) chloride (769 mg, 2.83 mmol) at room temperature under an atmosphere of nitrogen for 2 h. The reaction mixture was diluted with ethyl acetate, and filtered through a pad of celite. The filtrates were washed with H_2O and the combined organic layer was dried over MgSO_4 , filtered and concentrated to give crude guanidine (2.45 g).

3) To a solution of guanidine (2.45 g) and PPh_3 (1.01 mg, 3.86 mmol) in toluene (26 mL) was slowly added 2.2 M toluene solution of DEAD (1.76 mL, 3.86 mmol) at room temperature. After stirring for 1 h, excess amount of hexane was added to the reaction mixture, the resulting solid was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/ EtOAc ; 10:1 to 6:1) to give guanidine **13** (1.77 mg, 3 steps 97%) as clear oil.

Spectral data for **13**: $[\alpha]_D^{20} = -114.8$ (c 1.09, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.34-7.25 (m, 10H), 5.13 (d, $J = 12.4$ Hz, 1H), 4.93 (m, 2H), 4.80 (d, $J = 12.4$ Hz, 1H), 4.72 (brd, $J = 9.6$ Hz, 1H), 4.48 (d, $J = 3.2$ Hz, 1H), 3.98 (quint, $J = 6.4$ Hz, 1H), 3.83 (dd, $J = 6.9, 11.4$ Hz, 1H), 3.70 (m, 1H), 3.39 (dt, $J = 6.4, 11.9$ Hz, 1H), 3.19 (d, $J = 11.0$ Hz, 1H), 2.06 (m, 1H), 1.93 (dd, $J = 6.4, 12.8$ Hz, 1H), 1.42 (s, 9H), 1.39 (d, $J = 6.4$ Hz, 3H), 1.03 (m, 21H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.3, 155.1, 150.9, 136.7, 135.3, 128.7, 128.4, 128.3, 128.2, 128.1, 127.8, 80.5, 73.7, 68.9, 68.4, 67.0, 58.0, 57.2, 46.1, 32.8, 28.2, 20.5, 17.9, 12.0; HRMS (ESI, $\text{M}+\text{Na}^+$) calcd for $\text{C}_{38}\text{H}_{56}\text{N}_4\text{O}_7\text{SiNa}$ 731.3816 found 731.3803

Cyclic guanidine **15**



1) To a solution of guanidine **13** (1.22 g, 1.68 mmol) in CH_2Cl_2 (10 mL) was added TFA (5.0 mL) at 0 °C. Stirring for 3 h at room temperature, the reaction mixture was concentrated *in vacuo* to give crude amine (1.24 g).

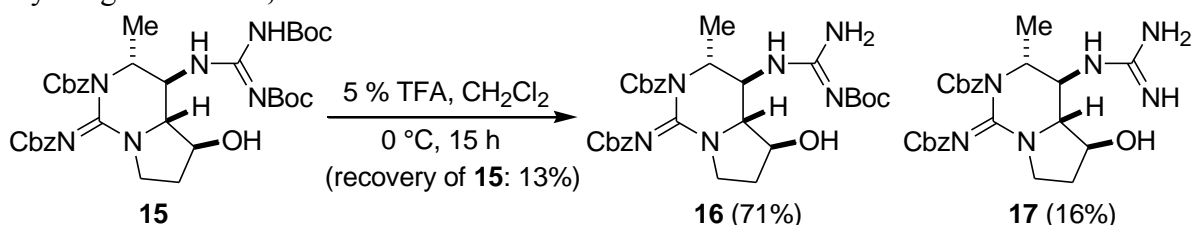
2) To a solution of the crude amine (1.24 g) in DMF (10 mL) was added thiopseudourea **14** (585 mg, 2.02 mmol), Et_3N (703 μL , 5.04 mmol) and Mercury (II) chloride (547 mg, 2.02 mmol) at room temperature under an atmosphere of nitrogen. After stirring for 1 h, the reaction mixture was diluted with ethyl acetate, and filtered through a pad of celite. The filtrates were washed with H_2O and the combined organic layer was then dried over MgSO_4 , filtered and concentrated *in vacuo*. Resulting residue was purified by silica gel column chromatography (hexane/EtOAc; 15:1 to 8:1 to 4:1) to give bis-guanidine (1.10 g, 77%) as clear oil.

Spectral data for **S1**: $[\alpha]_D^{20} = -137.9$ (c 0.78, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 11.43 (brs, 1H), 8.62 (brd, $J = 8.7$ Hz, 1H), 7.33-7.23 (m, 10H), 5.16 (d, $J = 12.4$ Hz, 1H), 4.94 (d, $J = 12.4$ Hz, 1H), 4.90 (d, $J = 12.4$ Hz, 1H), 4.81 (d, $J = 12.4$ Hz, 1H), 4.62 (d, $J = 3.2$ Hz, 1H), 4.09 (m, 1H), 4.04 (m, 1H), 3.85 (brdd, $J = 7.8, 11.5$ Hz, 1H), 3.71 (m, 1H), 3.31 (d, $J = 10.5$ Hz, 1H), 2.19 (m, 1H), 1.91 (dd, $J = 6.0, 13.3$ Hz, 1H), 1.49 (s, 9H), 1.45 (s, 9H), 1.42 (d, $J = 6.4$ Hz, 3H), 1.00 (brs, 21H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 163.1, 160.1, 156.1, 153.0, 151.0, 136.6, 135.2, 128.6, 128.4, 128.2, 128.1, 127.7, 83.8, 79.4, 73.6, 68.9, 68.5, 67.0, 57.1, 56.5, 46.2, 32.6, 28.1, 20.2, 17.9, 12.0; HRMS (ESI, $\text{M}+\text{Na}^+$) calcd for $\text{C}_{44}\text{H}_{66}\text{N}_6\text{O}_9\text{Si}$ 873.4558 found 873.4527

3) To a solution of bisguanidine (1.18 g, 1.39 mmol) in THF (14 mL) was added TBAF (545 mg, 2.09 mmol) at 0 °C. After stirring for 1 h at this temperature, the reaction mixture was quenched by saturated NH_4Cl aq. The resulting solution was extracted with EtOAc three times and the combined organic layer was dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc; 4:1 to 1:1) to give alcohol **15** (891 mg, 92%)

Spectral data for **15**: $[\alpha]_D^{26} = -42.9$ (*c* 1.90, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 11.33 (brs, 1H), 9.01 (brd, *J* = 6.4 Hz, 1H), 5.28 (d, *J* = 12.4 Hz, 1H), 4.94 (s, 2H), 4.83 (d, *J* = 11.9 Hz, 1H), 4.68 (q, *J* = 7.3 Hz, 1H), 4.19 (m, 2H), 3.84 (ddd, *J* = 2.3, 10.1, 12.4 Hz, 1H), 3.51 (dt, *J* = 8.2, 12.8 Hz, 1H), 3.28 (dd, *J* = 3.7, 7.8 Hz, 1H), 2.33 (m, 1H), 1.83 (dq, *J* = 9.6, 12.4 Hz, 1H), 1.47 (s, 18H), 1.27 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 161.9, 160.0, 155.6, 152.7, 152.6, 150.7, 136.6, 135.0, 128.6, 128.42, 128.35, 128.3, 128.2, 127.8, 84.0, 80.3, 75.1, 68.74, 68.65, 67.2, 57.4, 53.5, 45.0, 30.3, 28.0, 27.9, 18.0; HRMS (ESI, M+Na⁺) calcd for C₃₅H₄₆N₆O₉Na 717.3224 found 717.3191

Cyclic guanidine **16**, **17**



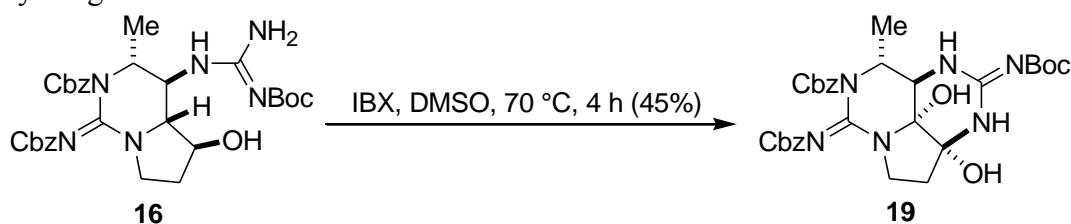
To a solution of alcohol **15** (1.23 g, 1.77 mmol) in CH₂Cl₂ (18 mL) was added TFA (900 μ L) at 0 °C. After stirring for 15 h at room temperature, the reaction mixture was cooled to 0 °C and quenched by slowly addition of 2 M NaOH aq. The resulting mixture was extracted with mixed solvent of CHCl₃/MeOH = 9:1 five times, and the combined organic layer was dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc; 1:1 to 0:1 and CHCl₃/MeOH; 9:1 to 0:1) to give mono-Boc-guanidine **16** (747 mg, 71%), Boc-free-guanidine **17** (148 mg, 16%) and starting material **15** (163 mg, 13%).

Spectral data for **16**: $[\alpha]_D^{20} = -119.9$ (*c* 1.36, CHCl₃); ¹H NMR (400 MHz, CD₃OD₃) δ 7.30 (m, 10H), 5.15 (d, *J* = 12.4 Hz, 1H), 4.90 (d, *J* = 12.4 Hz, 1H), 4.88 (d, *J* = 11.9 Hz, 1H), 4.84 (d, *J* = 12.4 Hz, 1H), 4.25 (m, 1H), 4.20 (m, 1H), 3.67 (m, 2H), 3.40 (m, 1H), 2.24 (m, 1H), 1.90 (m, 1H), 1.47 (s, 9H), 1.31 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 160.0, 156.7, 156.0, 152.7, 151.1, 136.0, 134.6, 128.6, 128.4, 128.3, 128.1, 127.8, 127.0, 77.6, 73.7, 68.9, 67.6, 66.3, 56.1, 55.1, 45.7, 30.4, 28.1, 18.3; HRMS (ESI, M+Na⁺) calcd for C₃₀H₃₈N₆O₇Na 617.2700 found 617.2719

Spectral data for **17**: $[\alpha]_D^{26} = -141.8$ (*c* 1.16, MeOH); ¹H NMR (400 MHz, CD₃OD₃)

δ 7.31 (m, 10H), 5.16 (d, $J = 11.9$ Hz, 1H), 4.89 (m, 2H), 4.83 (d, $J = 12.4$ Hz, 1H), 4.21 (brs, 1H), 4.16 (quint, $J = 6.4$ Hz, 1H), 3.68 (m, 2H), 3.52 (dd, $J = 6.4, 9.6$ Hz, 1H), 3.44 (brd, $J = 9.2$ Hz, 1H), 2.19 (m, 1H), 1.96 (m, 1H), 1.33 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 161.6, 158.6, 154.0, 153.2, 137.8, 136.5, 129.6, 129.5, 129.4, 129.1, 73.8, 69.8, 68.4, 67.6, 59.6, 58.2, 47.1, 32.7, 20.1; HRMS (ESI, $\text{M}+\text{Na}^+$) calcd for $\text{C}_{25}\text{H}_{30}\text{N}_6\text{O}_5\text{Na}$ 517.2175 found 517.2184

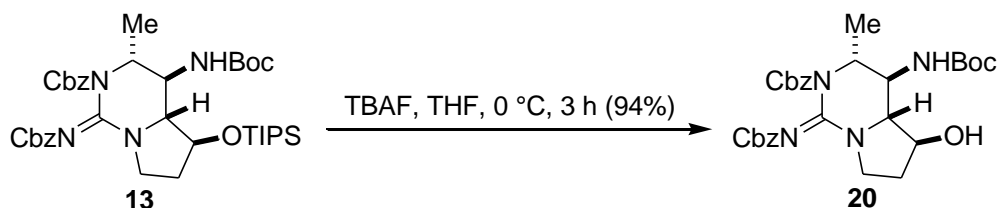
Bicyclic guanidine **19**



IBX (347 mg, 1.24 mmol) was added to a solution of mono-Boc-guanidine **16** (184 mg, 0.310 mmol) in DMSO (6.0 mL) at room temperature under an atmosphere of nitrogen and the mixture was heated to 70 °C. After stirring for 4 h, the reaction mixture was cooled to room temperature and quenched by 10% $\text{Na}_2\text{S}_2\text{O}_3$ aq. The resulting solution was extracted with EtOAc. The organic layer was washed with saturated NaHCO_3 aq. and brine once respectively. The combined organic layer was dried over MgSO_4 , filtered and concentrated in vacuo. Resulting residue was purified by silica gel column chromatography (hexane/EtOAc; 1:1 to 1:2 a) to give tricyclic guanidine **19** (84 mg, 45%).

Spectral data for **19**: $[\alpha]_D^{26} = 41.8$ (c 1.10, CHCl_3); ^1H NMR (400 MHz, CD_3OD) δ 7.30 (m, 10H), 5.06 (s, 2H), 4.90 (s, 2H), 4.61 (dq, $J = 1.2, 6.8$ Hz, 1H), 3.85 (d, $J = 1.2$ Hz, 1H), 3.60 (m, 2H), 2.40 (dt, $J = 9.9, 12.4$ Hz, 1H), 2.16 (m, 1H), 1.53 (d, $J = 6.8$ Hz, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.3, 161.3, 156.8, 155.1, 152.0, 138.1, 136.3, 129.9, 129.6, 129.5, 129.4, 129.1, 128.9, 86.6, 84.2, 70.3, 68.6, 57.7, 51.6, 33.2, 28.6, 18.6; HRMS (ESI, $\text{M}+\text{Na}^+$) calcd for $\text{C}_{30}\text{H}_{36}\text{N}_6\text{O}_8\text{Na}$ 631.2492 found 631.2524

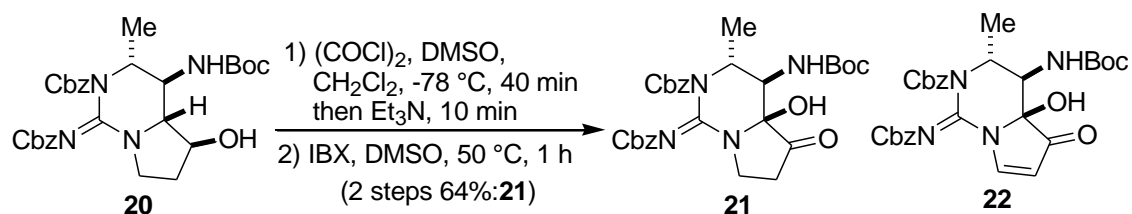
Alcohol **20**



To a solution of bisguanidine **13** (527 mg, 0.744 mmol) in a solution of THF (7.0 mL) was added TBAF (233 mg, 0.893 mmol) at 0 °C. After stirring for 3 h at this temperature, the reaction mixture was quenched by saturated NH₄Cl aq. The resulting solution was extracted with EtOAc three times and the combined organic layer was dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc; 2:1 to 01:1) to give alcohol **20** (387 mg, 94%) as clear oil.

Spectral data for **20**: $[\alpha]_D^{20} = -184.3$ (*c* 0.91, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.30-7.21 (m, 1H), 5.21 (brd, *J* = 6.9 Hz, 1H), 5.10 (d, *J* = 12.4 Hz, 1H), 4.94 (d, *J* = 12.4 Hz, 1H), 4.89 (d, *J* = 12.4 Hz, 1H), 4.84 (d, *J* = 12.4 Hz, 1H), 4.27 (q, *J* = 3.6 Hz, 1H), 4.05 (m, 1H), 3.79 (dt, *J* = 7.4, 12.4 Hz, 1H), 3.59 (ddd, *J* = 5.5, 7.8, 12.9 Hz, 1H), 3.49 (dt, *J* = 5.4, 8.7 Hz, 1H), 3.32 (m, 1H), 2.12 (m, 1H), 1.91 (m, 1H), 1.42 (s, 9H), 1.31 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 159.8, 155.8, 153.0, 151.3, 136.4, 135.0, 128.5, 128.4, 128.3, 128.2, 127.9, 80.7, 73.7, 68.6, 67.5, 67.2, 58.4, 56.7, 45.8, 31.4, 28.4, 20.0; HRMS (ESI, M+Na⁺) calcd for C₂₉H₃₆N₄O₇Na 575.2482 found 575.243

Aminal **21**



1) To a solution of DMSO (438 μ L, 6.11 mmol) in CH₂Cl₂ (10 mL) was added (COCl)₂ (446 μ L, 5.09 mmol) at -78 °C. After stirring for 5 min, secondary alcohol **20**

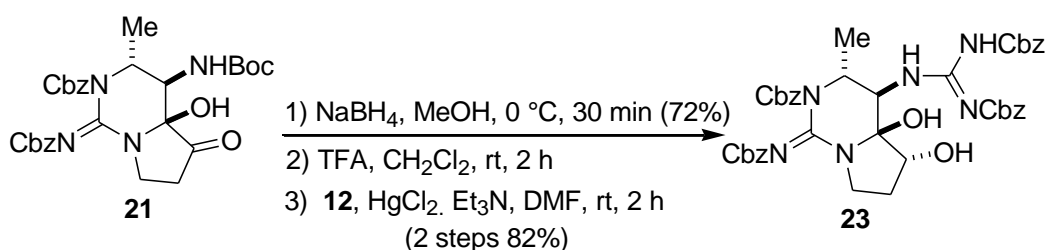
in CH₂Cl₂ (2 mL) was added to the above solution and the mixture was stirred for 45 min at -78 °C. Then Et₃N (1.77 mL, 12.73 mmol) was added to the mixture. After stirring for 5 min, the reaction was quenched by H₂O and warmed up to room temperature. The mixture was extracted with CH₂Cl₂ three times. The combined organic layer was dried over MgSO₄, filtered and concentrated to give crude ketone (316 mg).

2) To a solution of crude ketone (316 mg) in DMSO (5 mL) was added IBX (157 mg) at room temperature under a nitrogen atmosphere and then warmed up to 50 °C. After stirring for 1 h, the reaction was quenched by 10% Na₂S₂O₃ aq. and diluted with EtOAc. The mixture was washed with saturated NaHCO₃ aq. and brine once respectively. The combined aqueous layer was re-extracted with EtOAc and washed with NaHCO₃ aq. and brine. The combined organic layer was dried over MgSO₄, filtered and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc; 3:1 to 2:1) to give amina **21** (186 mg, 2 steps 64%) as mixture of the C12-hydrated adduct.

Spectral data for **21** as mixture of C12-hydrated adduct: $[\alpha]_D^{26} = -83.2$ (*c* 1.63, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ (for keto form) 7.27 (m, 10H), 5.27 (d, *J* = 10.0 Hz, 1H), 5.18 (d, *J* = 10.5 Hz, 1H), 4.90 (d, *J* = 11.7 Hz, 1H), 4.84 (s, 2H), 3.98 (m, 3H), 3.73 (t, *J* = 8.8 Hz, 1H), 2.75 (quint, *J* = 9.0 Hz, 1H), 2.63 (dd, *J* = 4.4, 15.4 Hz, 1H), 1.41 (s, 9H), 1.33 (d, *J* = 6.1 Hz, 3H) (for hydrate form) 7.27 (m, 10H), 6.19 (d, *J* = 2.9 Hz, 1H), 5.10 (d, *J* = 10.7 Hz, 1H), 4.88 (d, *J* = 10.7 Hz, 1H), 4.84 (s, 2H), 4.01-3.85 (m, 3H), 3.42 (m, 1H), 2.17 (dd, *J* = 11.8, 6.5 Hz, 1H), 1.97 (dd, *J* = 21.7, 10.5 Hz, 1H), 1.44 (s, 9H), 1.37 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 207.0, 160.00, 159.95, 157.7, 152.6, 152.5, 149.65, 149.39, 149.39, 136.4, 136.1, 135.3, 135.0, 128.74, 128.67, 128.5, 128.4, 128.3, 128.22, 128.19, 128.16, 128.10, 128.02, 127.8, 104.9, 87.9, 81.8, 81.3, 80.6, 68.6, 68.4, 67.6, 67.3, 58.3, 55.6, 53.6, 53.5, 50.9, 44.8, 41.4, 33.0, 29.7, 28.2, 28.1, 20.2, 19.8; HRMS (ESI, M+Na⁺) calcd for C₂₉H₃₄N₄O₈Na 589.2274 found 589.2299

Spectral data for **22**: $[\alpha]_D^{26} = -13.2$ (*c* 0.43, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.43 (d, *J* = 4.6 Hz, 1H), 7.33 (m, 10H), 5.65 (d, *J* = 4.1 Hz, 1H), 5.16 (d, *J* = 10.1 Hz, 1H), 5.10 (d, *J* = 11.9 Hz, 1H), 4.94 (d, *J* = 11.9 Hz, 1H), 4.86 (s, 2H), 4.07 (dq, *J* = 6.0, 8.2 Hz, 1H), 3.67 (t, *J* = 9.4 Hz, 1H), 1.42 (s, 9H), 1.36 (d, *J* = 6.0 Hz, 3H) HRMS (ESI, M+Na⁺) calcd for C₂₉H₃₂N₄O₈Na 587.2118 found 587.2151

Bis-guanidine **23**



1) To a solution of aminal **21** (8 mg, 0.015 mmol) in Methanol was added NaBH₄ (1 mg, 0.026 mmol) at 0 °C. After stirring for 30 min, H₂O was added to the reaction mixture and extracted with EtOAc three times. The combined organic layer was dried over MgSO₄, filtered and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc; 3:1) to give alcohol (6 mg, 72%)

Spectral data for alcohol: $[\alpha]_D^{26} = -85.5$ (*c* 0.42, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.26 (m, 10H), 5.23 (brd, *J* = 9.1 Hz, 1H), 5.10 (d, *J* = 12.3 Hz, 1H), 5.01 (brs, 1H), 4.90 (s, 1H), 4.85 (d, *J* = 12.3 Hz, 1H), 3.99 (brs, 1H), 3.96-3.89 (m, 3H), 3.68 (dt, *J* = 6.4 11.6 Hz, 1H), 2.21 (m, 1H), 1.94 (dd, *J* = 6.4 13.3 Hz, 1H), 1.45 (s, 9H), 1.39 (d, *J* = 5.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 159.7, 157.1, 152.8, 149.4, 136.2, 135.0, 128.7, 128.6, 128.4, 128.3, 128.2, 128.0, 91.2, 81.7, 76.3, 68.7, 67.5, 55.4, 54.0, 47.3, 28.8, 28.2, 20.5; HRMS (ESI, M+Na⁺) calcd for C₂₉H₃₆N₄O₈Na 591.2431 found 591.2417

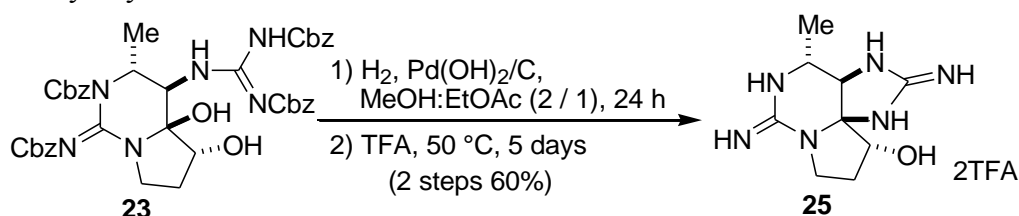
2) TFA (1 mL) was added to a solution of alcohol (83 g, 0.146 mmol) in CH₂Cl₂ (1 mL) at 0 °C. Stirring for 2 h at room temperature, the reaction mixture was

concentrated *in vacuo*. The resulting residue was dissolved in CH₂Cl₂ and desalinated with 2.0 M NaOH aq. and the mixture was extracted with EtOAc and washed 2.0 M NaOH aq. and brine. The aqueous layer was re-extracted with EtOAc and the combine organic layer was dried over MgSO₄, filtered and concentrated *in vacuo* to give crude amine (74 mg).

3) To the solution of the crude amine (74 mg), thiopseudourea **12** (58 mg, 0.161 mmol) and Et₃N (61 μL, 0.438 mmol) in DMF (1.5 mL) was added Mercury (II) chloride (44 mg, 0.161 mmol) at room temperature under an atmosphere of nitrogen. Stirring for 2 h, the reaction mixture was diluted with ethyl acetate, and filtered through a pad of celite. The filtrates were washed with H₂O and the resulting water layer was re-extracted with EtOAc. The combined organic layer was dried over MgSO₄, filtered and concentrated *in vacuo*. Resulting residue was purified by silica gel column chromatography (hexane/EtOAc; 4:1 to 2:1) to give bis-guanidine **23** (93 g, 2 steps 82%) as white solid.

Spectral data for **23**: $[\alpha]_D^{26} = -61.5$ (*c* 0.35, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 11.65 (s, 1H), 8.70 (d, *J* = 9.2 Hz, 1H), 7.33 (m, 20H), 6.52 (brs, 1H), 5.19-5.03 (m, 5H), 4.92 (d, *J* = 11.9 Hz, 1H), 4.83 (d, *J* = 12.4 Hz, 1H), 4.70 (d, *J* = 11.9 Hz, 1H), 4.39 (dd, *J* = 7.8, 9.2 Hz, 1H), 4.17 (quint, *J* = 6.4 Hz, 1H), 3.96 (m, 2H), 3.67 (dt, *J* = 6.0, 11.5 Hz, 1H), 2.28 (m, 1H), 1.94 (dd, *J* = 6.0, 12.8 Hz, 1H), 1.34 (d, *J* = 6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 162.5, 159.7, 156.1, 153.4, 152.6, 149.0, 136.1, 136.0, 134.0, 129.0, 128.9, 128.73, 128.70, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 91.2, 76.0, 68.8, 68.7, 67.44, 67.38, 56.1, 54.5, 47.1, 28.6, 20.4; HRMS (ESI, M+Na⁺) calcd for C₄₁H₄₂N₆O₁₀Na 801.2860 found 801.2844

Decarbamoyloxysaxitoxinol **25**



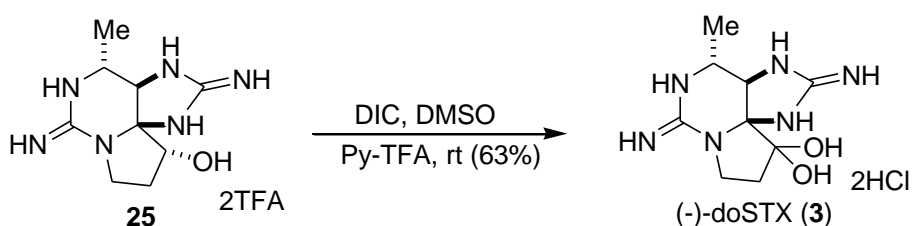
1) To a solution of bis-guanidine **23** (37 mg, 0.048 mmol) in mixed solvent of

methanol and EtOAc 2/1 (3 mL) was added catalytic amount of Pd(OH)₂/C and stirred for 24 h under an atmosphere of hydrogen. Then the reaction mixture was filtered through a pad of celite and the filtrates were concentrated *in vacuo* to give deprotected bis-guanidinechloride (15 mg).

2) A solution of crude bis-guanidine (15 mg) in 1 mL of TFA was warmed up to 50 °C and stirring for 5 days. The reaction mixture was then concentrated *in vacuo*. The resulting residue was dissolved in methanol and the desalinated with anion exchange resin (Amberlyst A-26(OH)). The solution was filtered and the filtrates were purified by cation column chromatography (Amberlite IRC-50) (H₂O/AcOH; 100:1 to H₂O/ TFA; 100:10) to give doSTXol as 2TFA salt (12 mg, 2 steps 60%).

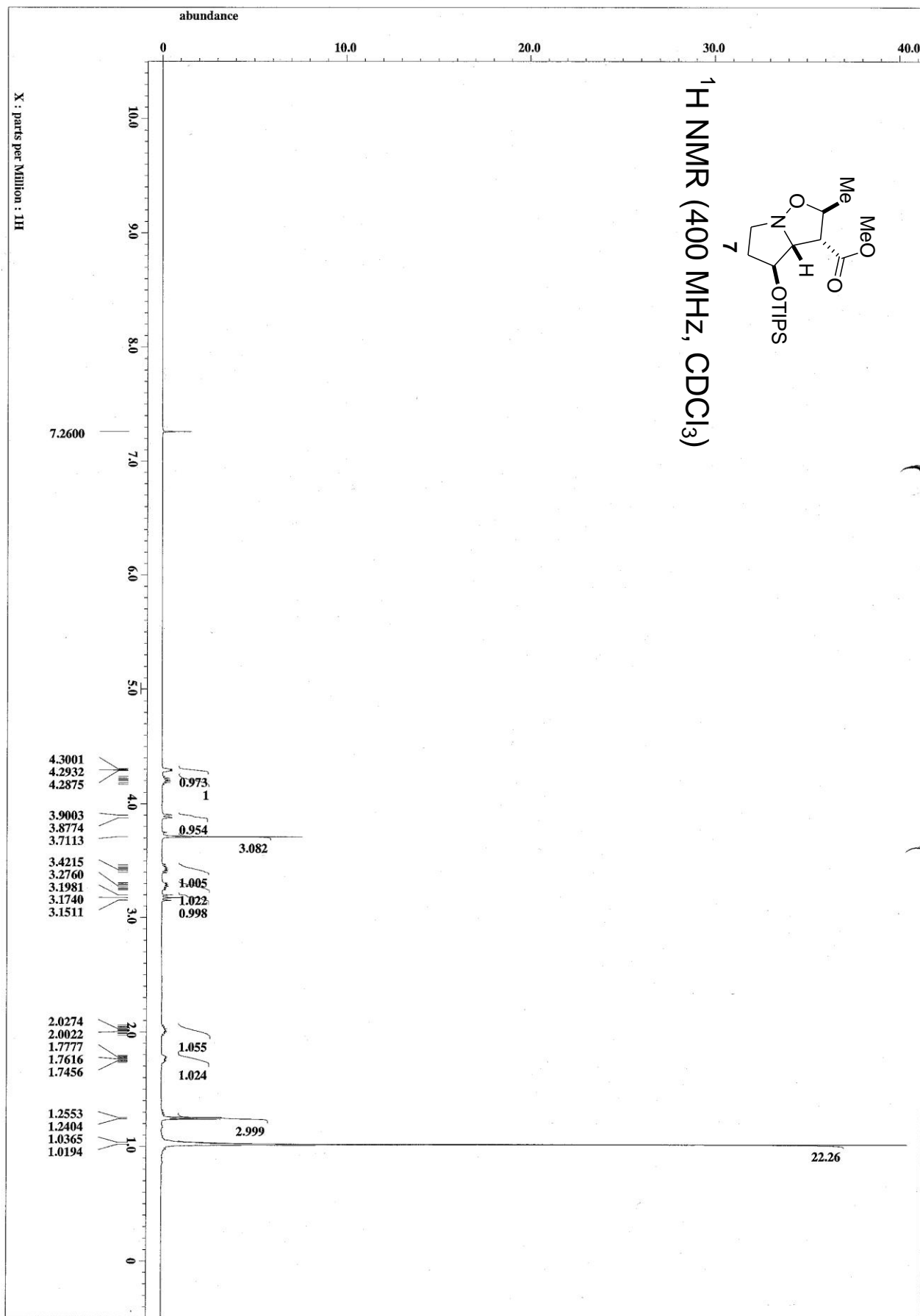
Spectral data for **25**: [α]_D²⁰ = -52.8 (*c* 0.43, MeOH); ¹H NMR (400 MHz, D₂O) δ 4.44 (d, *J* = 2.3 Hz, 1H), 4.26 (d, *J* = 3.7 Hz, 1H), 3.68 (dt, *J* = 2.3, 10.5 Hz, 1H), 3.65-3.57 (m, 2H), 2.35 (m, 1H), 2.16 (ddd, *J* = 1.4, 7.8, 14.7 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (100 MHz, CD₃OD) δ 158.8, 157.1, 84.6, 75.2, 61.3, 51.0, 44.8, 29.9, 18.8; HRMS (ESI, M+H⁺) calcd for C₉H₁₇N₆O₁ 225.1464 found 225.1487

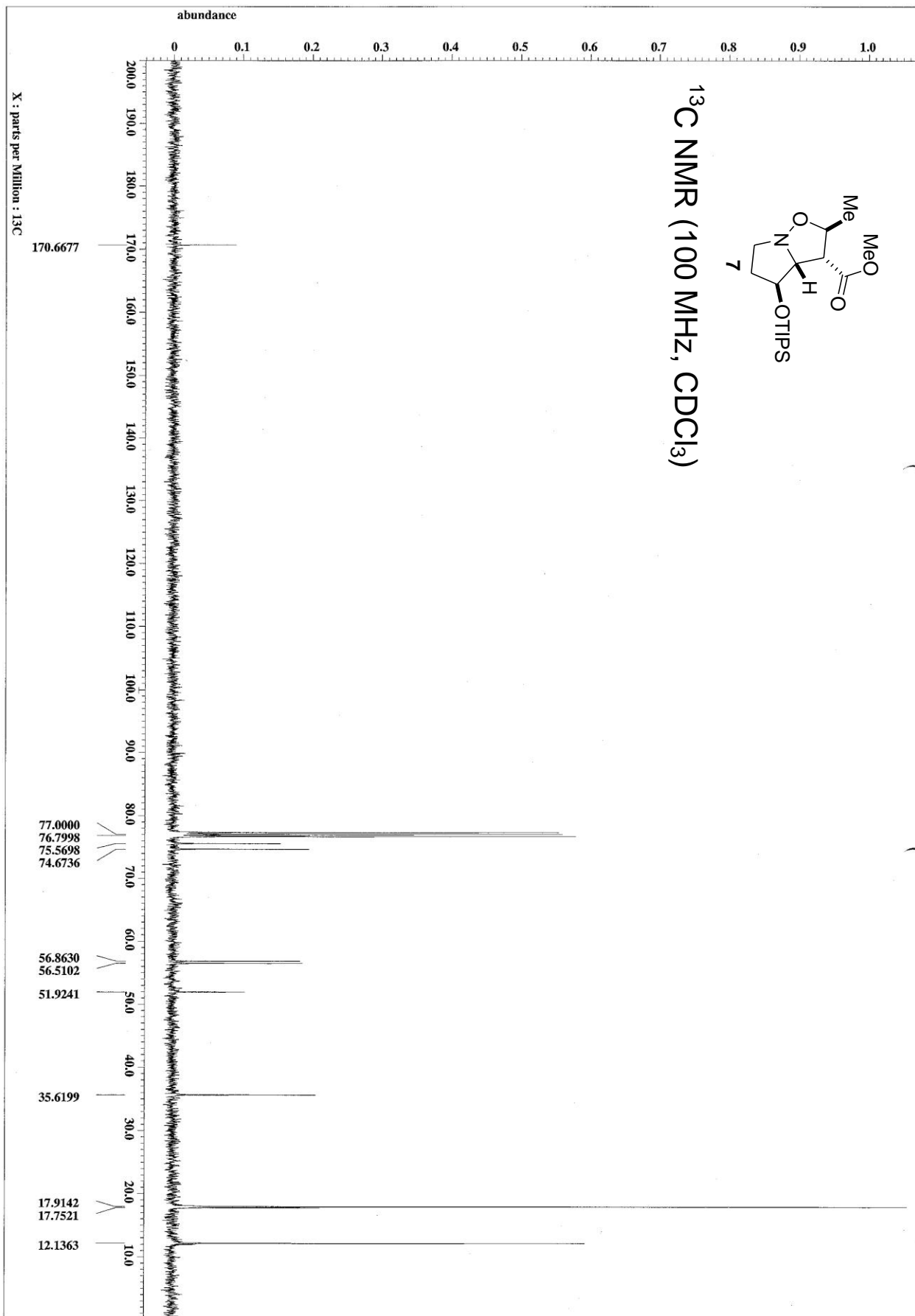
(-)-doSTX (**3**)



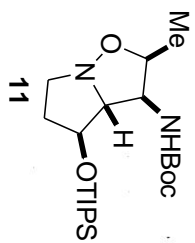
to a solution of doSTXol (**25**) (42 mg, 0.081 mmol) and pyridinium trifluoroacetate (63 mg, 0.325 mmol) in DMSO (800 μ L) was added DIC (101 μ L, 0.651 mmol) at room temperature. Stirring for 12 h, the reaction mixture was diluted with CH₂Cl₂ and extracted with H₂O twice. The combined aqueous layer was concentrated *in vacuo*. The resulting residue was purified by ion exchange column chromatography (Dowex 50 WX4-200; a sulfonic acid supported gel was used.) (H₂O/TFA; 100:5 to 6 N HCl aq.) to give (-)-doSTX (**3**) hydrochloride (20 mg, 63%)

Spectral data for **3**: $[\alpha]_D^{20} = -23.3$ (*c* 0.19, MeOH); ^1H NMR (400 MHz, D_2O) δ 4.46 (d, $J = 1.8$ Hz, 1H), 3.76 (dt, $J = 2.3, 10.7$ Hz, 1H), 3.65 (dq, $J = 1.8, 6.9$ Hz, 1H), 3.55 (m, 1H), 2.36 (m, 1H), 1.24 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, 4% CD_3COOD in D_2O , determined by HMBC) δ 159.0, 157.5, 100.3, 84.2, 61.2, 51.9, 44.6, 34.4, 19.7 ; HRMS (ESI, $\text{M}+\text{H}^+$) calcd for $\text{C}_9\text{H}_{17}\text{N}_6\text{O}_2$ 241.1413 found 241.1452

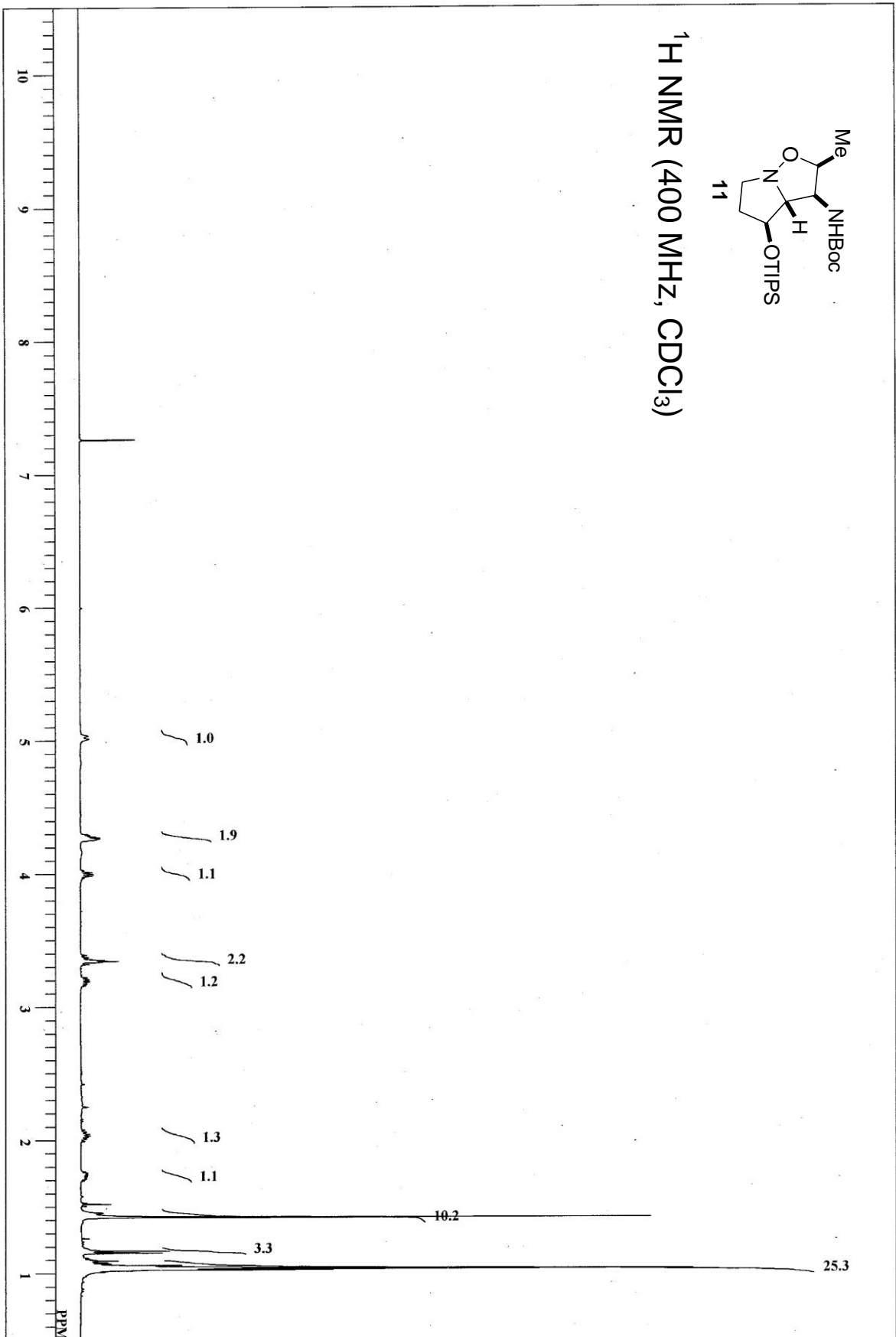




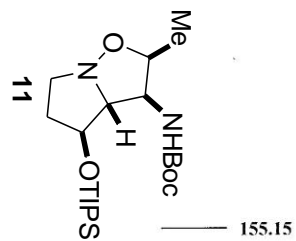
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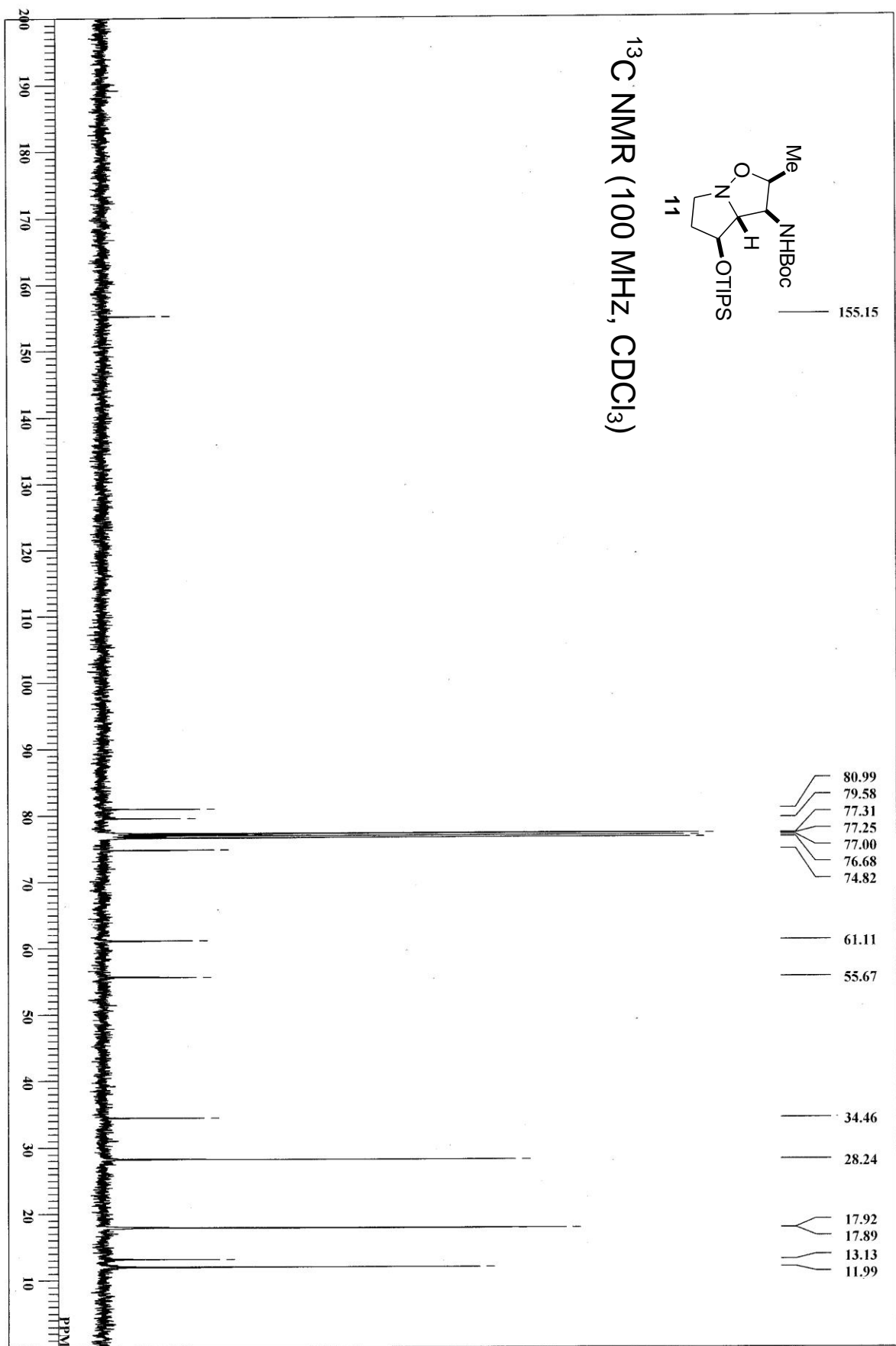
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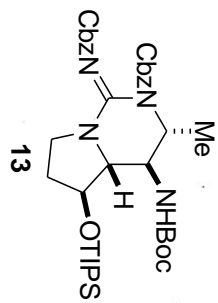
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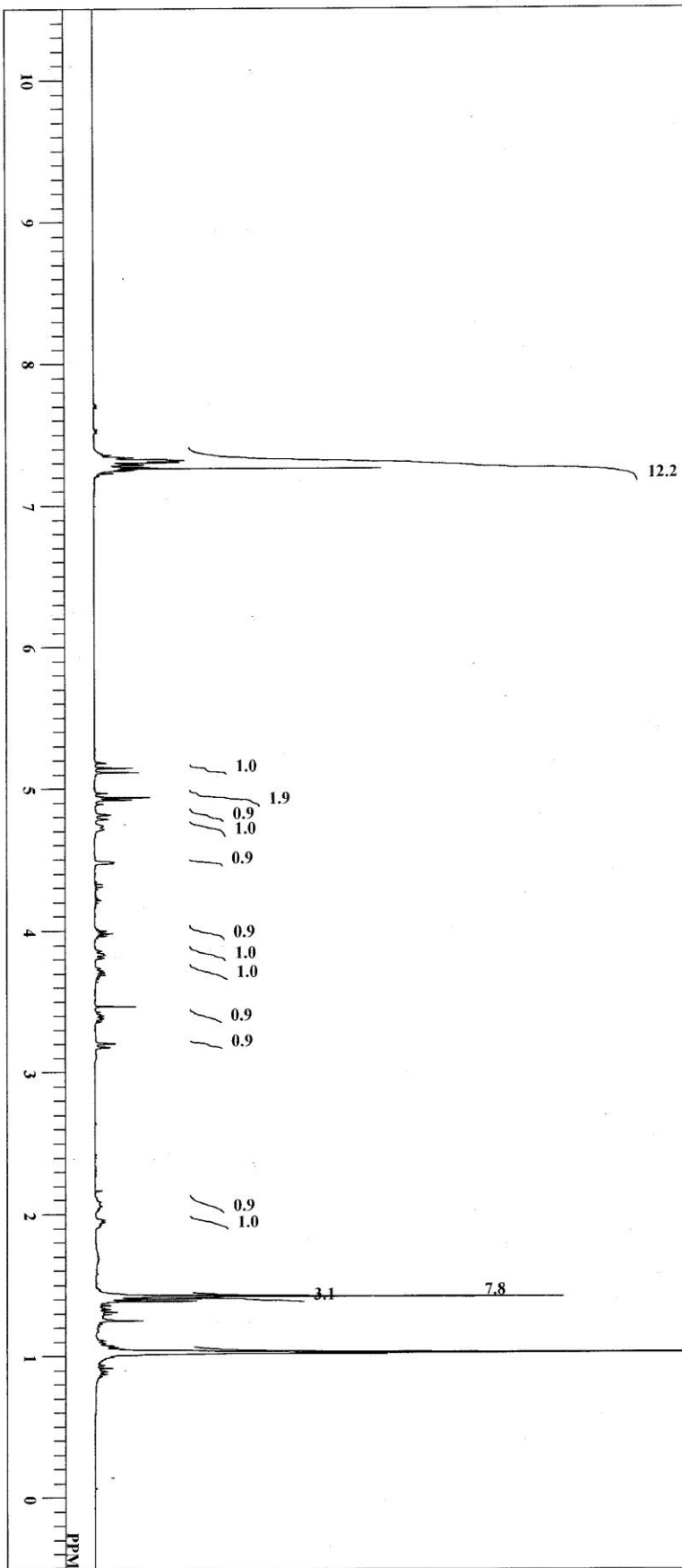
^{13}C NMR (100 MHz, CDCl_3)



single_pulse

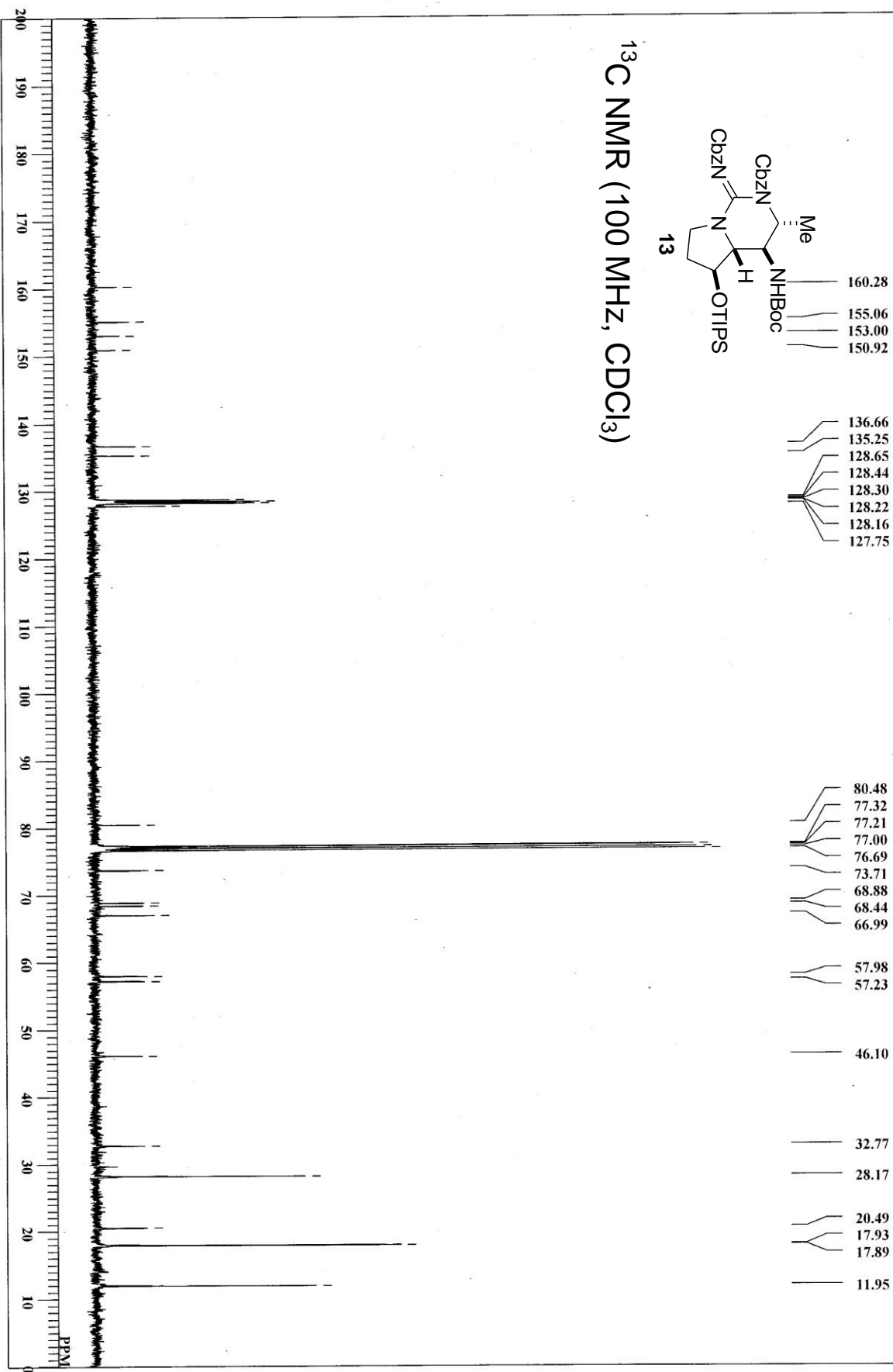
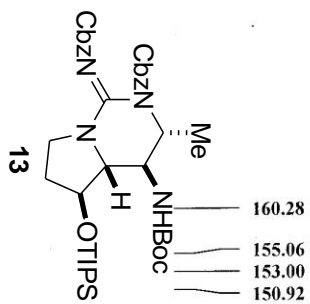


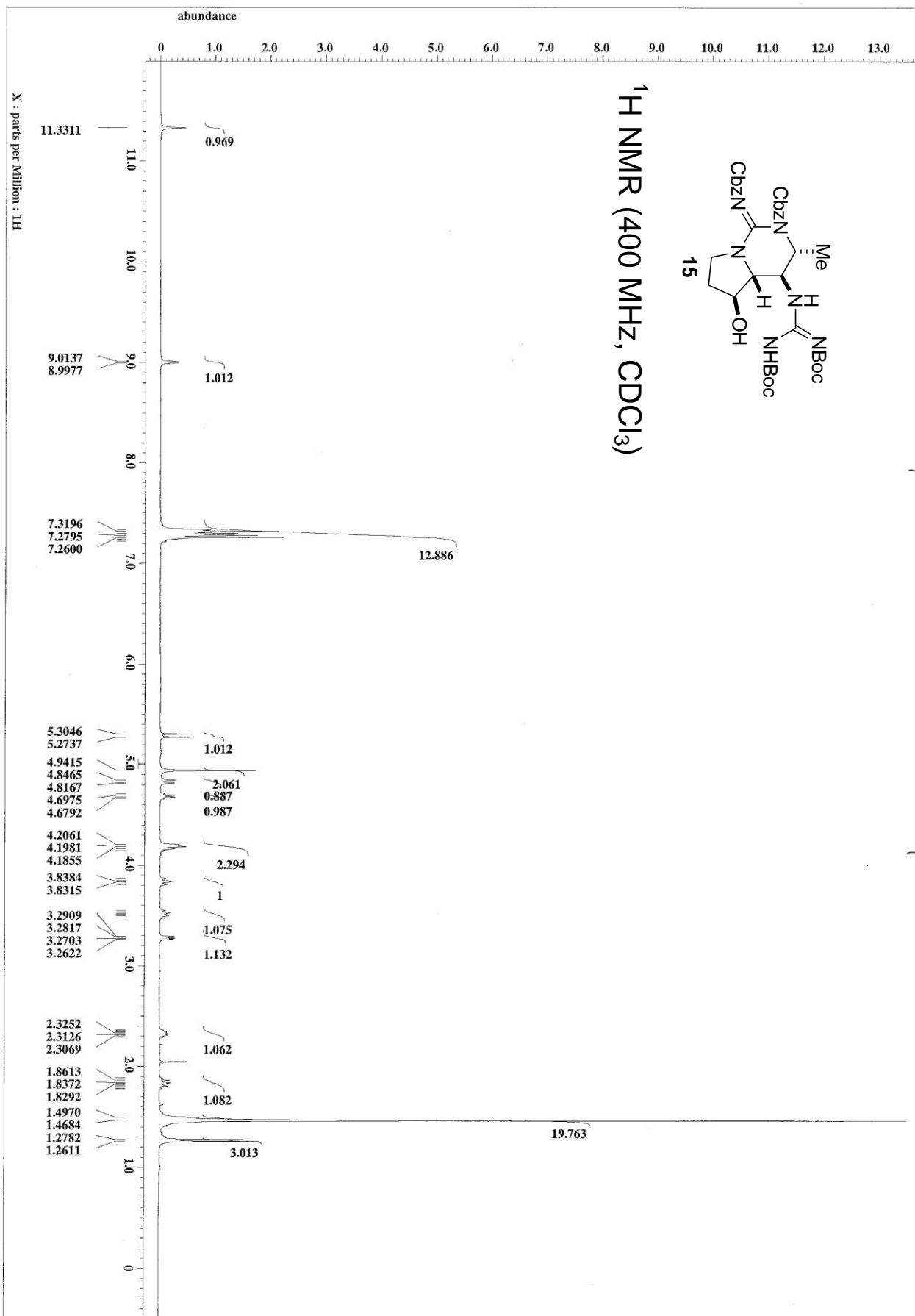
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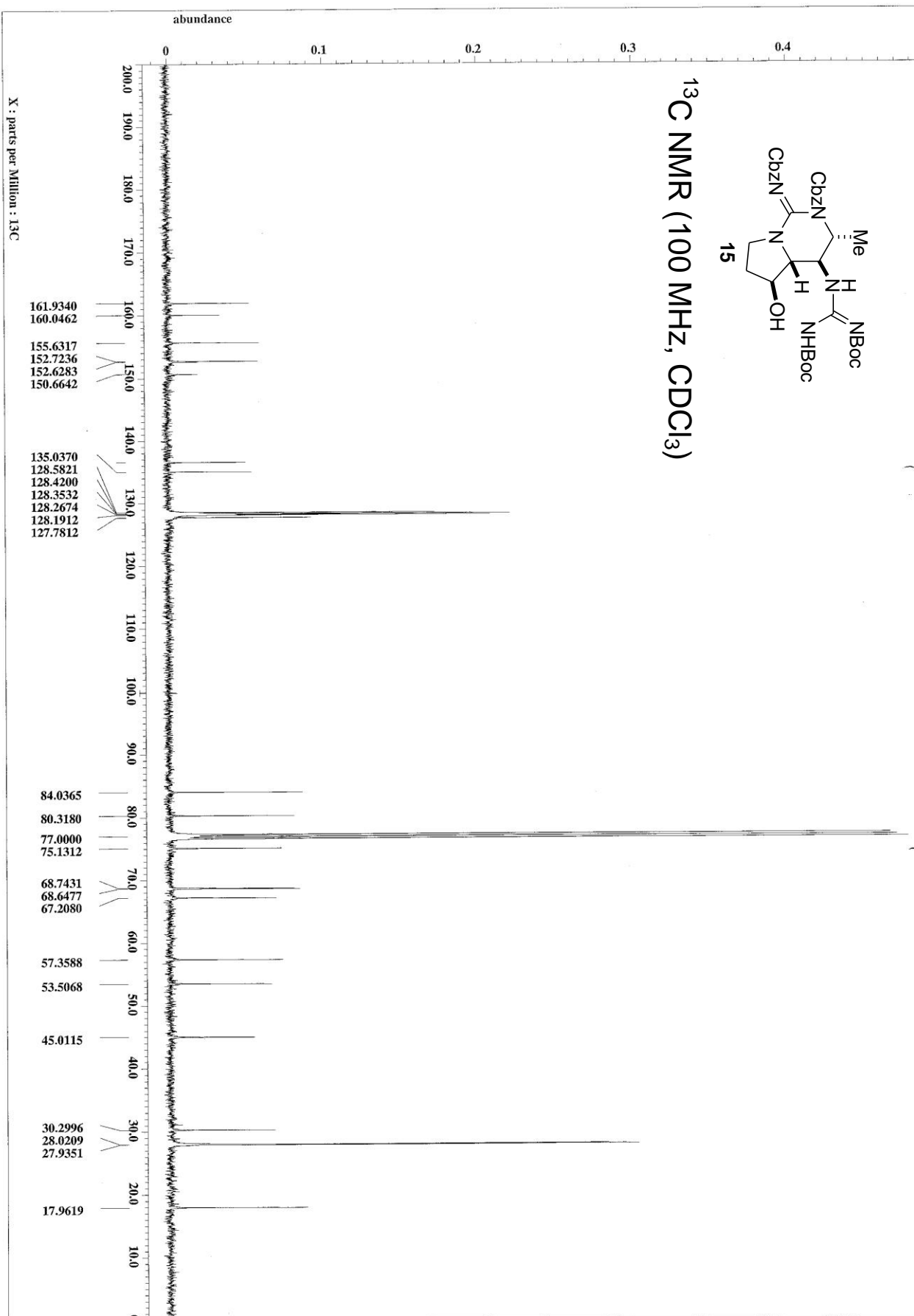


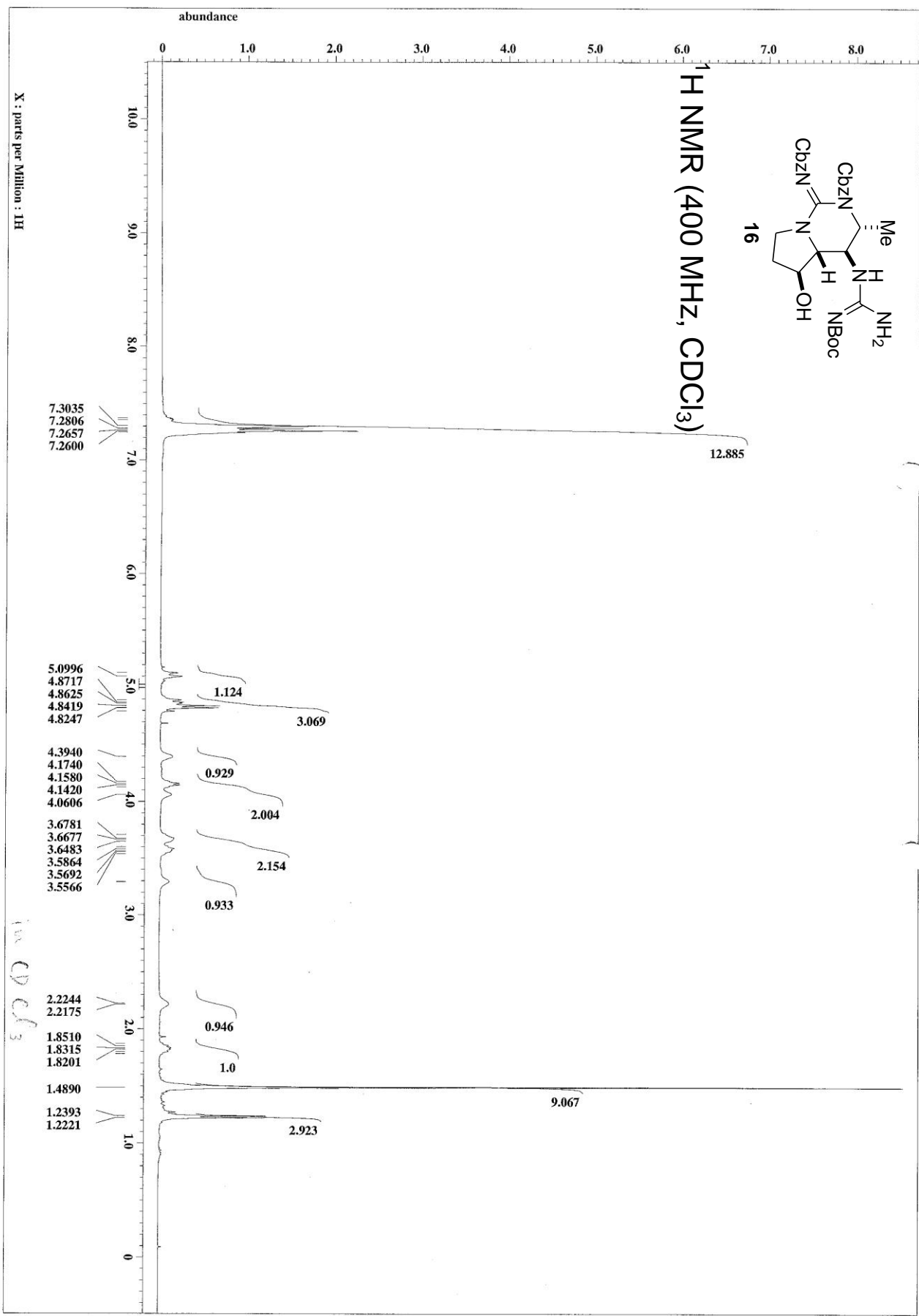
single pulse decoupled gated NOE

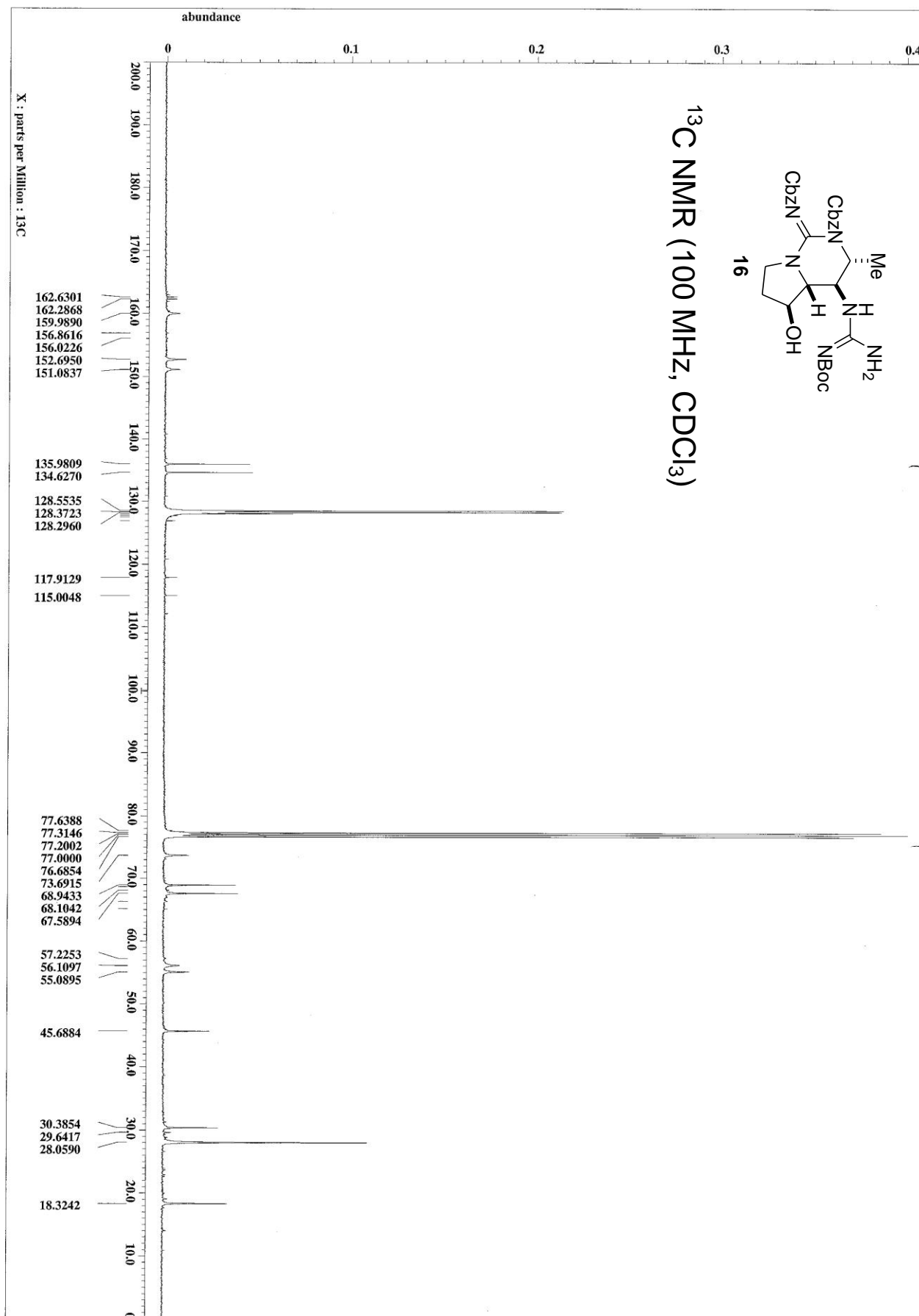
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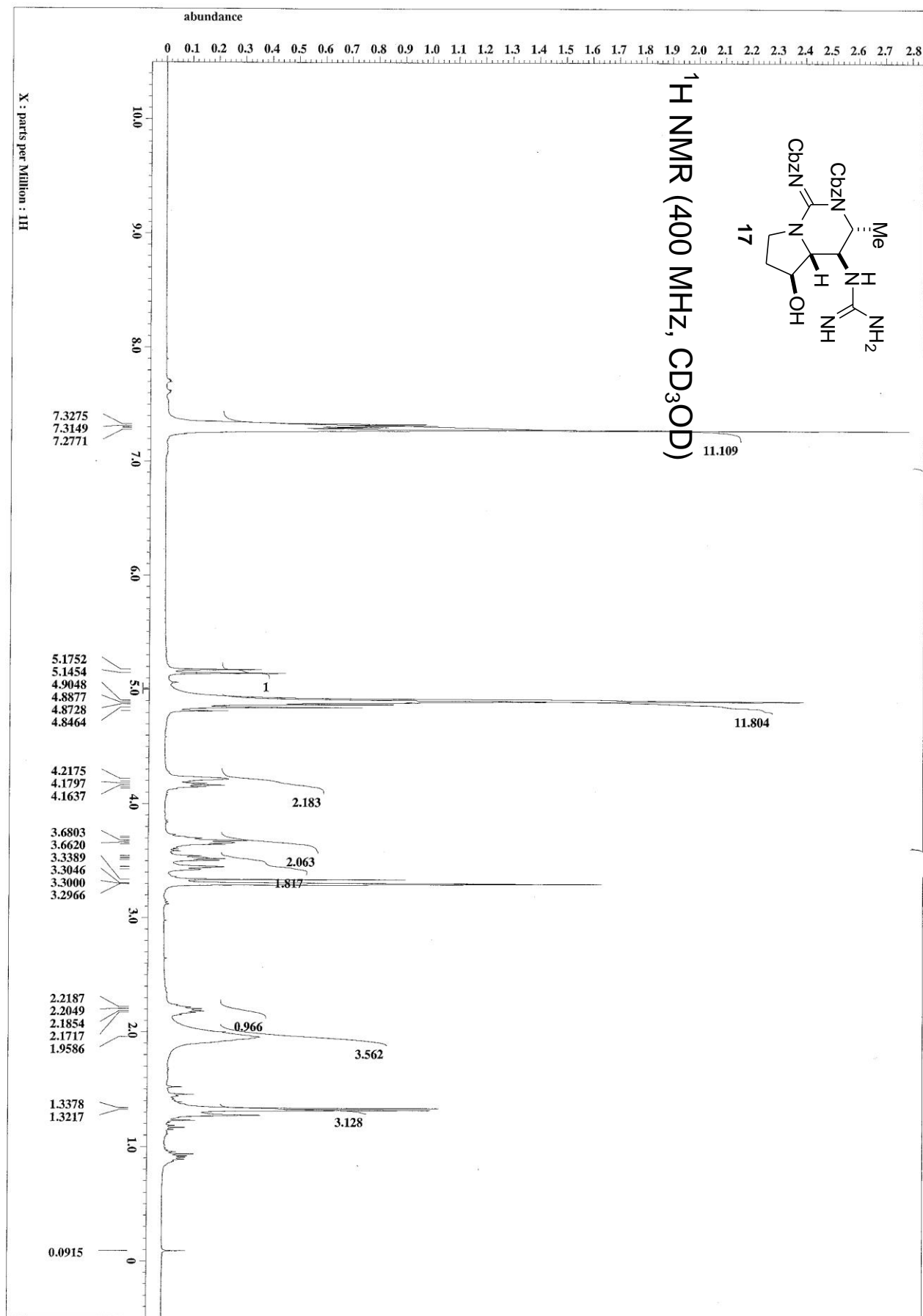




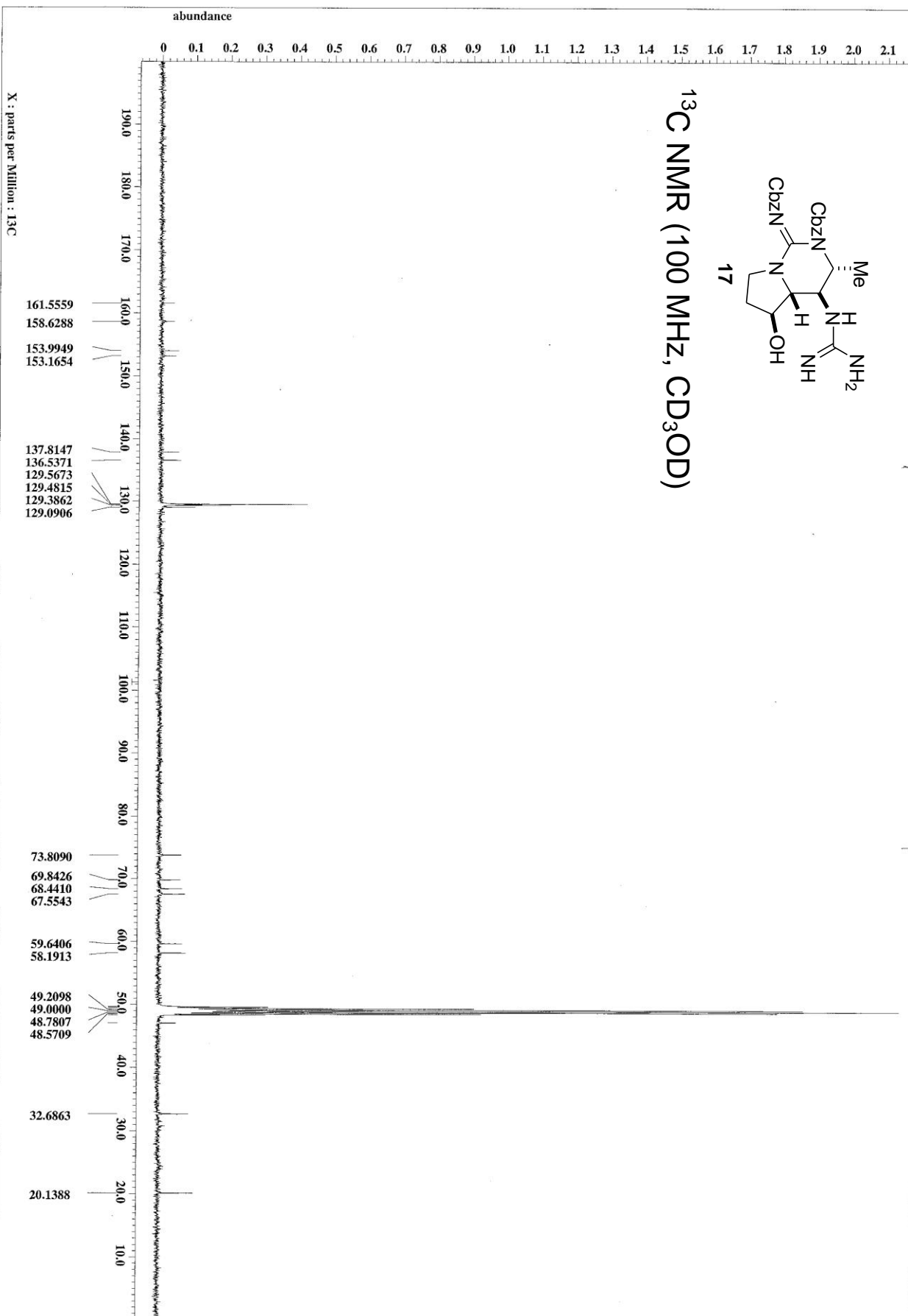
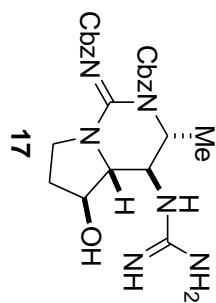


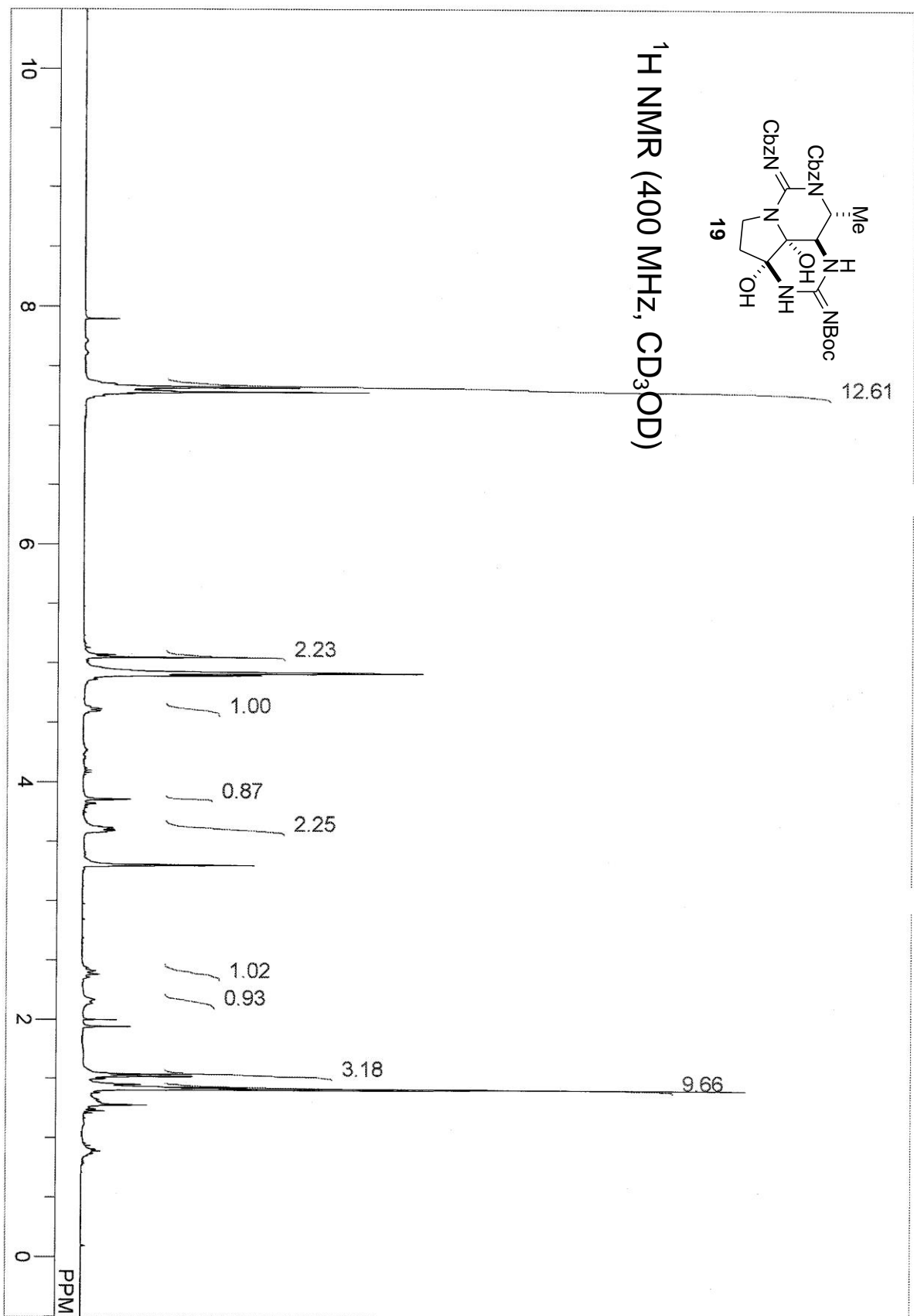


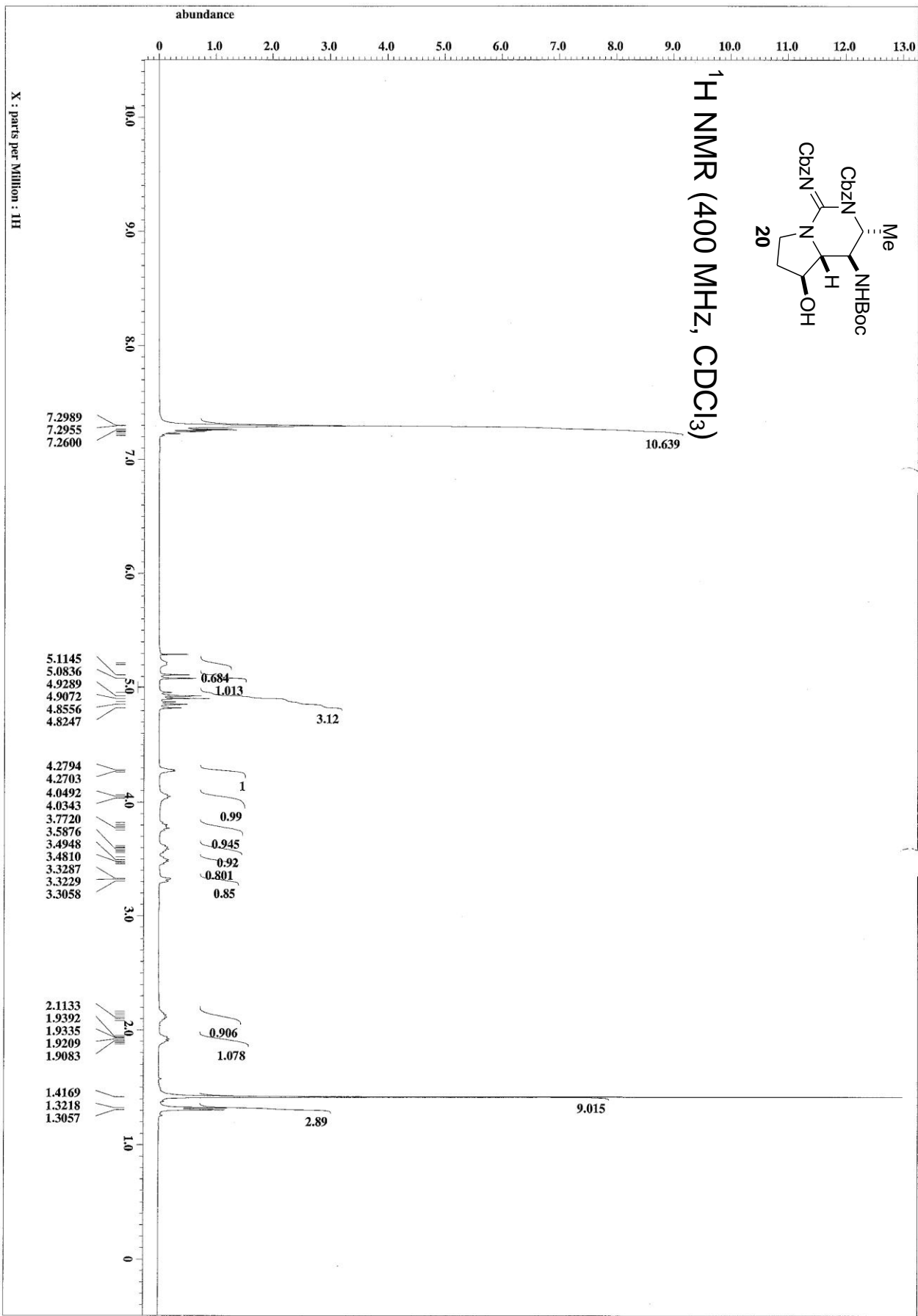


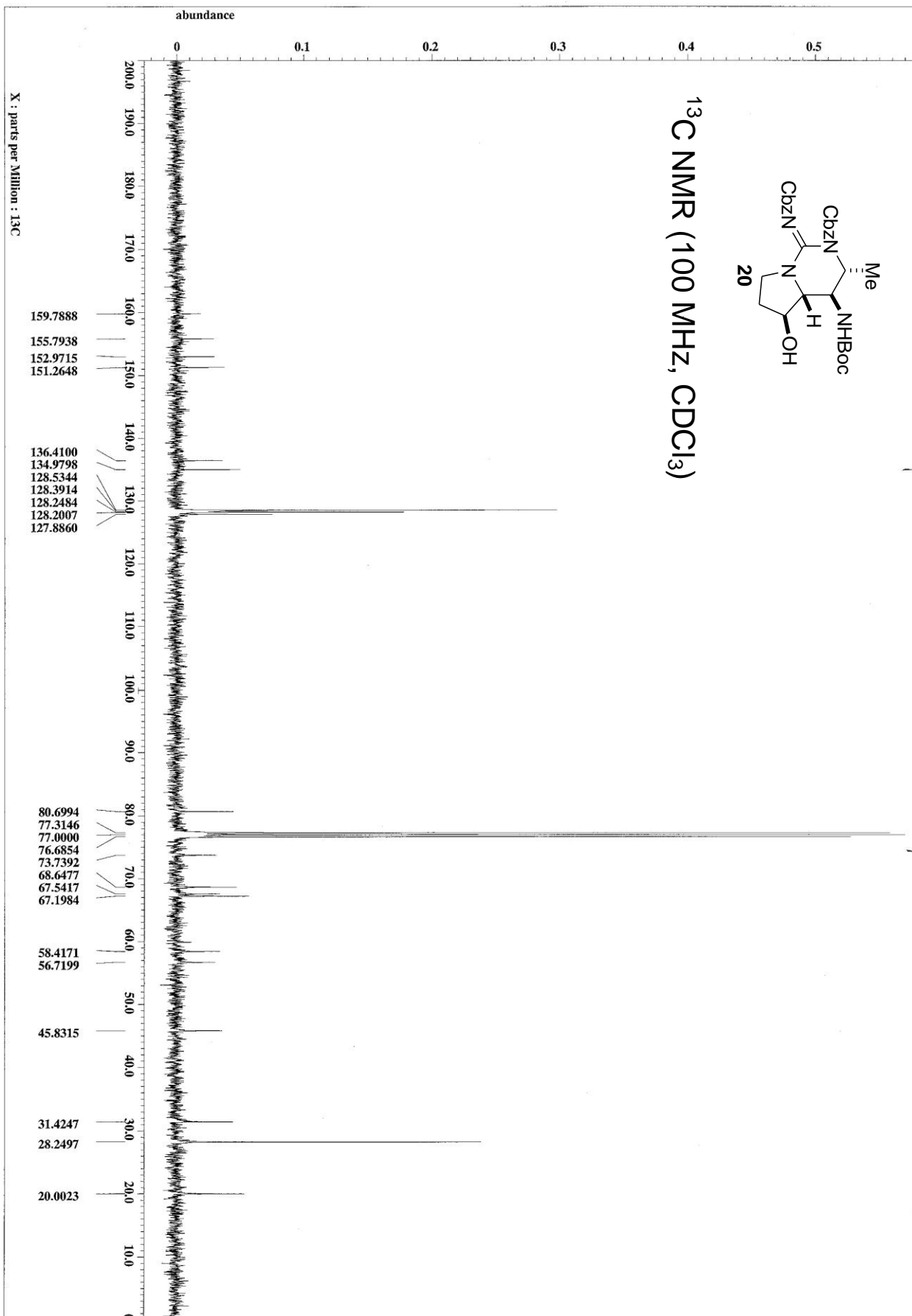


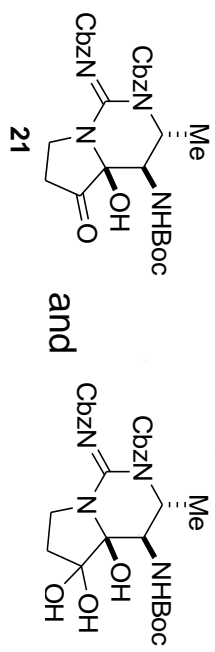
¹³C NMR (100 MHz, CD₃OD)



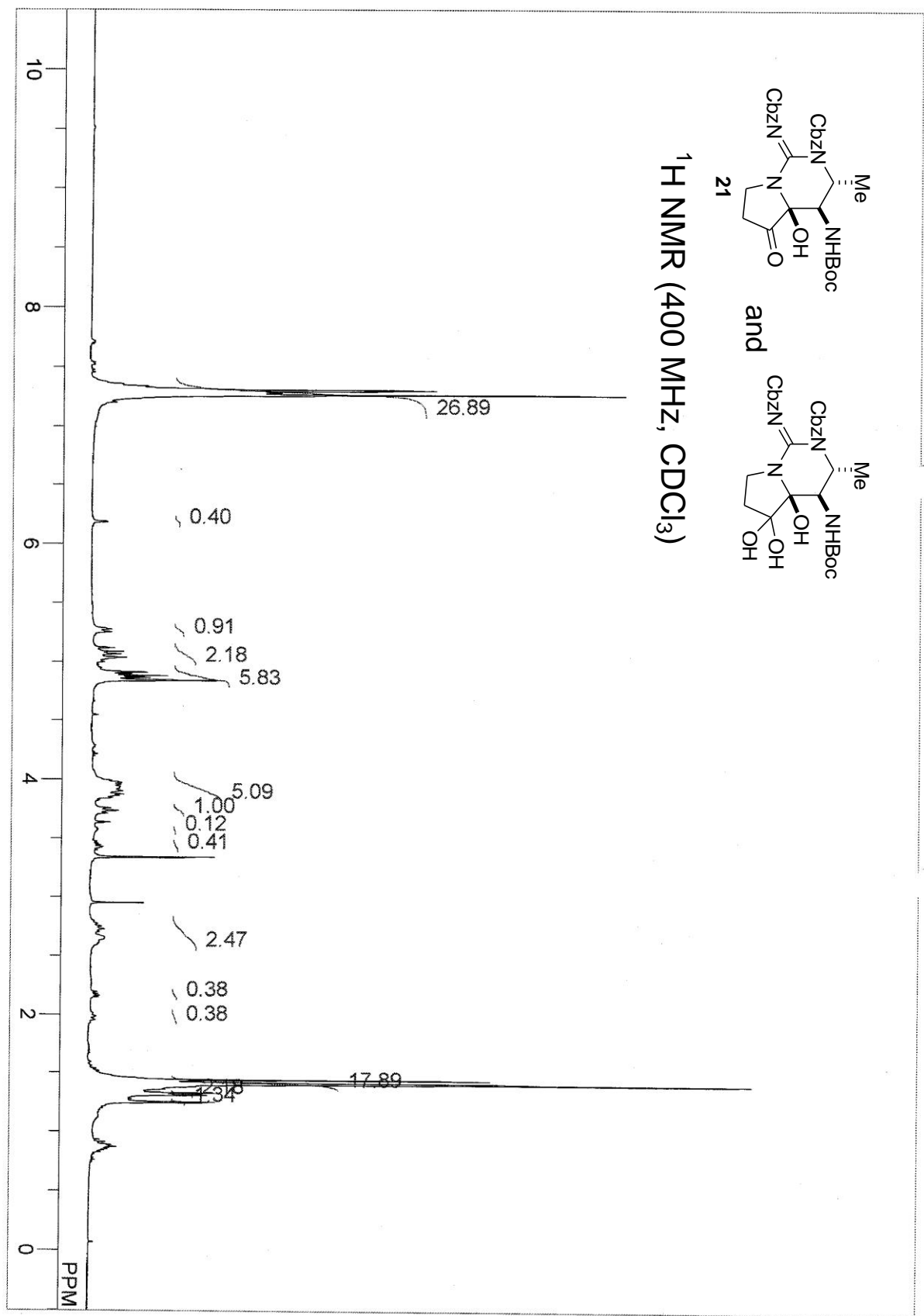




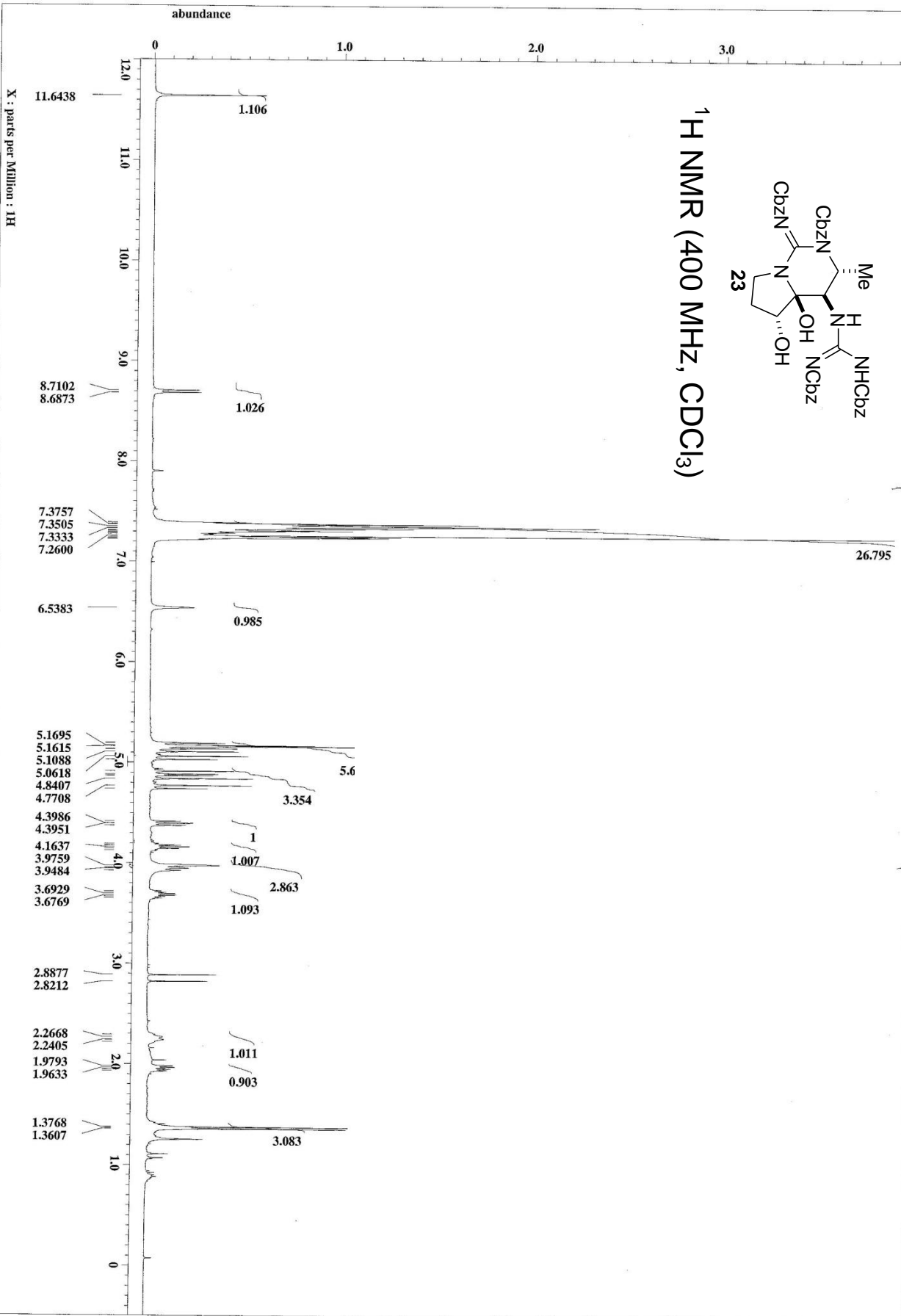
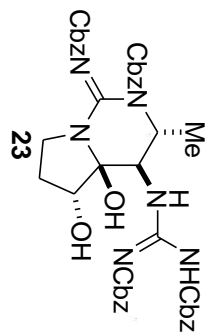




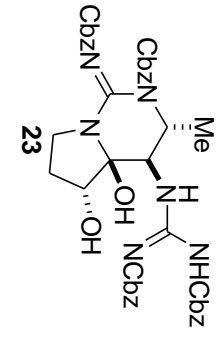
¹H NMR (400 MHz, CDCl₃)



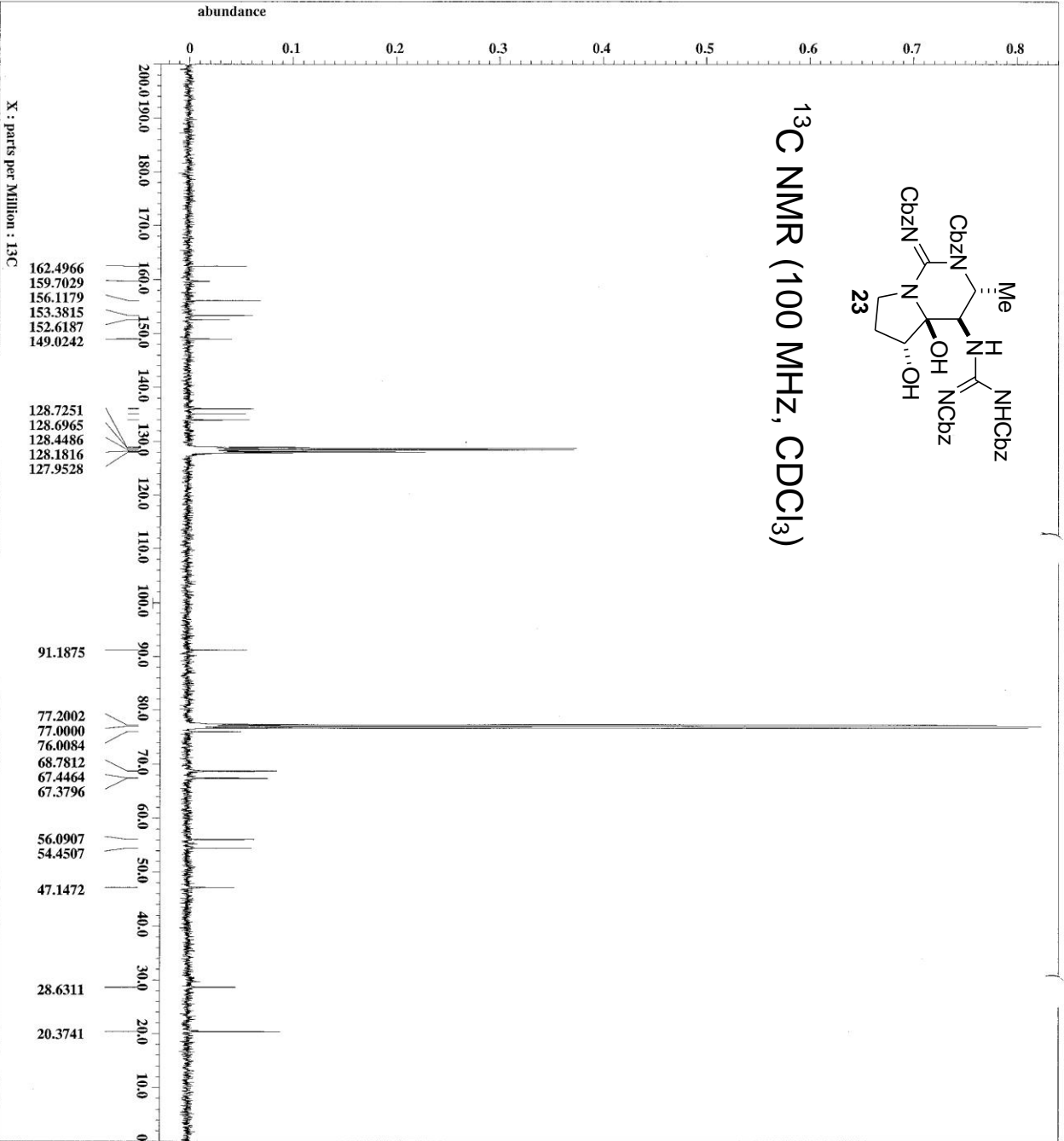
¹H NMR (400 MHz, CDCl₃)



1923A2



¹³C NMR (100 MHz, CDCl₃)



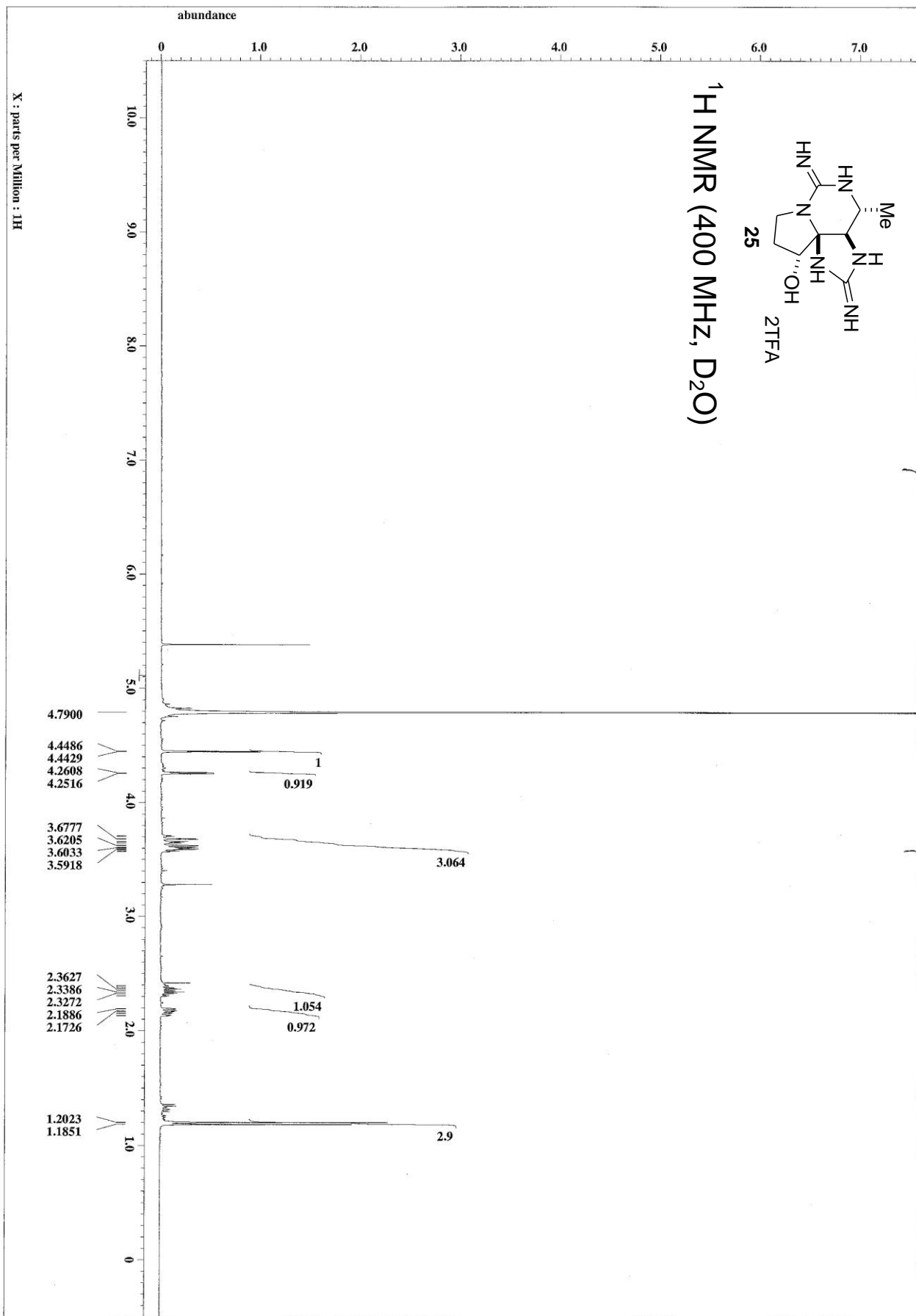
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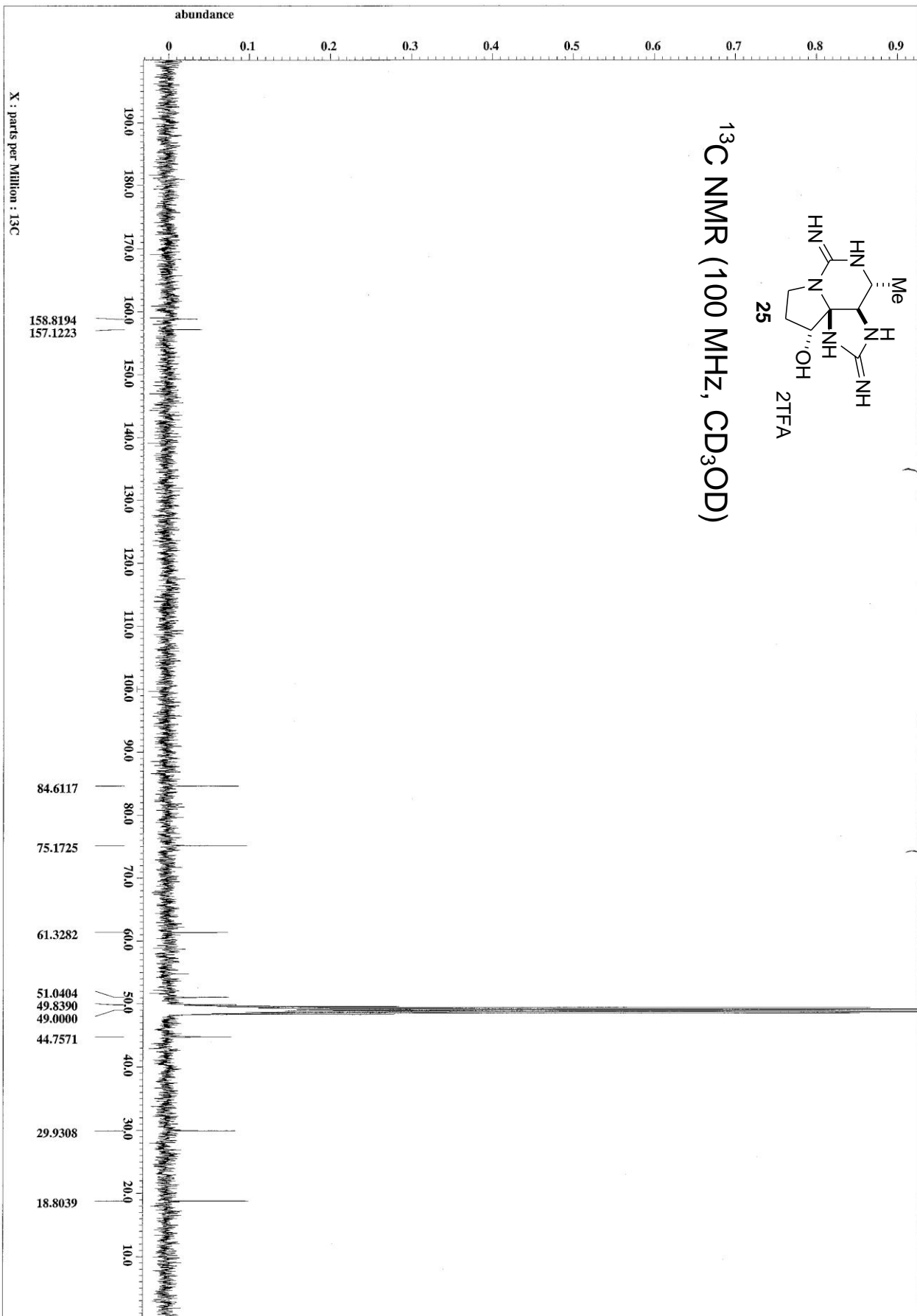
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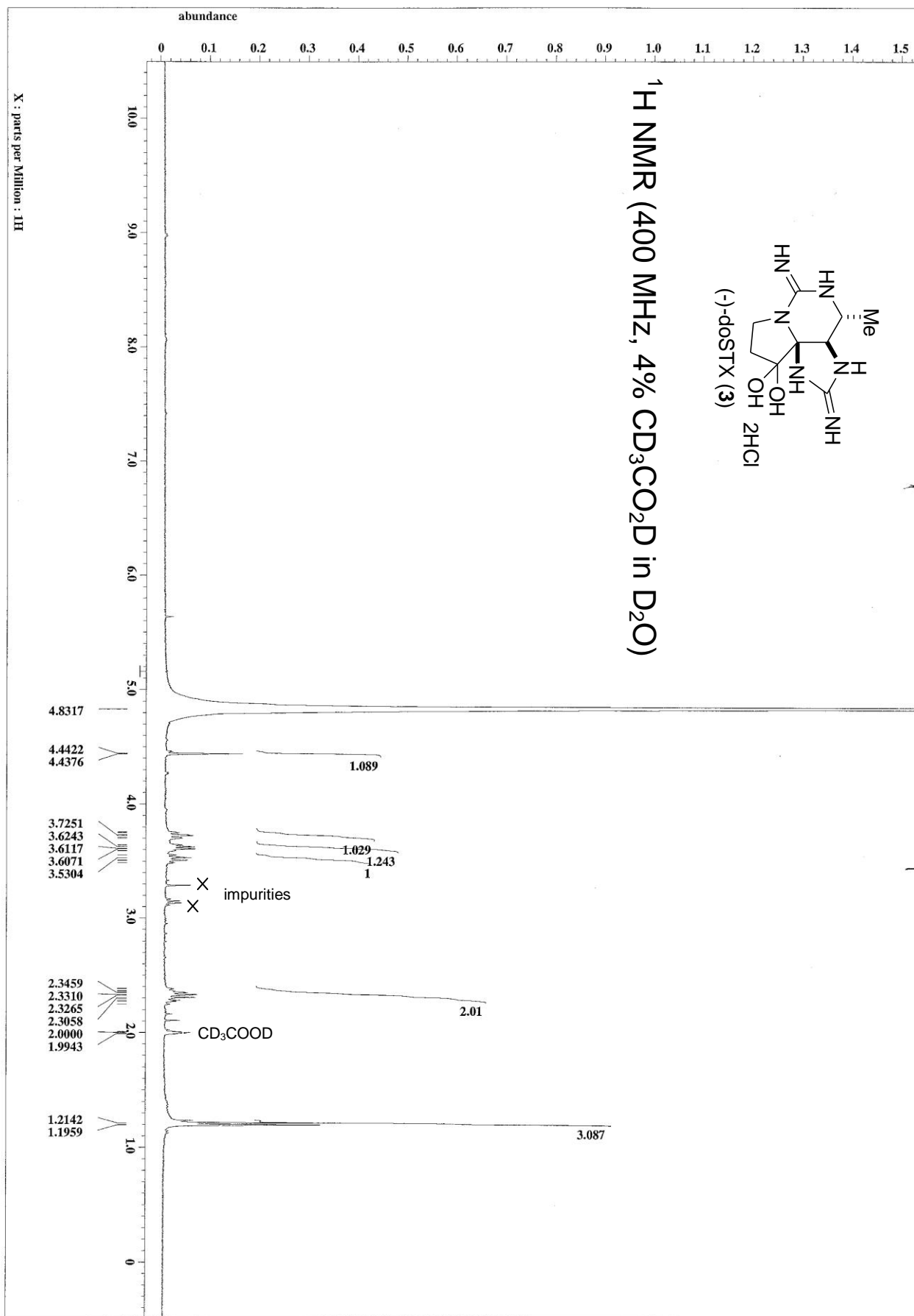
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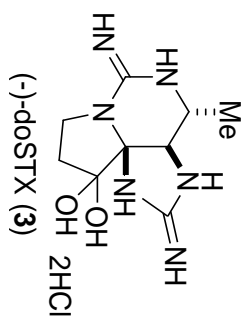
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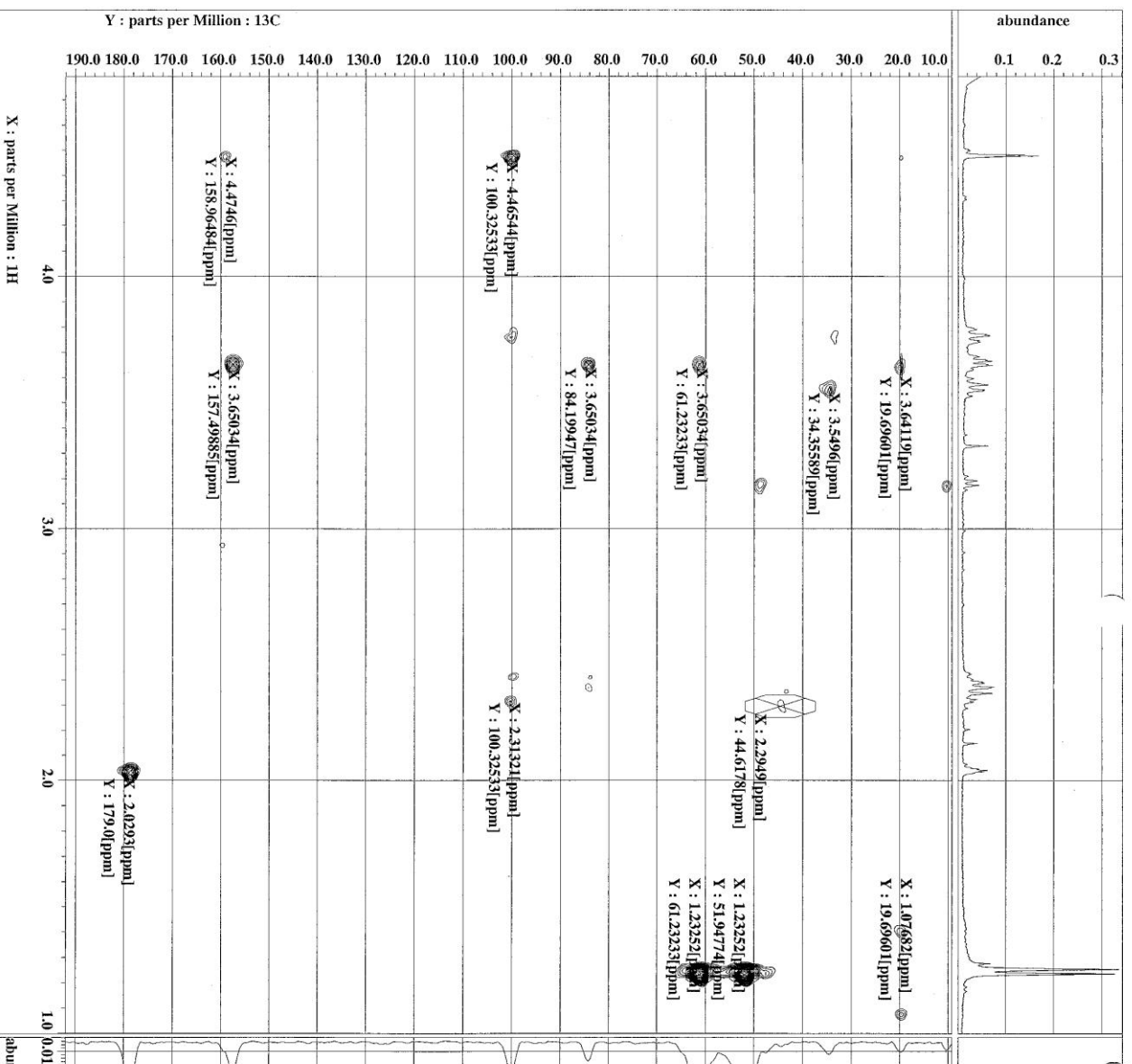




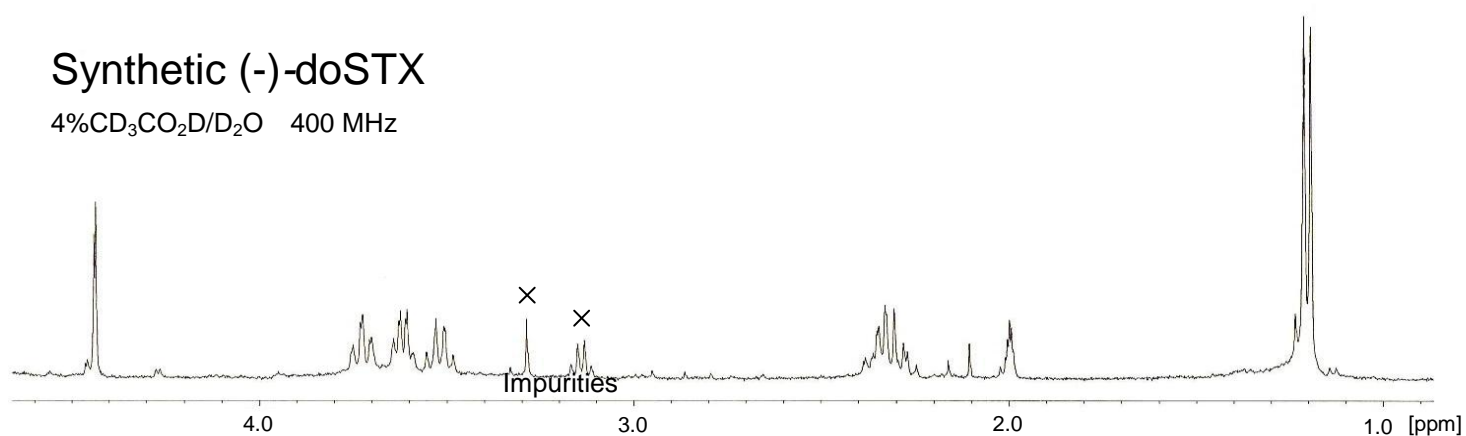
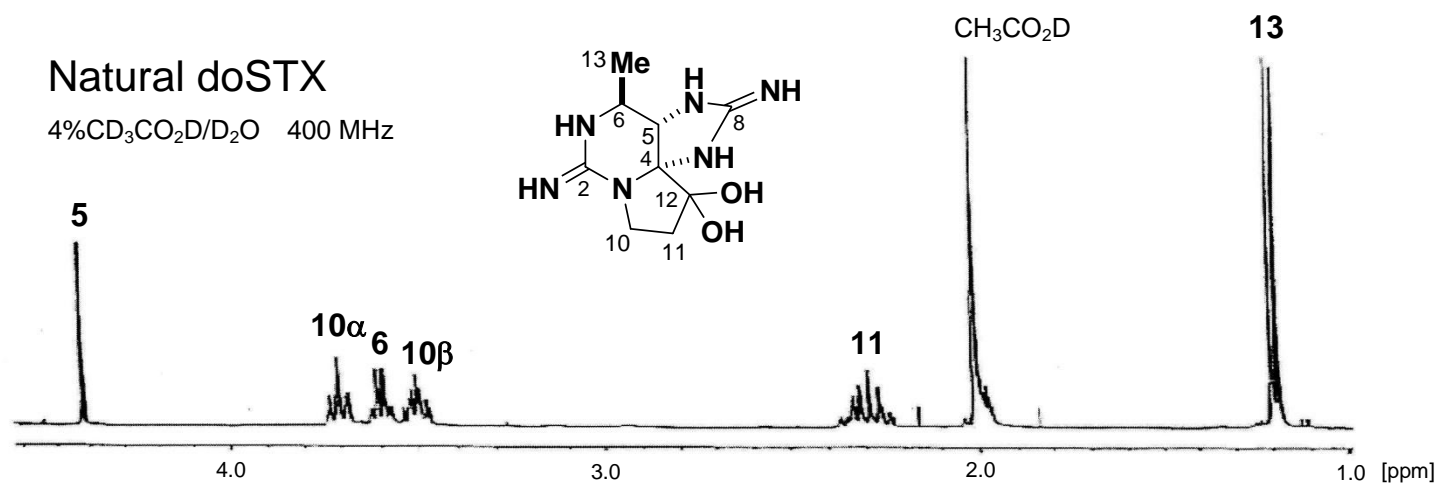




¹H - ¹³C HMBBC
(400 MHz, 4% CD₃CO₂D in D₂O)



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Position	Natural	Synthetic
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5	61.3	61.2
6	51.9	51.9
8	159.5	159.0

10	44.2	44.6
11	Not reported	34.4
12	100.2	100.3
13	19.8	19.7

¹³C NMR spectrum [ppm]

X ray crystallographic analysis data for **19** and **23**

CCDC-655367 (**19**) and CDCC-653880 (**23**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

The crystallographic structures of **19** and **23** were shown below.

