Angewandte
Eine Zeitschrift der Gesellschaft Deutscher Chemiker
Chemie

Supporting Information

Total Synthesis of 11-Saxitoxinethanoic Acid and Evaluation of its Inhibitory Activity on Voltage-Gated Sodium Channels

*Chao Wang, Mana Oki, Toru Nishikawa, Daisuke Harada, Mari Yotsu-Yamashita, and Kazuo Nagasawa**

anie_201604155_sm_miscellaneous_information.pdf

Supporting Information

Table of contents

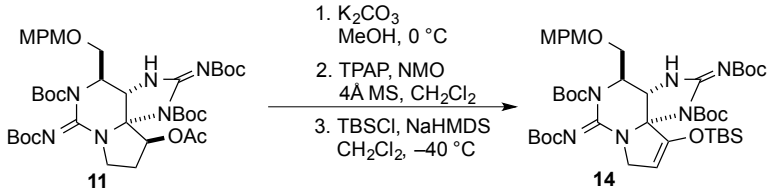
1. General S2
2. Experimental Procedures for **S2**-**S8**, **7**-**9**, **14**-**17**, **19**-**25** S3
   - Synthesis of silyl enol ether **14** S3
   - Synthesis of Mukaiyama aldol condensation adduct **15** S4
   - Synthesis of Mukaiyama aldol condensation adduct **16a-f** S5
   - Synthesis of **17** S8
   - Synthesis of silyl enol ether **19** S8
   - Synthesis of **20** S16
   - Synthesis of **21** S16
   - Synthesis of **22** S17
   - Synthesis of **23** S18
   - Synthesis of **7**, **8**, **9** S19
   - Synthesis of **25** S22
   - Reference: S24
3. Copies of NMR spectra of intermediates for **S2**-**S8**, **7**-**9**, **14**-**17**, **19**-**25** S24
   - Precise assignment of **7** S65
   - Spectral data for synthetic and natural SEA (**7**) S67
   - HPLC data of the SEA (**7**) S68
   - Precise assignment of **8** S70
   - Precise assignment of **9** S73

1. General

Flash chromatography was performed on Silica gel 60 (spherical, particle size 40~100 μm; Kanto), Chromatorex NH (particle size 75~150 μm; Fuji Silysia). Optical rotations were measured on a JASCO P-2200 polarimeter, using the sodium D line. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-ECX 300 or 400. The spectra are referenced internally according to residual solvent signals of $CDCl_3$ (^{1}H NMR; δ = 7.26 ppm, ^{13}C NMR; δ = 77.16 ppm), D_2O (^{1}H NMR; δ = 4.80 ppm). For compounds **7**, **8**, **9** and **25**, 1,4-dioxane was used as internal standard, which is referenced at 3.75 ppm (^{1}H NMR) and 67.4 ppm (^{13}C NMR), respectively. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; 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 a JEOL JMS-T100X spectrometer with ESI-MS mode using methanol or methanol/H_2O as solvent.

2. Experimental Procedures for S2-S8, 7-9, 14-17, 19-25

Synthesis of silyl enol ether 14:



To a solution of protected STXol **11** (100 mg, 0.125 mmol) in methanol (2 mL) was added K_2CO_3 (35 mg, 0.25 mmol) at 0 °C. After stirring for 15 min, the reaction was diluted with EtOAc (5 mL) and H_2O (5 mL), and extracted with EtOAc (5 mL) three times. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give alcohol, which was used without further purification.

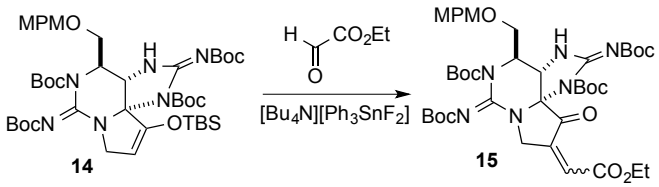
To a solution of the alcohol in CH_2Cl_2 (2 mL) was added NMO (59 mg, 0.5 mmol) and 4Å MS (63 mg) at 0 °C. After stirring for 10 min, TPAP (5 mg, 0.0125 mmol) was added, and the reaction mixture was stirred for another 1 h at room temperature. Then, reaction mixture was diluted with hexane/EtOAc (1:1) (2 mL) and filtered through a pad of neutral silica gel, and then, washed with hexane/EtOAc (1:1) (10 mL). The filtrates were concentrated *in vacuo* to give ketone.

To a solution of the ketone in CH_2Cl_2 (1 mL) was added NaHMDS (0.33 mL, 0.63 mmol) under Ar atmosphere at –40 °C. After stirring for 10 min, TBSCl (75 mg, 0.5 mmol) was added and the reaction mixture was stirred overnight at –40 °C. Then, the reaction was quencher with H_2O (2 mL) and warmed to room temperature and extracted with CH_2Cl_2 (3 mL) three times. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by neutral silica gel column chromatography (hexane/EtOAc; 5:1 to 3:1) to give silyl enol ether **14** (87 mg, 80% three steps).

Spectral data for **14**: $[\alpha]^{25}_{D}$ = +19.9 (*c* 1.4 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.3 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 4.82 (t, *J* = 4.1 Hz, 1H), 4.58-4.54 (m, 2H), 4.33 (s, 2H), 4.09 (d, *J* = 14.8 Hz, 1H), 3.80 (s, 3H), 3.73-3.69 (m, 1H), 3.64-3.58 (m, 1H), 3.51 (d, J = 15.1 Hz, 1H), 1.51 (s, 9H), 1.45 (s, 18H), 1.44 (s,

9H), 0.87 (s, 9H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 159.1, 151.0, 150.7, 149.1, 146.5, 146.2, 129.9, 129.7, 113.4, 98.5, 84.9, 83.9, 82.8, 81.2, 79.2, 77.4, 73.2, 70.9, 58.8, 55.2, 52.4, 28.2, 28.1, 28.0, 27.8, 25.3, 17.8, -4.7, -5.2; HRMS (ESI, M+Na)$^+$ calcd for $C_{43}H_{68}N_6O_{11}SiNa$ 895.4613 found 895.4579.

Synthesis of Mukaiyama aldol condensation adduct 15:

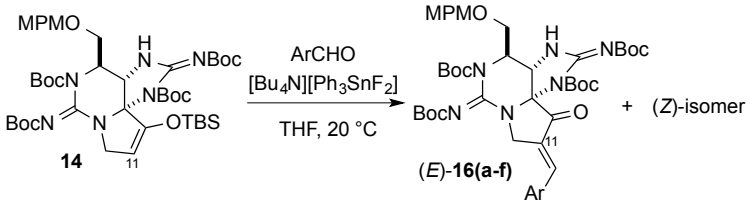


To a solution of silyl enol ether **14** (87 mg, 0.10 mmol) in THF (4 mL) was added ethyl glyoxylate (80 μL) at 0 °C. After stirring for 10 min, $[Bu_4][Ph_3SnF_2]$ (67 mg, 0.11 mmol) was added and the reaction was stirred for another 2 hrs at the same temperature. Then, the reaction was quenched with sat. NH_4Cl aq (3 mL), and the solution was extracted with EtOAc (5 mL) three times. The combined organic layers was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by neutral silica gel column chromatography (hexane/EtOAc; 3:1) to give **15** (81 mg, 96%).

Spectral data for **15**: $[\alpha]^{25}_D$ = +24.6 (*c* 2.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.02 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.6 Hz, 1H), 6.40 (t, *J* = 2.4 Hz, 0.75H), 6.34-6.28 (m, 0.15H), 4.92 (d, *J* = 2.4 Hz, 1H), 4.72-4.44 (m, 3H), 4.27-4.10 (m, 4H), 3.82 (d, *J* = 10.3 Hz, 1H), 3.78 (s, 3H), 3.67-3.57 (m, 1H), 1.53 (s, 9H), 1.45 (s, 18H), 1.34 (s, 9H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 164.5, 159.5, 151.2, 151.1, 149.1, 145.9, 143.9, 130.0, 128.8, 121.0, 113.9, 88.3, 83.7, 81.9, 79.9, 78.2, 77.4, 73.54, 73.45, 71.7, 61.5, 57.8, 55.4, 55.2, 29.8, 28.3, 28.0, 27.9, 27.8, 14.3; HRMS (ESI, M+Na)$^+$ calcd for $C_{41}H_{58}N_6O_{13}Na$ 865.3960 found 865.3959.

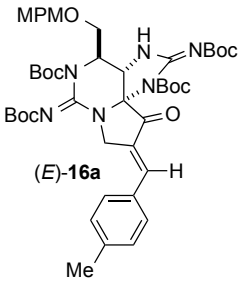
Synthesis of Mukaiyama aldol condensation adduct 16a-f

General procedure for the Mukaiyama aldol condensation:

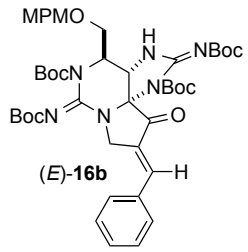


To a solution of silyl enol ether **14** (1 equiv) in THF was added aldehyde (5 equiv) at 0 °C. After stirring for several minutes, $[Bu_4][Ph_3SnF_2]$ (1.05 equiv) was added and the reaction was stirred at the same temperature. Upon completion of the reaction (2-48 h), the reaction was quenched with sat. NH_4Cl aq., and the solution was extracted with EtOAc three times. The combined organic layers was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified with preparative thin layer chromatography (hexane/EtOAc; 1:1).

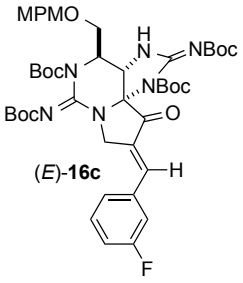
Spectral data for (*E*)-**16a-f:**



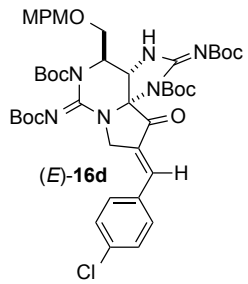
(*E*)-**16a**: $[\alpha]^{25}_{D}$ = +13.2 (*c* 0.6 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58(s, 1H), 7.39 (s, 1H), 7.22-7.16 (m, 4H), 6.91 (d, *J* = 8.2 Hz, 2H), 6.45 (d, *J* = 8.6 Hz, 2H), 4.90 (t, *J* = 2.8 Hz, 1H), 4.69 (s, 1H), 4.64 (d, *J* = 17.4 Hz, 1H), 4.31 (d, *J* = 17.4 Hz, 1H), 4.11 (s, 2H), 3.84-3.78 (m, 1H), 3.62 (dd, *J* = 3.6, 10.1Hz, 1H), 3.60 (s, 3H), 2.41 (s, 1H), 1.56 (s, 9H), 1.47 (s, 18H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 159.7, 159.1, 152.0, 151.5, 151.1, 149.2, 146.2, 141.8, 134.7, 131.5, 131.0, 130.0, 129.8, 129.0, 128.5, 113.6, 87.2, 83.6, 81.7, 79.9, 78.6, 77.8, 77.4, 73.7, 73.6, 71.8, 58.6, 54.9, 52.1, 29.8, 28.4, 28.1, 28.0, 27.9, 21.8; HRMS (ESI, M+Na)$^+$ calcd for $C_{45}H_{60}N_6O_{11}Na$ 883.4217 found 883.4175.



(*E*)-**16b**: $[\alpha]^{25}_{D}$ = +16.8 (*c* 1.7 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (s, 1H), 7.44-7.38 (m, 4H), 7.31-7.27 (m, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.46 (d, *J* = 8.6 Hz, 2H), 4.91 (t, *J* = 3.0, 1H), 4.71-4.62 (m, 2H, overlap), 4.35 (d, *J* = 15.5 Hz, 1H), 4.11 (s, 2H), 3.86-3.79 (m, 1H), 3.66-3.57 (m, 4H, overlap), 1.58 (s, 9H), 1.46 (s, 18 H), 1.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.2, 159.6, 159.0, 151.9, 151.4, 151.1, 149.2, 146.2, 134.5, 133.6, 131.3, 130.9, 129.7, 129.5, 129.2, 128.9, 113.6, 87.3, 83.6, 81.7, 79.9, 78.5, 77.4, 73.7, 73.5, 71.8, 58.5, 55.0, 52.1, 28.3, 28.1, 28.0, 27.8; HRMS (ESI, M+Na)$^+$ calcd for $C_{44}H_{58}N_6O_{11}Na$ 869.4061 found 869.4048.

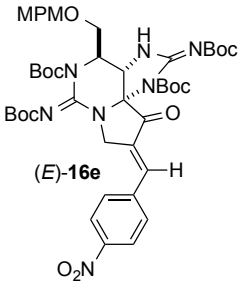


(*E*)-**16c**: $[\alpha]^{25}_{D}$ = +17.9 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.37 (dd, *J* = 7.9, 14.1 Hz, 1H), 7.30 (s, 1H), 7.16-7.07 (m, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 2H), 6.45 (d, *J* = 8.3 Hz, 2H), 4.91 (s, 1H), 4.69 (s, 1H), 4.61 (d, *J* = 15.5 Hz, 1H), 4.28 (d, *J* = 15.5 Hz, 1H), 4.14 (d, *J* = 11.2 Hz, 1H), 4.09 (d, *J* = 11.0 Hz, 1H), 3.86 (d, *J* = 8.3 Hz, 1H), 3.69-3.58 (m, 4H), 1.57 (s, 9H), 1.47 (s, 18H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 164.6, 159.6, 159.1, 151.8, 151.4, 151.1, 149.2, 146.2, 135.6, 135.5, 132.9, 130.7, 129.8, 128.9, 127.0, 118.0, 117.8, 117.6, 117.4, 113.5, 87.4, 83.7, 81.8, 80.0, 78.4, 78.0, 77.4, 73.8, 73.7, 72.2, 58.5, 55.0, 51.9, 28.4, 28.1, 28.0, 27.9; HRMS (ESI, M+Na)$^+$ calcd for $C_{44}H_{57}N_6O_{11}FNa$ 887.3967 found 887.3966.



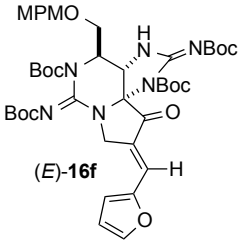
(*E*)-**16d**: $[\alpha]^{25}_{D}$ = +21.0 (*c* 1.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.36 (d, *J* = 8.6 Hz, 2H), 7.29 (s, 1H), 7.15 (d, *J* = 8.3 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.40 (d, *J* = 8.3 Hz, 2H), 4.91 (t, *J* = 2.4 Hz, 1H), 4.69 (s, 1H), 4.58 (dd, *J* = 2.1, 15.8 Hz, 1H), 4.22 (dd, *J* = 2.1, 15.8 Hz, 1H), 4.11 (dd, *J* = 11.0, 14.4 Hz, 2H), 3.88 (dd, *J* = 2.1, 10.3 Hz, 1H), 3.66 (dd, *J* = 3.5,10.0 Hz, 1H), 3.59 (s, 3H), 1.57 (s, 9H) , 1.47 (s, 9H) , 1.46 (s, 9H), 1.24 (s, 9H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 197.2, 159.6, 159.1, 151.9, 151.4, 151.1, 149.2, 146.2, 137.2, 132.9, 132.4, 132.0, 129.8, 129.5, 128.9, 113.5, 87.3, 83.7, 81.8, 80.0, 78.4, 78.0, 77.4, 73.8, 72.4, 58.6, 54.9, 51.9, 28.3, 28.1, 28.0, 27.8; HRMS (ESI, M+Na)$^+$ calcd for $C_{44}H_{57}N_6O_{11}ClNa$ 903.3672 found 903.3691.



(*E*)-**16e**

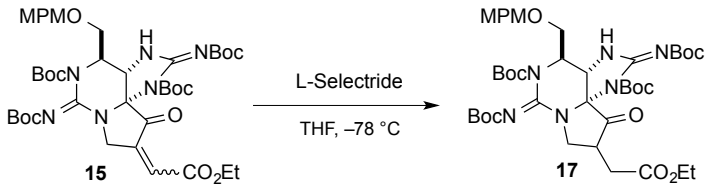
(*E*)-**16e**: $[\alpha]^{25}_D$ = +32.7 (*c* 0.8 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.54 (s, 1H), 8.20 (d, *J* = 8.6 Hz, 2H), 7.35-7.28 (m, 3H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.31 (d, *J* = 8.6 Hz, 2H), 4.92 (s, 1H), 4.69 (s, 1H), 4.66-4.57 (m, 1H), 4.30-4.20 (m, 1H), 4.14 (d, *J* = 11.0 Hz, 1H), 4.07 (d, *J* = 10.7 Hz, 1H), 3.91 (d, *J* = 9.3 Hz, 1H), 3.75-3.65 (m, 2H), 3.52 (s, 3H), 1.57 (s, 9H) , 1.47 (s, 9H) , 1.46 (s, 9H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.2, 159.5, 159.0, 151.8, 151.2, 151.0, 149.2, 148.4, 146.1, 139.2, 133.1, 131.6, 130.9, 129.8, 128.9, 124.2, 113.4, 87.5, 83.9, 81.9, 80.2, 78.2, 77.4, 73.9, 72.8, 58.6, 54.8, 51.9, 28.3, 28.0, 27.9, 27.8; HRMS (ESI, M+Na)$^+$ calcd for $C_{44}H_{57}N_7O_{13}Na$ 914.3912 found 914.3900.



(*E*)-**16f**

(*E*)-**16f**: $[\alpha]^{25}_D$ = +27.5 (*c* 1.3 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (s, 1H), 7.57 (s, 1H), 7.11 (s, 1H), 6.97 (d, *J* = 8.9 Hz, 2H), 6.68 (d, *J* = 3.5 Hz, 1H), 6.54 (d, *J* = 8.6 Hz, 2H), 6.52-6.49 (m, 1H), 4.90 (t, *J* = 2.8 Hz, 1H), 4.68 (s, 1H), 4.61 (d, *J* = 16.8 Hz, 1H), 4.33 (d, *J* = 16.8 Hz, 1H), 3.83 (dd, *J* = 2.4, 10.0 Hz, 1H), 3.70-3.60 (m, 4H, overlap), 1.55 (s, 9H) , 1.46 (s, 9H) , 1.45 (s, 9H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.5, 159.7, 159.1, 151.8, 151.5, 151.1, 150.8, 149.2, 147.1, 146.2, 129.8, 129.1, 127.0, 119.7, 119.0, 113.4, 113.0, 87.2, 83.5, 81.7, 79.8, 79.0, 78.0, 77.4, 73.6, 71.9, 58.5, 55.0, 52.1, 28.3, 28.1, 27.9, 27.8; HRMS (ESI, M+Na)$^+$ calcd for $C_{42}H_{56}N_6O_{12}Na$ 859.3854 found 859.3899.

Synthesis of 17:



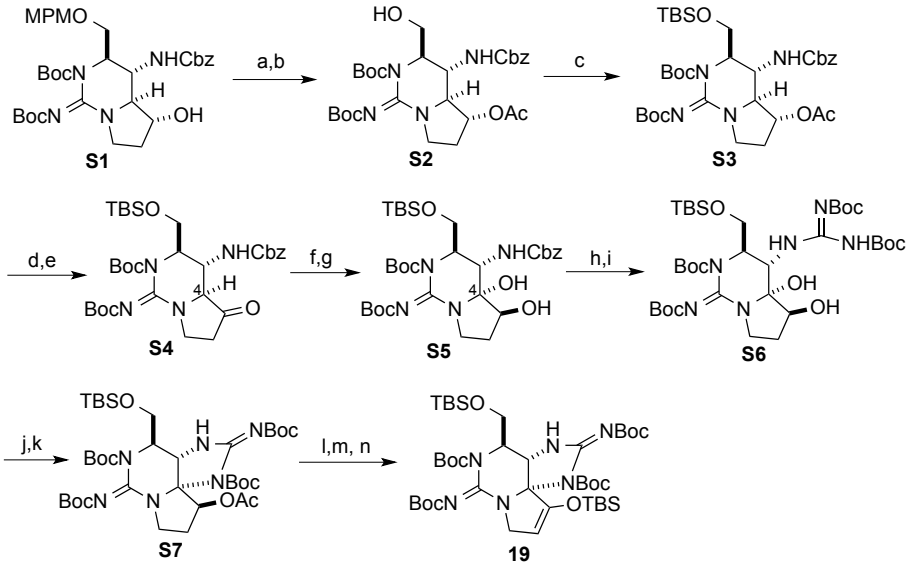
To a solution of **15** (20 mg, 0.024 mmol) in THF (1 mL) was added L-selectride (71 μL, 0.071 mmol) at –78 °C. After stirring for 5 min, the reaction was quenched with sat. NH_4Cl aq (1 mL), and the solution was extracted with EtOAc (2 mL) three times. The combined organic layers was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified immediately by neutral silica gel column chromatography (hexane/EtOAc; 2:1) to give **17** (15.4 mg, 76%).

Spectral data for **17**: $[\alpha]^{25}_{D}$ = +13.3 (*c* 2.6 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.86 (t, *J* = 4.1 Hz, 1H), 4.54 (s, 1H), 4.39 (dd, *J* = 11, 17.4 Hz, 2H), 4.17-4.09 (m, 2H), 3.98 (t, *J* = 10.1 Hz, 1H), 3.78 (s, 3H), 3.75-3.63 (m, 2H), 3.49 (t, *J* = 9.2 Hz, 1H), 2.78 (dd, *J* = 4.6, 17.0 Hz, 1H), 2.72-2.62 (m, 1H), 2.38 (dd, *J* = 8.7, 13.3 Hz, 1H), 1.52 (s, 9H) , 1.50 (s, 9H) , 1.45 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.7, 171.4, 159.6, 151.2, 148.6, 144.0, 130.2, 129.1, 114.0, 87.7, 83.4, 82.0, 79.5, 78.6, 77.4, 73.4, 71.8, 70.9, 60.9, 58.2, 55.3, 51.6, 42.5, 33.3, 28.3, 28.0, 14.3; HRMS (ESI, M+Na)$^+$ calcd for $C_{41}H_{60}N_6O_{13}Na$ 867.4116 found 867.4090.

Synthesis of silyl enol ether 19:[1]

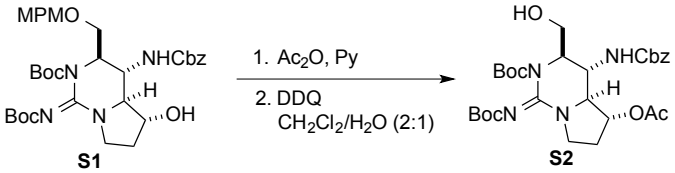
The route was commenced with the known compound **S1** (Scheme S1), acylation of the hydroxyl group with acetic anhydride followed by removal of the MPM group with DDQ afforded **S2** and further protection with TBS gave **S3**. Hydrolysis of the acetate with potassium carbonate followed by Swern oxidation gave ketone **S4**. With the ketone **S4** in hand, oxidation at the C-4 position was carried out with IBX followed by reduction with $NaBH_4$ generated diol **S5**. Remove the Cbz group with

$Pd(OH)_2$ in MeOH then the second guanidine group was introduced by treatment with bis(Boc)-2-methyl-2-thiopeudourea in presence of Mercury(II) chloride to give **S6**. Esterification of the diol with acetic anhydride and cyclization in presence of $ZnCl_2$ yielded the fully protected saxitoxinol **S7** with TBS protecting group at the C13 position. With intermediate **S7** in hand, following the same reaction conditions abovementioned (Scheme 3), silyl enol ether **19** with TBS protecting group at the C13 position was obtained.



Scheme S2. Synthesis of silyl enol ether **19** with TBS protecting group at the C13 position. Reagents and conditions: a) Ac_2O (10 equiv), pyridine (20 equiv), rt, 10 h; b) DDQ (10 equiv), CH_2Cl_2/H_2O (2:1), rt, overnight, 79% (2 steps); c) TBSOTf (2 equiv), 2,6-lutidine (4 equiv), CH_2Cl_2, rt, 20 min, 87%; d) K_2CO_3 (2 equiv), MeOH, 0 °C, 20 min; e) $(COCl)_2$ (3.5 equiv), DMSO (4.2 equiv), CH_2Cl_2, –78 °C, 1 h, then Et_3N (10 equiv), –78 °C, 10 min; f) IBX (1.1 equiv), DMSO, 50 °C, 1 h; g) $NaBH_4$ (0.5 equiv), MeOH, 0 °C, 20min, 68% (4 steps); h) $Pd(OH)_2$ (20% wt), MeOH, rt, 2.5 h; i) NBoc=C(SMe)NHBoc (1 equiv), $HgCl_2$ (1 equiv), Et_3N (3 equiv), DMF, rt, 1 h, 94% (2 steps); j) Ac_2O (10 equiv), DMAP (0.1 equiv), pyridine (20 equiv), rt, 3 h; k) $ZnCl_2$ (1.5 equiv), CH_2Cl_2, –20 °C, 5 h, 80% (2 steps); l) K_2CO_3 (2 equiv), MeOH, 0 °C, 20 min; m) NMO (4.0 equiv), 4Å MS (500 mg/mmol), CH_2Cl_2, 0 °C, 10 min; then, TPAP (0.1 equiv), rt, 1 h; n) NaHMDS (5 equiv), TBSCl (4 equiv), CH_2Cl_2, –40 °C, overnight, 85% (3 steps). DDQ = 2,3-dichloro-5,6-dicyano-p-benzoquinone, TBSOTf = tert-butyldimethylsilyl trifluoromethanesulfonate, DMSO = dimethyl sulfoxide, IBX = 2-iodoxybenzoic acid, DMAP = 4-(dimethylamino)pyridine, NMO = *N*-methylmorpholine-*N*-oxide, TPAP = tetrapropylammonium perruthenate.

Synthesis of S2

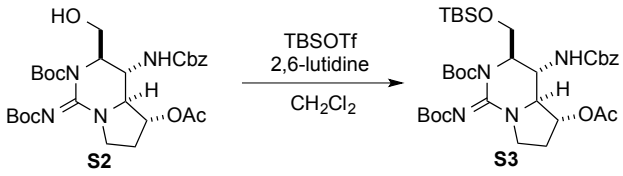


To a solution of alcohol S**1** (7.6 g, 11.38 mmol) in pyridine (10 mL) was added acetic anhydride (5 mL) at room temperature. After stirring for 3 hrs, the reaction mixture was concentrated *in vacuo* to give ester.

To a solution of ester in a mixture solvent (CH_2Cl_2 = 130 mL, H_2O = 65 mL) was added DDQ (25.85 g, 113.8 mmol) at 0 °C. After stirring overnight at room temperature, the reaction was quenched with sat. $NaHCO_3$ aq (75 mL), and the solution was extracted with CH_2Cl_2 (100 mL) three times. The combined organic layers was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc; 2:1 to 1:1) to give **S2** (5.2 g, 79% two steps).

Spectral data for **S2**: $[\alpha]^{25}_D$ = +117.9 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.32 (m, 5H), 5.37 (br, 1H), 5.29 (d, *J* = 8.7 Hz, 1H), 5.22 (d, *J* = 3.2 Hz, 1H), 5.17 (d, *J* = 9.2 Hz, 1H), 5.10 (d, *J* = 9.0 Hz, 1H), 3.99-3.80 (m, 4H), 3.66-3.55 (m, 3H), 2.33-2.21 (m, 1H), 2.10-2.04 (m, 4H), 1.49 (s, 9H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 162.4, 156.1, 150.6, 136.1, 128.6, 128.3, 128.1, 83.3, 80.0, 77.4, 75.6, 67.3, 64.5, 61.7, 60.8, 52.7, 46.4, 28.8, 28.3, 28.2, 21.1; HRMS (ESI, M+Na)$^+$ calcd for $C_{28}H_{40}N_4O_9Na$ 599.2693 found 599.2644.

Synthesis of S3

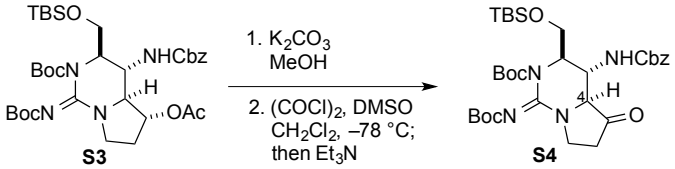


To a solution of alcohol **S2** (5.2 g, 9.02 mmol) in CH_2Cl_2 (55 mL) was added 2,6-lutidine (4.20 mL, 36.08 mmol) at 0 °C, then TBSOTf (4.14 mL, 18.04 mmol) was added and the reaction mixture was stirred at rt for 1 h. After that, the reaction

was quenched with sat. $NaHCO_3$ aq (30 mL), and the solution was extracted with CH_2Cl_2 (50 mL) three times. The combined organic layers was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc; 5:1 to 2:1) to give **S3** (5.42 g, 87%).

Spectral data for **S3**: $[\alpha]^{25}_D$ = +58.0 (*c* 2.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.30 (m, 5H), 5.30 (d, *J* = 5.8 Hz, 1H), 5.21 (d, *J* = 3.9 Hz, 1H), 5.14 (d, *J* = 9.3 Hz, 1H), 5.10 (d, *J* = 9.3 Hz, 1H), 4.12 (s, 1H), 4.09-3.99 (br, 1H), 3.91-3.82 (m, 2H), 3.75-3.70 (m, 1H), 3.66-3.59 (m, 1H), 3.43 (d, *J* = 11.5 Hz, 1H), 2.24-2.11 (m, 1H), 2.10-2.01 (m, 4H), 1.47 (s, 18H), 0.86 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 159.0, 156.0, 151.6, 151.1, 136.2, 128.5, 128.2, 128.0, 82.6, 78.1, 77.4, 75.9, 67.0, 64.7, 64.3, 61.0, 53.7, 45.8, 29.1, 28.6, 28.2, 25.9, 21.1, 18.4, -5.3, -5.8; HRMS (ESI, M+Na)$^+$ calcd for $C_{34}H_{55}N_4O_9SiNa$ 691.3738 found 691.3780.

Synthesis of S4

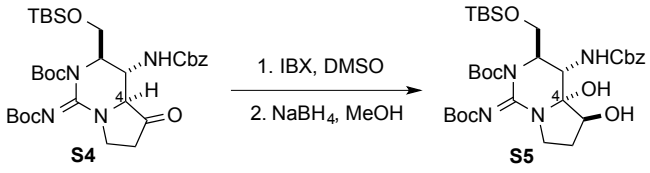


To a solution of **S3** (5.42g, 7.84 mmol) in methanol (50 mL) was added K_2CO_3 (2.17 g, 15.69 mmol) at 0 °C under N_2 atmosphere. After stirring for 15 min, the reaction was quenched with water (40 mL) and extracted with EtOAc (50 mL) three times. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude alcohol.

To a solution of DMSO (2.36 mL, 32.95 mmol) in CH_2Cl_2 (150 mL) was slowly added oxalychloride (2.40 mL, 27.46 mmol) at –78 °C under N_2 atmosphere. The reaction mixture was stirred for 30 min, and then crude alcohol was added as a solution in CH_2Cl_2 (30 mL) under N_2 atmosphere. After stirring for 1 h, Et_3N (10.93 mL, 78.45 mmol) was added to the reaction mixture. After stirring for another 5 min, the reaction was rapidly quenched with water (20 mL), warmed to room temperature and extracted with CH_2Cl_2 (50 mL) three times. The combined organic layer was

dried over $MgSO_4$, filtered and concentrated *in vacuo* to give ketone **S4**.

Synthesis of S5

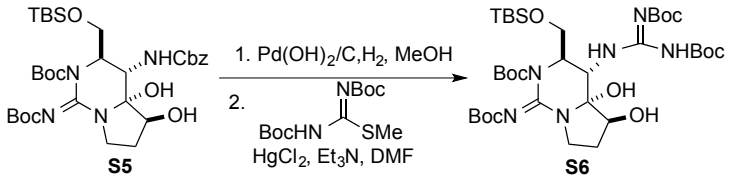


To a solution of ketone **S4** in DMSO (65 mL) and H_2O (0.24 mL) was added IBX (2.43 g, 8.63 mmol) at room temperature. Then the reaction mixture was warmed to 50 °C and stirred for 1 h. After that, the reaction was quenched with 10% $Na_2S_2O_3$ aq (30 mL) and saturated $NaHCO_3$ aq (30 mL). Then, the solution was diluted with EtOAc (50 mL). The organic layer was washed with water (100 mL) three times. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give aminal.

To a solution of aminal in methanol (45 mL) was added $NaBH_4$ (0.15g, 3.92 mmol) at 0 °C. After stirring for 15 min, the reaction was quenched with water (60 mL), and the solution was extracted with EtOAc (100 mL) three times. The combined organic layers 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 diol **S5** (3.56g, 68% four steps).

Spectral data for **S5**: $[\alpha]^{25}_{D}$ = +41.8 (*c* 1.9 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.33 (m, 5H), 5.30 (d, *J* = 9.0 Hz, 1H), 5.16 (d, *J* = 9.0 Hz, 1H), 5.09 (d, *J* = 9.2 Hz, 1H), 4.95 (s, 1H), 4.56 (dd, *J* = 6.0, 9.2 Hz, 1H), 2.17-2.05 (m, 1H), 2.00-1.95 (m, 1H), 1.47 (s, 9H), 1.46 (s, 9H), 0.85 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 157.3, 151.7, 149.1, 135.7, 128.7, 128.5, 128.3, 91.3, 83.0, 78.8, 77.4, 67.8, 64.3, 58.9, 52.4, 46.4, 29.1, 28.4, 28.3, 25.8, 18.1, -5.4, -5.6; HRMS (ESI, M+Na)$^+$ calcd for $C_{32}H_{52}N_4O_9SiNa$ 687.3401 found 687.3438.

Synthesis of S6

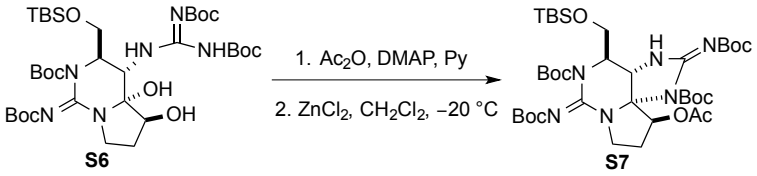


To a solution of diol **S5** (3.56 g, 5.36 mmol) in methanol (45 mL) was added 20% $Pd(OH)_2$ (0.71 g). The suspension was vigorously stirred under H_2 atmosphere (balloon) at room temperature for 3 hrs and then was filtered through a pad of Celite. The filtrates were concentrated *in vacuo* to give amine.

To a solution of the amine, Et_3N (2.24 mL, 16.08 mmol) and bis(Boc)-2-methyl-2-thiopseudourea (1.92 g, 5.36 mmol) in DMF (30 mL) was added $HgCl_2$ (1.46 g, 5.36 mmol) at room temperature under N_2 atmosphere. After stirring for 1 h, the reaction mixture was diluted with EtOAc (45 mL) and filtered through a pad of Celite. The filtrate was washed with water (50 mL) and brine (50 mL) twice. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give yellow oil. The crude mixture was purified by chromatorex NH gel column chromatography (hexane/EtOAc; 4:1 to 1:1) to give bis-guanidine **S6** (3.89 g, 94% two steps).

Spectral data for **S6**: $[\alpha]^{25}_{D}$ = +27.7 (*c* 1.9 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (s, 1H), 8.74 (d, *J* = 13.2 Hz, 1H), 6.90 (s, 1H), 4.88 (dd, *J* = 5.5, 8.7 Hz, 1H), 4.21-4.16 (m, 1H), 4.00-3.90 (m, 3H), 3.70-3.62 (m, 2H), 2.30 (s, 1H), 2.18-1.99 (m, 2H), 1.51 (m, 18H), 1.48 (s, 9H), 1.45 (s, 9H), 0.83 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 158.8, 155.8, 152.8, 151.5, 148.7, 91.5, 83.9, 83.1, 79.8, 78.9, 77.4, 76.2, 64.6, 59.0, 52.6, 46.5, 29.0, 28.4, 28.21, 28.17, 28.1, 25.7, 18.1, -5.4, -5.6; HRMS (ESI, M+Na)$^+$ calcd for $C_{35}H_{64}N_6O_{11}SiNa$ 795.4300 found 795.4312.

Synthesis of S7

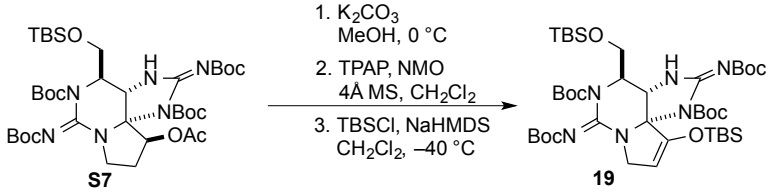


To a solution of bis-guanidine **S6** (3.89 g, 5.03 mmol) in pyridine (16 mL) was added catalytic amount of DMAP (62 mg, 0.05 mmol) and acetic anhydride (8 mL) at room temperature. After stirring for 1 h, the reaction mixture was concentrated *in vacuo* to give diester.

To a solution of diester in CH_2Cl_2 (60 mL) was added $ZnCl_2$ (1.03 g, 7.55 mmol) under Ar atmosphere at –20 °C. After stirring for 3 hrs, the reaction mixture was quenched with saturated $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (50 mL) three times. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by Chromatorex NH column chromatography (hexane/EtOAc; 10:1 to 6:1) to give protected STXol **S7** (3.20 g, 80% two steps).

Spectral data for **S7**: $[\alpha]^{25}_{D}$ = +45.2 (*c* 1.9 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (br, 1H), 5.90 (t, *J* = 9.2 Hz, 1H), 4,96 (s, 1H), 4. 64 (dd, *J* = 5.5, 10.1 Hz, 1H), 3.90 (dd, *J* = 5.5, 10.5 Hz, 1H), 3.84-3.77 (m, 1H), 3.64 (t, *J* = 10.1 Hz, 1H), 3.40 (t, *J* = 10.1 Hz, 1H), 2.42-2.35 (m, 1H), 2.08 (s, 3H), 1.89-1.78 (m, 1H), 1.58 (s, 9H), 1.48 (s, 9H), 1.45 (s, 9H), 1.44 (s, 9H), 0.91(s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 159.2, 151.1, 150.9, 149.3, 149.2, 146.3, 86.5, 83.7, 83.0, 81.5, 79.5, 77.4, 76.7, 66.6, 62.5, 60.1, 46.7, 29.0, 28.4, 28.2, 28.1, 27.8, 26.0, 20.8, 18.4, -5.2, -5.3; HRMS (ESI, M+Na)$^+$ calcd for $C_{37}H_{64}N_6O_{11}SiNa$ 819.4300 found 819.4311.

Synthesis of silyl enol ether 19



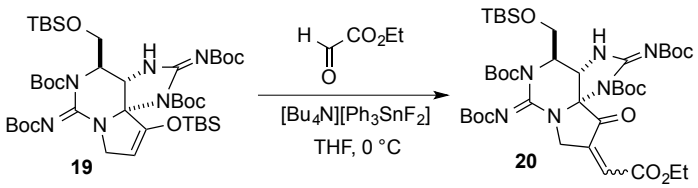
To a solution of protected STXol **S7** (0.95 g, 1.19 mmol) in methanol (12 mL) was added K_2CO_3 (0.33 g, 2.38 mmol) at 0 °C. After stirring for 15 min, the reaction was diluted with EtOAc (10 mL)and H_2O (10 mL), and extracted with EtOAc (15 mL) three times. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude alcohol.

To a solution of crude alcohol in CH_2Cl_2 (12 mL) was added NMO (0.56 g, 4.76 mmol) and 4Å MS (0.60 g) at 0 °C. After stirring for 10 min, TPAP (42 mg, 0.119 mmol) was added, and the reaction mixture was stirred for another 1 h at room temperature. Then, reaction mixture was diluted with hexane/EtOAc (2:1) (12 mL) and filtered through a pad of neutral silica gel, and then, washed with hexane/EtOAc (2:1) (50 mL). The filtrates were concentrated *in vacuo* to give ketone.

To a solution of ketone in CH_2Cl_2 (8 mL) was added NaHMDS (3.14 mL, 5.97 mmol) under Ar atmosphere at –40 °C. After stirring for 10 min, TBSCl (0.72 g, 4.77mmol) was added and the reaction mixture was stirred overnight at –40 °C. Then, the reaction was quenched with H_2O (10 mL) and warmed to room temperature and extracted with CH_2Cl_2 (10 mL) three times. The combined organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by neutral silica gel column chromatography (hexane/EtOAc; 8:1 to 3:1) to give silyl enol ether **19** (0.88 g, 85% three steps).

Spectral data for **19**: $[\alpha]^{25}_{D}$ = +13.6 (*c* 1.2 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (s, 1H), 4.72-4.68 (m, 2H), 4.35 (d, *J* = 18.8 Hz, 1H), 3.92-3.84 (m, 2H), 3.37 (t, *J* = 12.4 Hz, 1H), 1.50 (s, 9H), 1.48 (s, 9H), 1.45 (s, 18H), 0.88 (s, 9H), 0.86 (s, 9H), 0.21 (s, 6H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 151.1, 150.0, 149.1, 147.3, 146.4, 97.7, 85.1, 83.5, 82.9, 81.2, 79.4, 77.4, 69.0, 62.4, 60.1, 52.1, 28.19, 28.15, 28.0, 27.8, 26.0, 25.3, 18.4, 17.8, -4.7, -4.9, -5.2, -5.6; HRMS (ESI, M+Na)$^+$ calcd for $C_{41}H_{75}N_6O_{10}Si_2Na$ 867.5083 found 867.5045.

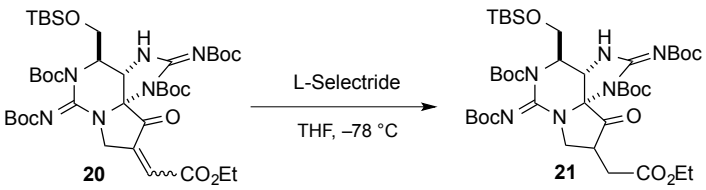
Synthesis of 20



To a solution of silyl enpl ether **19** (0.23 g, 0.27 mmol) in THF (10 mL) was added ethyl glyoxylate (210 μL) at 0 °C. After stirring for several minutes, $[Bu_4][Ph_3SnF_2]$ (0.177 g, 0.28 mmol) was added and the reaction was stirred for another 2 hrs at the same temperature. Then, the reaction was quenched with sat. NH_4Cl aq (5 mL), and the solution was extracted with EtOAc (10 mL) three times. The combined organic layers was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by neutral silica gel column chromatography (hexane/EtOAc; 3:1) to give **20** (0.19 g, 85%).

Spectral data for **20**: $[\alpha]^{25}_D$ = +11.3 (*c* 0.7 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (s, 1H), 6.70 (t, *J* = 2.4 Hz, 0.75 H), 6.62-6.57 (m, 0.15 H), 4.86-4.78 (m, 4H), 4.33-4.25 (m, 2H), 3.89 (dd, *J* = 5.2, 10.7 Hz, 1H), 3.44 (dd, *J* = 7.6, 10.6 Hz, 1H), 1.51 (s, 9H), 1.47 (s, 9H), 1.45 (s, 9H), 1.39 (s, 9H), 1.31 (t, *J* = 7.2 Hz, 3H), 0.79 (s, 9H), -0.03 (s, 3H), -0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 164.6, 159.3151.0, 149.1, 145.8, 143.3, 122.9, 88.5, 83.8, 81.9, 80.1, 77.8, 77.4, 72.2, 63.2, 61.9, 59.0, 51.4, 28.3, 28.0, 27.9, 27.8, 26.0, 18.6, 14.4, -5.4, -5.6; HRMS (ESI, M+Na)$^+$ calcd for $C_{39}H_{64}N_6O_{12}SiNa$ 859.4249 found 859.4262.

Synthesis of 21

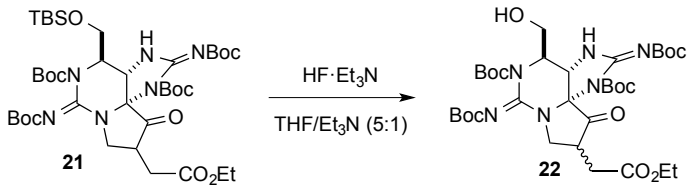


To a solution of **20** (190 mg, 0.23 mmol) in THF (8 mL) was added L-selectride (0.68 mL, 0.68 mmol) at –78 °C. After stirring for 5 min, the reaction was quenched

with sat. NH_4Cl aq (10 mL), and the solution was extracted with EtOAc (10 mL) three times. The combined organic layers was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified immediately by neutral silica gel column chromatography (hexane/EtOAc; 3:1) to give **21** (145 mg, 76%).

Spectral data for **21**: $[\alpha]^{25}_D$ = +5.2 (*c* 1.3 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 4.35 (dd, *J* = 5.9, 8.3 Hz, 1H), 4.75 (s, 1H), 4.30 (dd, *J* = 8.9, 10.3 Hz, 1H), 4.21-4.13 (m, 2H), 3.95 (dd, *J* = 5.8, 10.6 Hz, 1H), 3.66 (dd, *J* = 8.9, 11.0 Hz, 1H), 3.50 (t, *J* = 9.5 Hz, 1H), 3.04-2.94 (m, 2H), 2.60 (dd, *J* = 10.3, 17.9 Hz, 1H), 1.52 (s, 9H), 1.49 (s, 9H), 1.47 (s, 9H), 1.44 (s, 9H), 1.28 (t, *J* = 6.9 Hz, 3H), 0.84 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 207.6, 171.5, 159.3, 151.2, 150.0, 148.8, 148.5, 143.8, 87.8, 83.6, 81.9, 79.7, 78.0, 77.4, 69.9, 62.5, 61.1, 59.0, 51.3, 42.9, 33.4, 29.7, 28.2, 27.9, 25.9, 18.3, 14.3, -5.4; HRMS (ESI, M+Na)$^+$ calcd for $C_{39}H_{66}N_6O_{12}SiNa$ 861.4406 found 861.4400.

Synthesis of 22

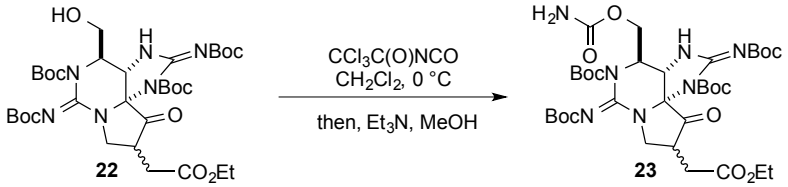


To a solution of **21** (145 mg, 0.17 mmol) in a mixture solvent (THF = 4 mL, Et_3N = 0.8 mL) was added HF·Et_3N (150 μL) at 0 °C. After stirring for 5 hrs at room temperature, the reaction was quenched with sat. $NaHCO_3$ aq (5 mL), and the solution was extracted with EtOAc (5 mL) three times. The combined organic layers was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by neutral silica gel column chromatography (hexane/EtOAc; 2:1 to 1:1) to give **22** as diastereomers mixture (109 mg, 87%). Major diastereomer was obtained by further purified with preparative thin layer chromatography (hexane/EtOAc; 1:1).

Spectral data for **22**: $[\alpha]^{25}_D$ = –1.4 (*c* 0.8 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 4.92 (d, *J* = 3.5 Hz, 1H), 4.89 (d, *J* = 3.8 Hz, 1H), 4.41 (dd, *J* = 9.3,

11.0 Hz, 1H), 4.21-4.14 (m, 2H), 3.69-3.57 (m, 2H), 3.44 (t, J = 11.3 Hz, 1H), 3.03-2.92 (m, 2H), 2.58 (dd, J = 10.0, 17.5 Hz, 1H), 1.52 (s, 9H), 1.50 (s, 9H), 1.46 (s, 9H), 1.45 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.5, 171.2, 161.2, 151.1, 150.3, 148.8, 148.4, 143.9, 88.3, 83.6, 82.1, 81.0, 78.0, 77.4, 70.8, 61.5, 61.2, 60.3, 50.8, 42.7, 33.2, 28.0, 27.9, 27.84, 27.78, 14.2; HRMS (ESI, M+Na)$^+$ calcd for $C_{33}H_{52}N_6O_{12}Na$ 747.3541 found 747.3551.

Synthesis of 23

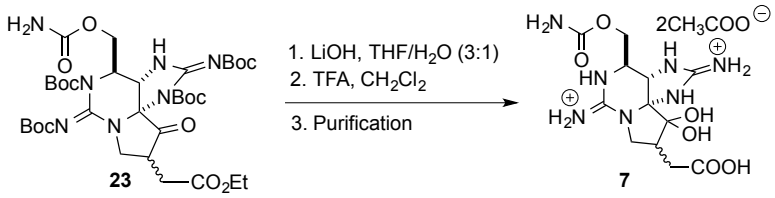


To a solution of **22** (109 mg, 0.15 mmol) in CH_2Cl_2 (6 mL) was added $CCl_3C(O)NCO$ (90 μL, 0.75 mmol). After stirring for 15 min, Et_3N (0.48 mL) and MeOH (2 mL) were added, and the reaction temperature was increased to room temperature. After stirring for another 5 hrs, the resulting mixture was concentrated *in vacuo*. The residue was purified by neutral silica gel column chromatography (hexane/EtOAc; 1:1) to give **23** as diastereomers mixture (78 mg, 68%). Major diastereomer was obtained by further purified with preparative thin layer chromatography (hexane/EtOAc; 1:2).

Spectral data for **23**: $[\alpha]^{25}_D$ = –58.0 (*c* 1.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 4.93 (dd, J = 5.5, 9.3 Hz, 1H), 4.49 (s, 1H), 4.42-4.30 (m, 2H, overlap), 4.17 (dd, J = 7.2, 14.4 Hz, 2H), 4.15-4.08 (m, 1H), 3.69 (dd, J = 9.3, 10.3 Hz, 1H), 3.38-3.29 (m, 1H), 3.03 (dd, J = 3.8, 17.5 Hz, 1H), 2.59 (dd, J = 10, 17.5 Hz, 1H), 1.52 (s, 9H), 1.49 (s, 9H), 1.48 (s, 9H), 1.44 (s, 9H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHZ, $CDCl_3$,): 207.6, 171.8, 159.3, 156.1, 150.9, 149.5, 148.8, 148.5, 144.4, 88.1, 83.9, 82.1, 80.0, 78.1, 77.4, 70.3, 62.9, 61.2, 57.2, 51.3, 42.6, 33.3, 28.3, 28.0, 27.9, 14.4; HRMS (ESI, M+Na)$^+$ calcd for $C_{34}H_{53}N_7O_{13}Na$ 790.3599 found 790.3606.

Synthesis of 7, 8, 9

Synthesis of 11-saxitoxinethanoic acid (7)

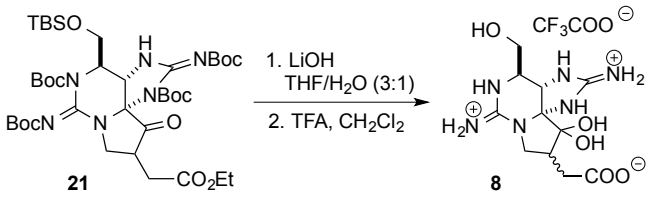


To a solution of **23** (78 mg, 0.10 mmol) in a mixture solvent (THF = 2 mL, H_2O = 0.6 mL) was added LiOH·H_2O (21 mg, 0.51 mmol) at 0 °C. After stirring for 1.5 h, the reaction was quenched with 1.2 *N* HCl aq until the pH reached 1, and the solution was extracted with EtOAc (3 mL) three times. The combined organic layers was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude carboxylic acid.

To a solution of crude carboxylic acid in CH_2Cl_2 (1 mL) was added TFA (0.5 mL) at room temperature. After stirring for 1 h, the reaction was concentrated *in vacuo*. The residue was dissolved in milli-Q (2 mL), and filtered through Millex filter unit (Millipore, 0.45 μm). The filtrate was lyophilized and the residue was perified by reverse phase HPLC (CH_3CN: 0.1% CH_3COOH aq. = 15: 85, Shiseido Cancel Pak AQ C18 column, Rt= 8.5 min, 214 nm UV detection) to give SEA (**7**) as diacetate salt.

Spectral data for **7**: $[\alpha]^{25}_{D}$ = +15 (*c* 0.1 in MeOH); ^{1}H NMR (300 MHz, D_2O, after 12 h), δ 4.74 (s, 1H), 4.25 (dd, *J* = 9.3, 11.7 Hz, 1H), 4.02 (dd, *J* = 5.5, 11.7 Hz, 1H), 3.90 (d, *J* = 10 Hz, 1H) 3.80 (dd, *J* = 5.2, 8.9 Hz, 1H), 3.18 (t, *J* = 10.0 Hz, 1H), 2.68 (d, *J* = 16.5Hz, 1H), 2.49 (d, *J* = 16.1 Hz, 1H), 1.90 (s, 6H); ^{13}C NMR (100 MHz, D_2O; 1,4-dioxan (67.4 ppm) was used as internal standard) δ 182.2, 181.0, 159.3, 158.3, 156.1, 99.3, 83.6, 63.6, 57.5, 53.5, 48.2, 39.9, 34.1, 24.0; HRMS (ESI, M+H)$^+$ calcd for $C_{12}H_{20}N_7O_6$ 358.1475 found 358.1482.

Synthesis of 8

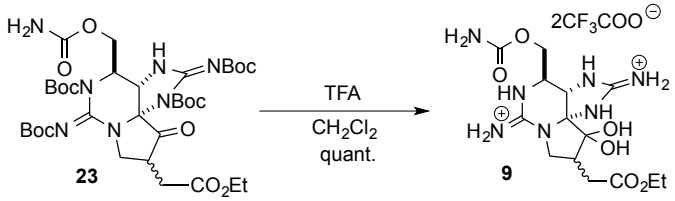


To a solution of **21** (22 mg, 0.0256mmol) in a mixture solvent (THF = 0.6 mL, H_2O = 0.2 mL) was added LiOH·H_2O (6 mg, 0.128 mmol) at 0 °C. After stirring for 2 h, the reaction was quenched with 1.2 *N* HCl aq until the pH reached 1, and the solution was extracted with EtOAc (2 mL) three times. The combined organic layers was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude carboxylic acid.

To a solution of crude carboxylic acid in CH_2Cl_2 (1 mL) was added TFA (0.5 mL) at room temperature. After stirring for 1 h, the reaction was concentrated *in vacuo*. The residue was dissolved in milli-Q (2 mL), and filtered through Millex filter unit (Millipore, 0.45 μm). The filtrate was lyophilized to give **8** as an analytically pure material (7 mg, 90%).

Spectral data for **8**: $[\alpha]^{25}_{D}$ = +48.3 (*c* 0.4 in MeOH); ^{1}H NMR (300 MHz, D_2O, after 12 h in D_2O) δ 4.72 (s, 1H), 3.98 (d, *J* =10 Hz, 1H), 3.71-3.55 (m, 3H), 3.19 (d, *J* = 10 Hz, 1H), 2.80 (d, *J* = 16.8 Hz, 1H), 2.57 (d, J = 17.1 Hz); ^{13}C NMR (100 MHz, D_2O; 1,4-dioxan (67.4 ppm) was used as internal standard) δ 177.4, 158.1, 156.1, 99.6, 83.1, 61.7, 57.2, 56.0, 48.3, 31.7; HRMS (ESI, M+H)$^+$ calcd for $C_{11}H_{18}N_6O_5$ 315.1417 found 315.1430.

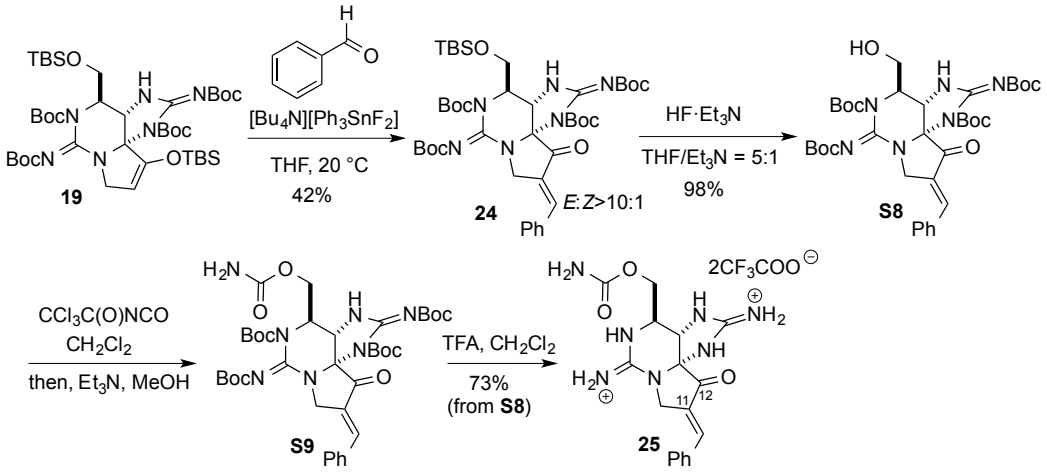
Synthesis of 9



To a solution of **23** (11.8 mg, 0.015 mmol) in CH_2Cl_2 (1 mL) was added TFA (0.5 mL) at room temperature. After stirring for 1 h, the reaction was concentrated *in vacuo*. The residue was dissolved in milli-Q (2 mL), and filtered through Millex filter unit (Millipore, 0.45 μm). The filtrate was lyophilized to give **9** as an analytically pure material (6 mg, quant.).

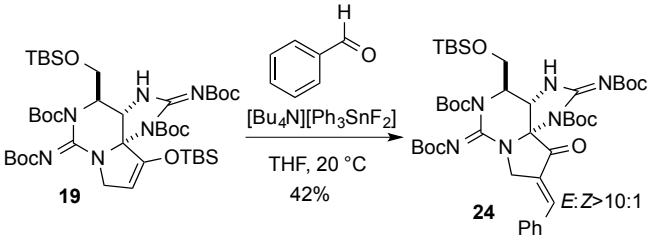
Spectral data for **9**: $[\alpha]^{25}_{D}$ = +49.5 (*c* 0.6 in MeOH); ^{1}H NMR (300 MHz, D_2O, after 12 h in D_2O) δ 4.75 (d, *J* = 1.1Hz, 1H), 4.25 (dd, *J* = 9.6, 11.7 Hz, 1H), 4.17 (dd, *J* = 7.2, 14.4 Hz, 2H), 4.05-3.96 (m, 2H), 3.80 (dd, *J* = 5.2, 10.3 Hz, 1H), 3.25 (d, *J* = 10.3 Hz, 1H), 2.83 (d, *J* = 16.5 Hz, 1H), 2.62 (d, *J* = 16.8 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, D_2O, 1,4-dioxan (67.4 ppm) was used as internal standard) δ 174.0, 158.3, 157.2, 155.1, 98.4, 82.1, 62.5, 62.0, 56.5, 52.5, 47.3, 38.5, 30.7, 13.1; HRMS (ESI, M+H)$^+$ calcd for $C_{14}H_{24}N_7O_6$ 386.1788 found 386.1766.

Synthesis of 25



Scheme S2. Synthesis of **25**

Synthesis of 24

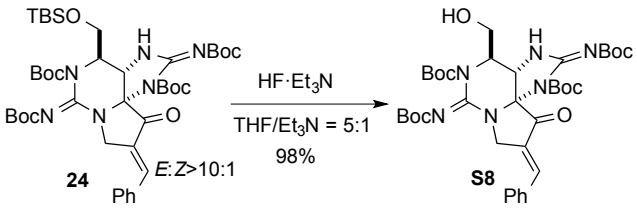


To a solution of silyl enol ether **19** (140mg, 0.162 mmol) in THF (3 mL) was added benzaldehyde (164 μL, 1.62 mmol) at 0 °C. After stirring for several minutes, $[Bu_4N][Ph_3SnF_2]$ (107 mg, 0.17 mmol) was added. After stirring for 24 hrs at room temperature, the reaction was quenched with sat. NH_4Cl aq (5 mL), and the solution was extracted with EtOAc (10 mL) three times. The combined organic layers was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by neutral silica gel column chromatography (hexane/EtOAc; 4:1 to 1:1) to give **24** (57 mg, 42%).

Spectral data for **24**: $[\alpha]^{25}_D = -10.4$ (*c* 5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.58 (s, 1H), 7.49 (s, 5H), 4.81- 4.90 (m, 3H), 4.65 (d, *J* = 15.57 Hz, 1H), 3.85 (dd, *J* = 5.0, 10.6 Hz, 1H), 3.38 (t, *J* = 10.1, 8.7 Hz, 1H), 1.52 (s, 9H), 1.48 (s, 9H), 1.46 (s, 9H), 1.35 (s, 9H), 0.75 (s, 9H), –0.09 (s, 3H), –0.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.4, 159.4, 151.4, 151.1, 150.9, 149.2, 146.1, 136.2, 133.6,

131.4, 131.3, 129.5, 129.0, 87.5, 83.8, 81.7, 80.2, 78.0, 77.4, 71.9, 62.9, 59.4, 51.1, 28.3, 28.1, 28.0, 25.9, 18.5, -5.4, -5.6; HRMS (ESI, M+Na)$^+$ calcd for $C_{42}H_{64}N_6O_{10}SiNa$ 863.4350 found 863.4385.

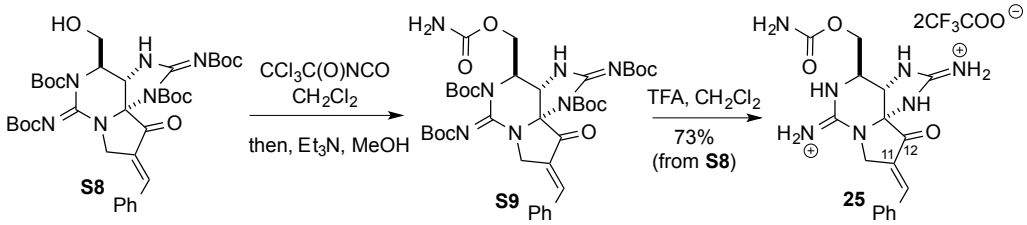
Synthesis of S8



To a solution of **24** (8 mg, 0.009 mmol) in a mixture solvent (THF = 0.5 mL, Et_3N = 0.1 mL) was added HF·Et_3N (40 μL) at 0 °C. After stirring for 5 h at room temperature, the reaction was quenched with sat. $NaHCO_3$ aq (1 mL), and the solution was extracted with EtOAc (3 mL) three times. The combined organic layers was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by neutral silica gel column chromatography (hexane/EtOAc; 2:1 to 1:1) to give **S8** (6.8 mg, 98%).

Spectral data for **S8**: $[\alpha]^{25}_D$ = –20.9 (*c* 2.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.62 (s, 1H), 7.50 (s, 5H), 4.92- 4.88 (m, 2H), 4.75 (d, *J* = 16.0 Hz, 1H), 4.33 (s, 1H), 3.53 (dd, *J* = 3.7, 11.9 Hz, 1H), 3.16 (dd, *J* = 11.9 Hz, 1H), 1.53 (s, 9H), 1.47 (s, 18H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1, 161.4, 151.3, 151.2, 150.1, 149.1, 146.3, 137.3, 133.2, 131.8, 131.5, 129.6, 127.8, 87.9, 84.1, 82.0, 81.8, 77.9, 77.4, 72.7, 61.6, 60.9, 50.8, 28.11, 28.1, 27.9; HRMS (ESI, M+Na)$^+$ calcd for $C_{36}H_{50}N_6O_{10}Na$ 749.3486 found 749.3473.

Synthesis of 25



To a solution of **S8** (7 mg, 0.0096 mmol) in CH_2Cl_2 (0.5 mL) was added $CCl_3C(O)NCO$ (5.7 μL, 0.048 mmol). After stirring for 15 min, Et_3N (48 μL) and MeOH (0.2 mL) were added, and the reaction temperature was increased to room temperature. After stirring for another 5 hrs, the resulting mixture was concentrated *in vacuo* to give **S9** (5.4 mg), which was used without further purification.

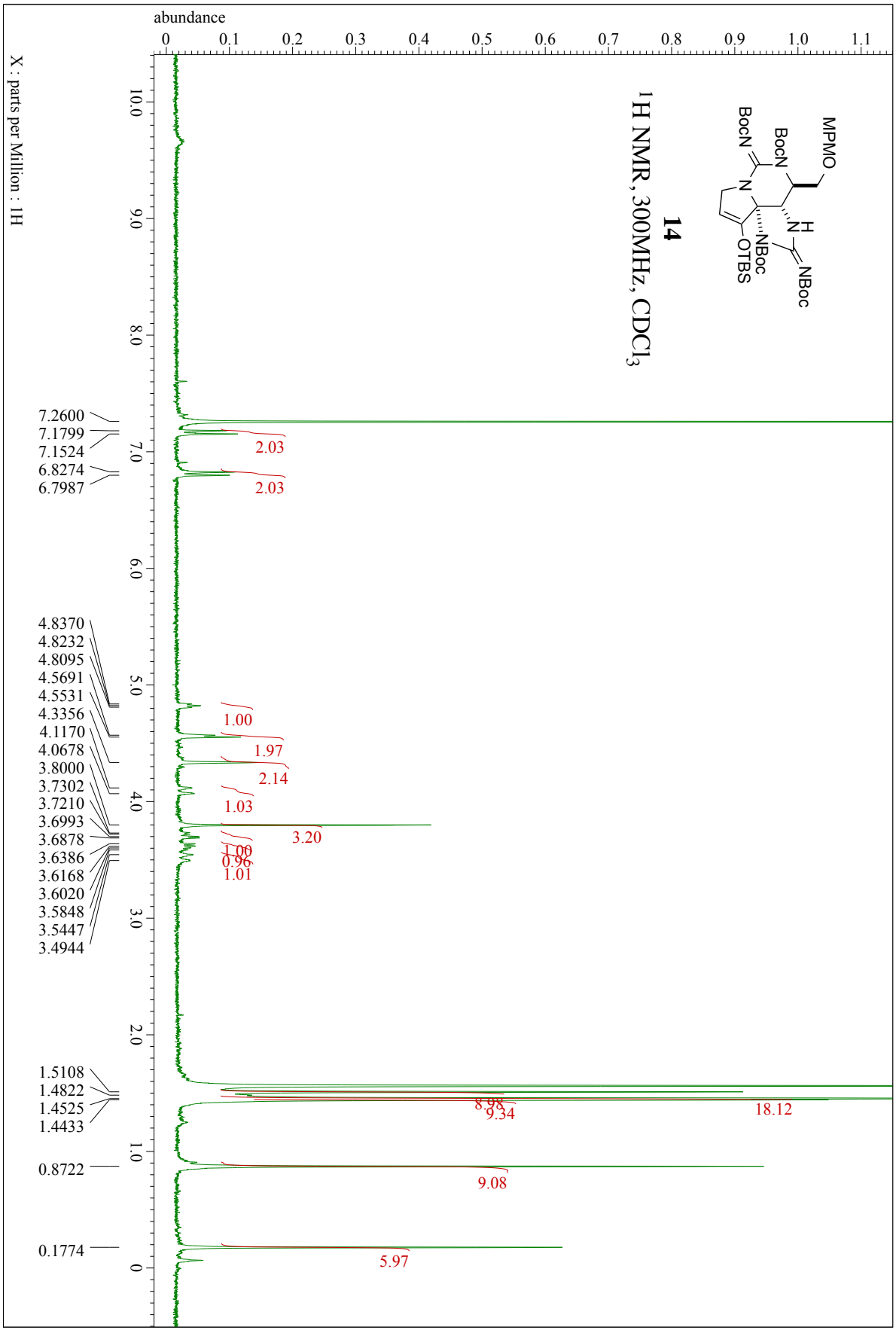
To a solution of **S9** (5.4 mg) in CH_2Cl_2 (0.5 mL) was added TFA (0.25 mL) at room temperature. After stirring for 1 h, the reaction was concentrated *in vacuo*. The residue was dissolved in milli-Q (1 mL), washed with CH_2Cl_2 (5 mL) and filtered through Millex filter unit (Millipore, 0.45 μm). The filtrate was lyophilized to give **25** as an analytically pure material (2.6 mg, 73% 2 steps).

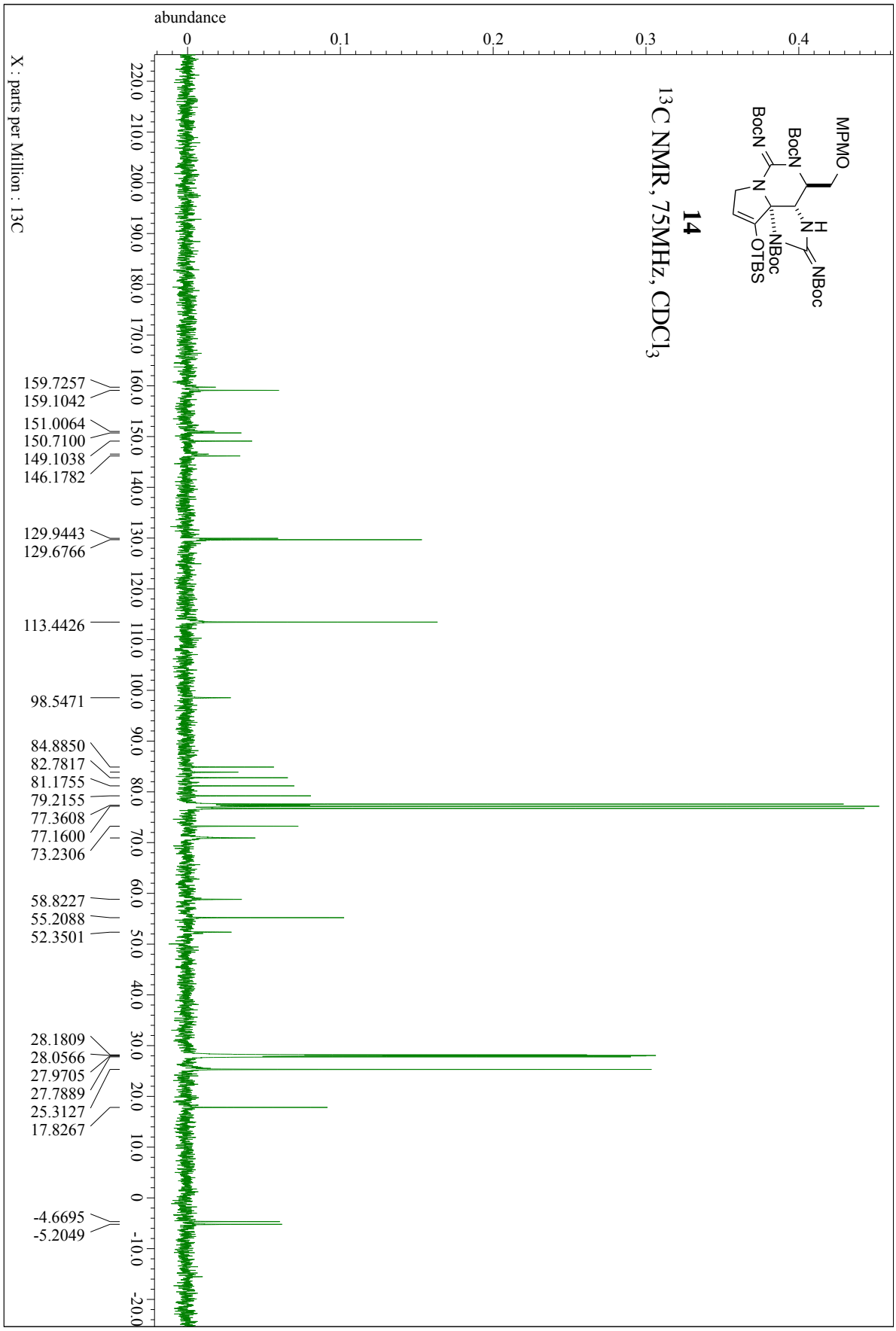
Spectral data for **25**: $[\alpha]^{25}_D$ = –36.4 (*c* 0.2 in MeOH); ^{1}H NMR (300 MHz, D_2O) δ 7.92 (s, 1H), 7.63-7.57 (m, 5H), 4.96 (s, 1H), 4.85 (s, 1H), 4.75 (s, 1H), 4.26 (dd, *J* = 4.5, 12.4 Hz, 1H), 4.16 (dd, *J* = 3.8, 12.4 Hz, 1H), 3.96 (t, *J* = 3.8, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, D_2O; 1,4-dioxan (67.4 ppm) was used as internal standard) δ 194.1, 158.6, 158.1, 157.0, 142.6, 133.6, 133.4, 132.7, 130.3, 124.7, 76.4, 65.9, 61.9, 53.0, 48.8; HRMS (ESI, M+H)$^+$ calcd for $C_{17}H_{20}N_7O_3$ 370.1627 found 370.1660.

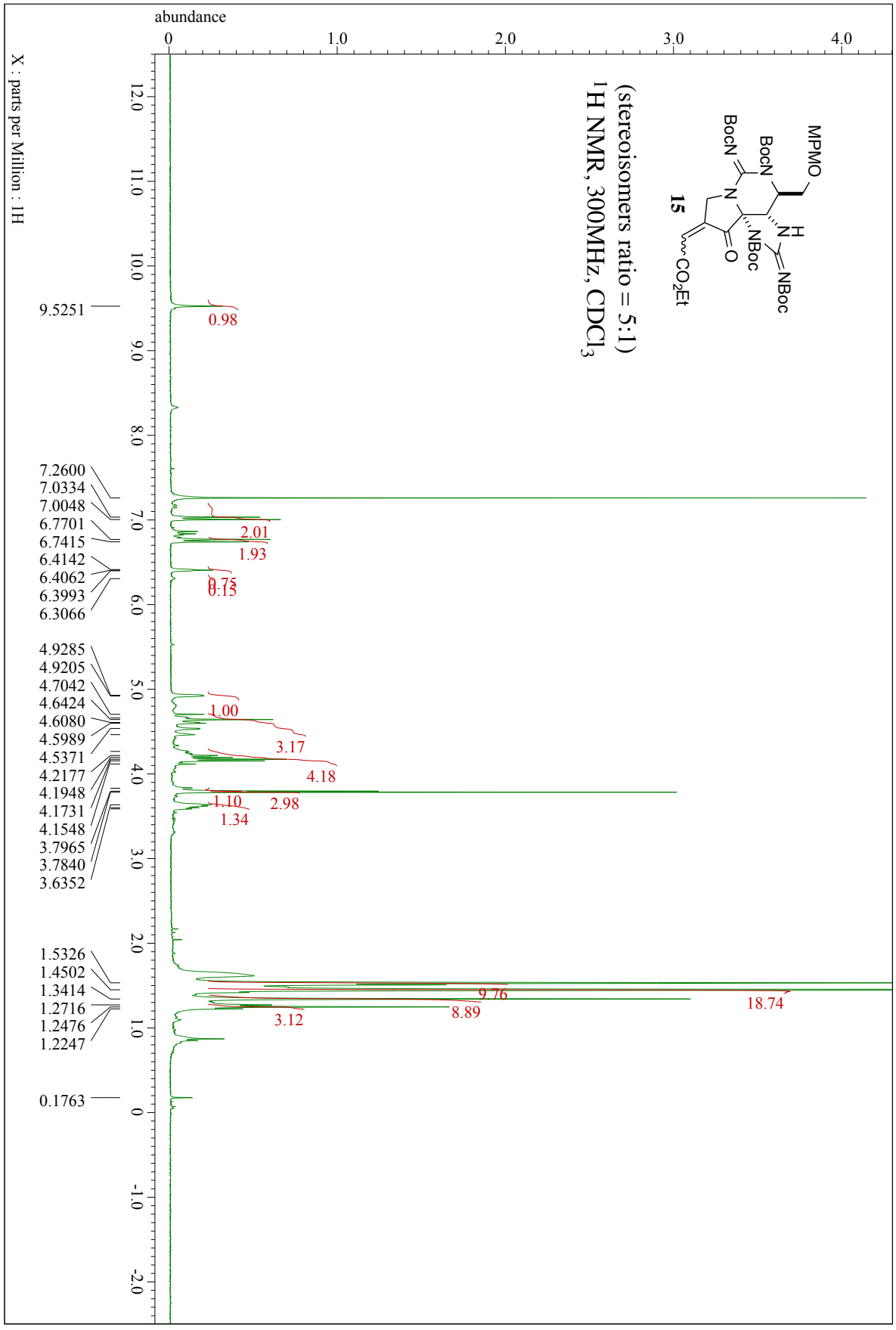
Reference:

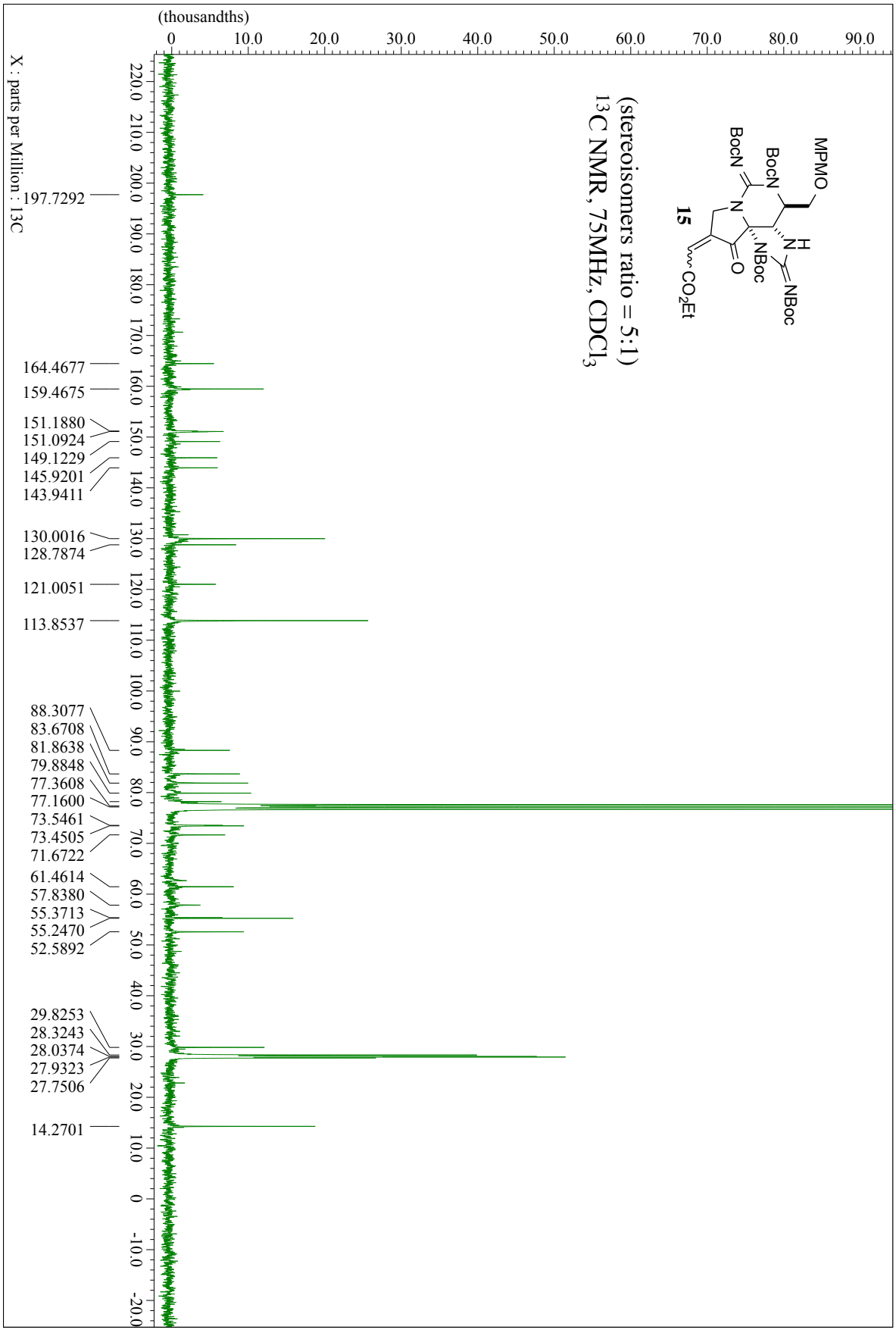
[1] O. Iwamoto, K. Nagasawa, *Org. Lett.* **2010**, *12*, 2150–2153.

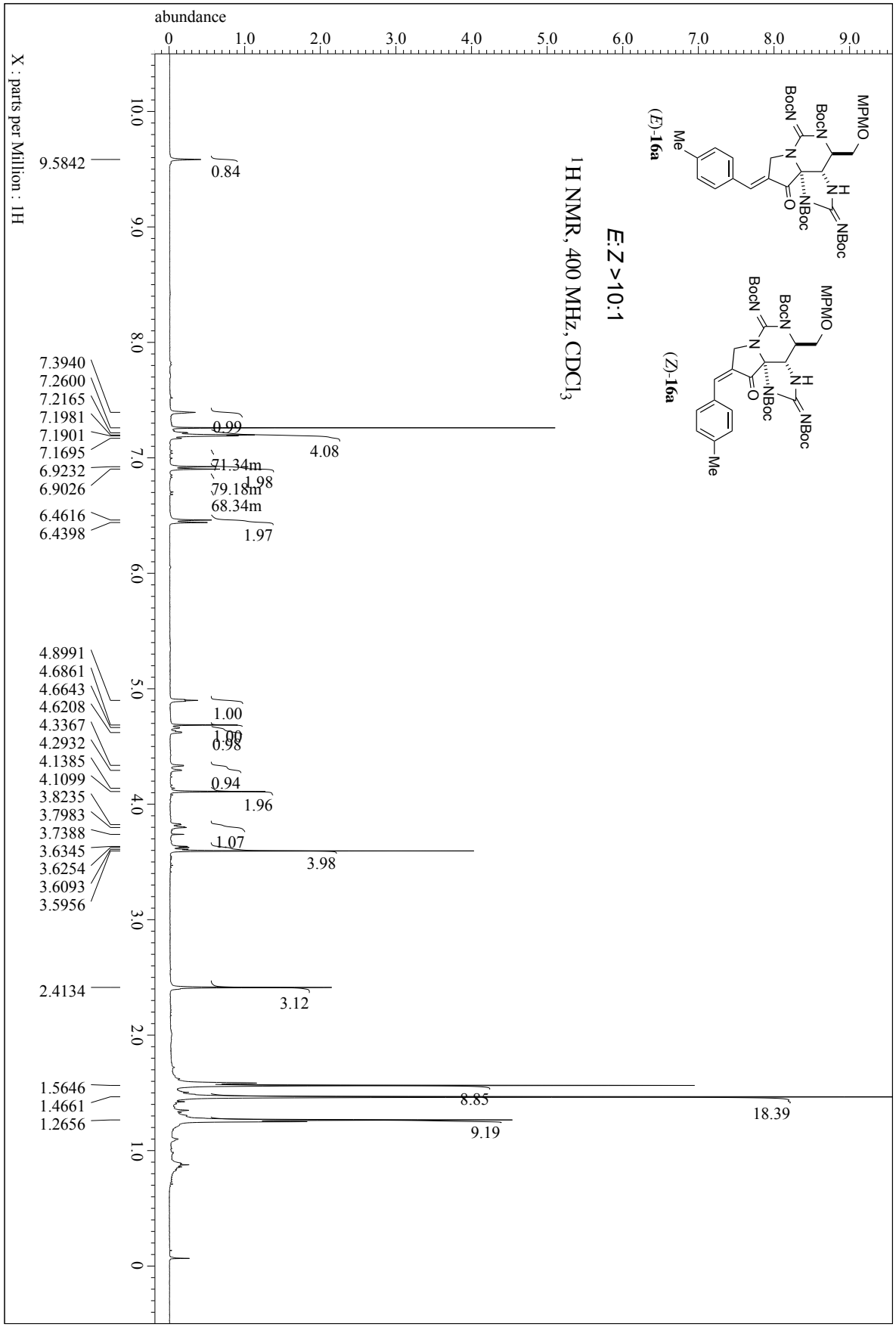
3. Copies of NMR spectra of intermediates for S2-S8, 7-9, 14-17, 19-25

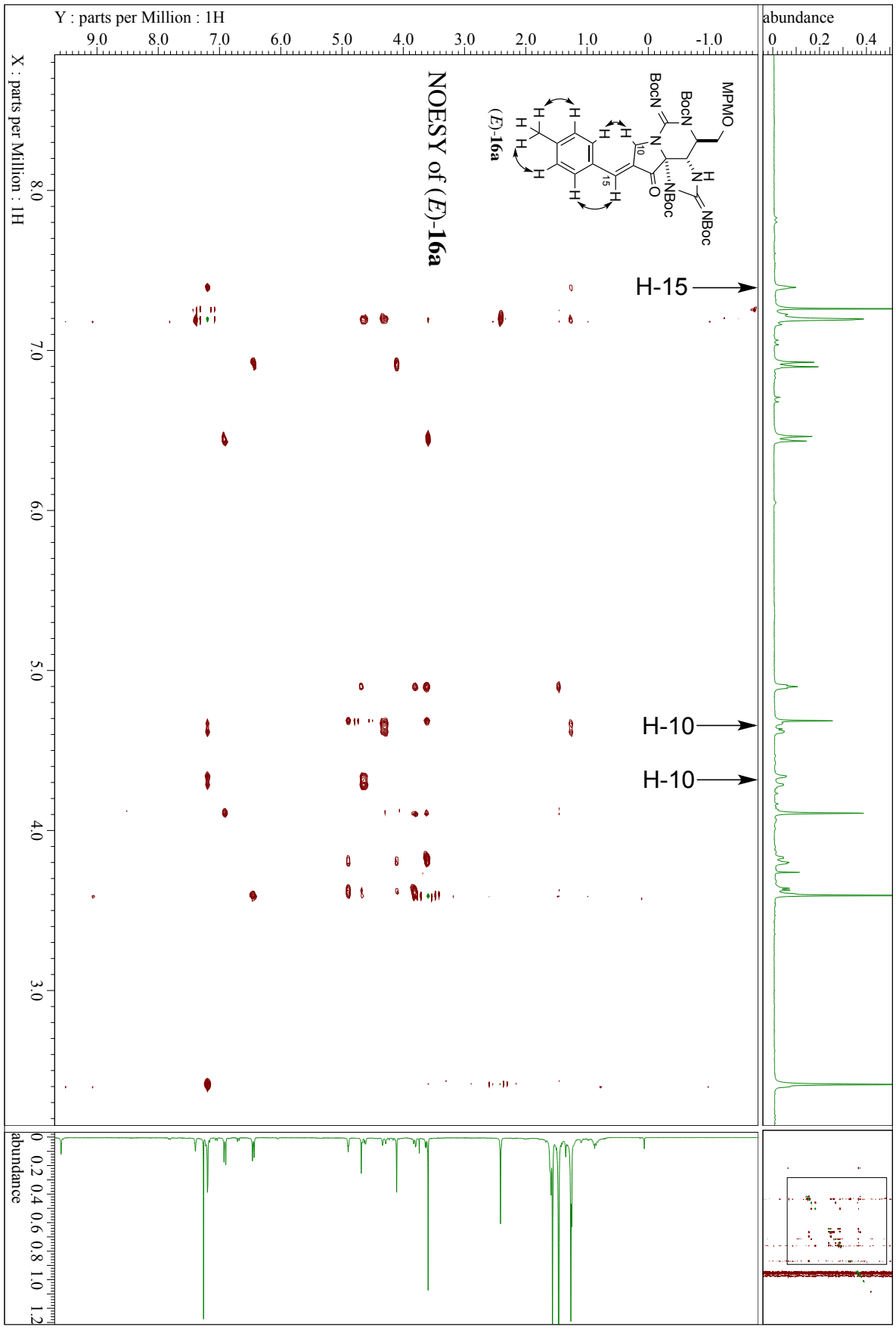

abundance
X : parts per Million : 1H
14
^{1}H NMR, 300MHz, CDCl$_3$
MPMO
BocN
BocN
N
H
N
NBoc
OTBS
NBoc
7.2600
7.1799
7.1524
6.8274
6.7987
4.8370
4.8232
4.8095
4.5691
4.5531
4.3356
4.1170
4.0678
3.8000
3.7302
3.7210
3.6993
3.6878
3.6386
3.6168
3.6020
3.5848
3.5447
3.4944
1.5108
1.4822
1.4525
1.4433
0.8722
0.1774
2.03
2.03
1.00
1.97
2.14
1.03
3.20
1.00
0.96
1.01
8.98
9.34
18.12
9.08
5.97

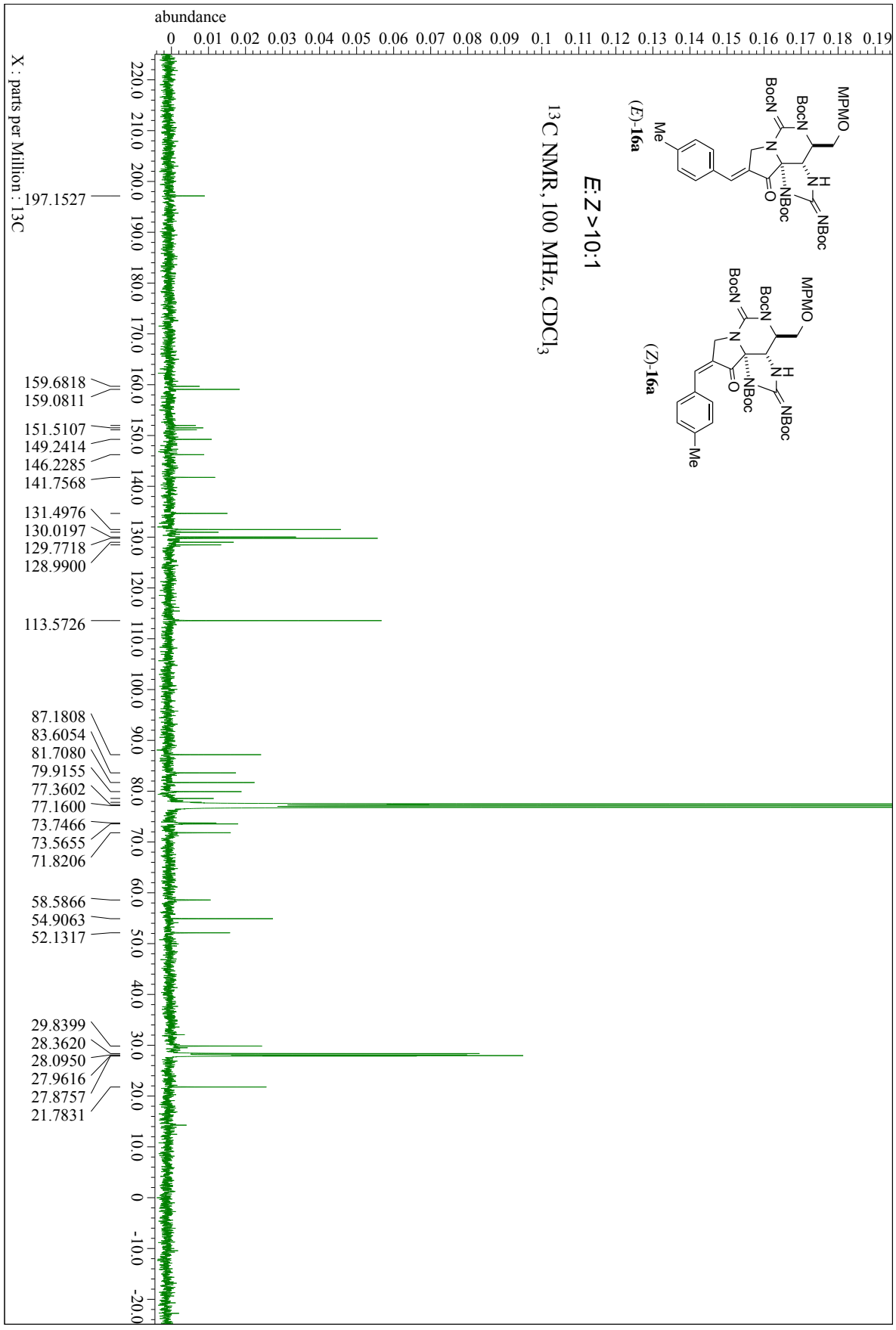

abundance
0
0.1
0.2
0.3
0.4
X : parts per Million : 13C
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
159.7257
159.1042
151.0064
150.7100
149.1038
146.1782
129.9443
129.6766
113.4426
98.5471
84.8850
82.7817
81.1755
79.2155
77.3608
77.1600
73.2306
58.8227
55.2088
52.3501
28.1809
28.0566
27.9705
27.7889
25.3127
17.8267
-4.6695
-5.2049
14
13C NMR, 75MHz, CDCl3
MPMO
BocN
BocN
N
H
N
NBoc
NBoc
OTBS

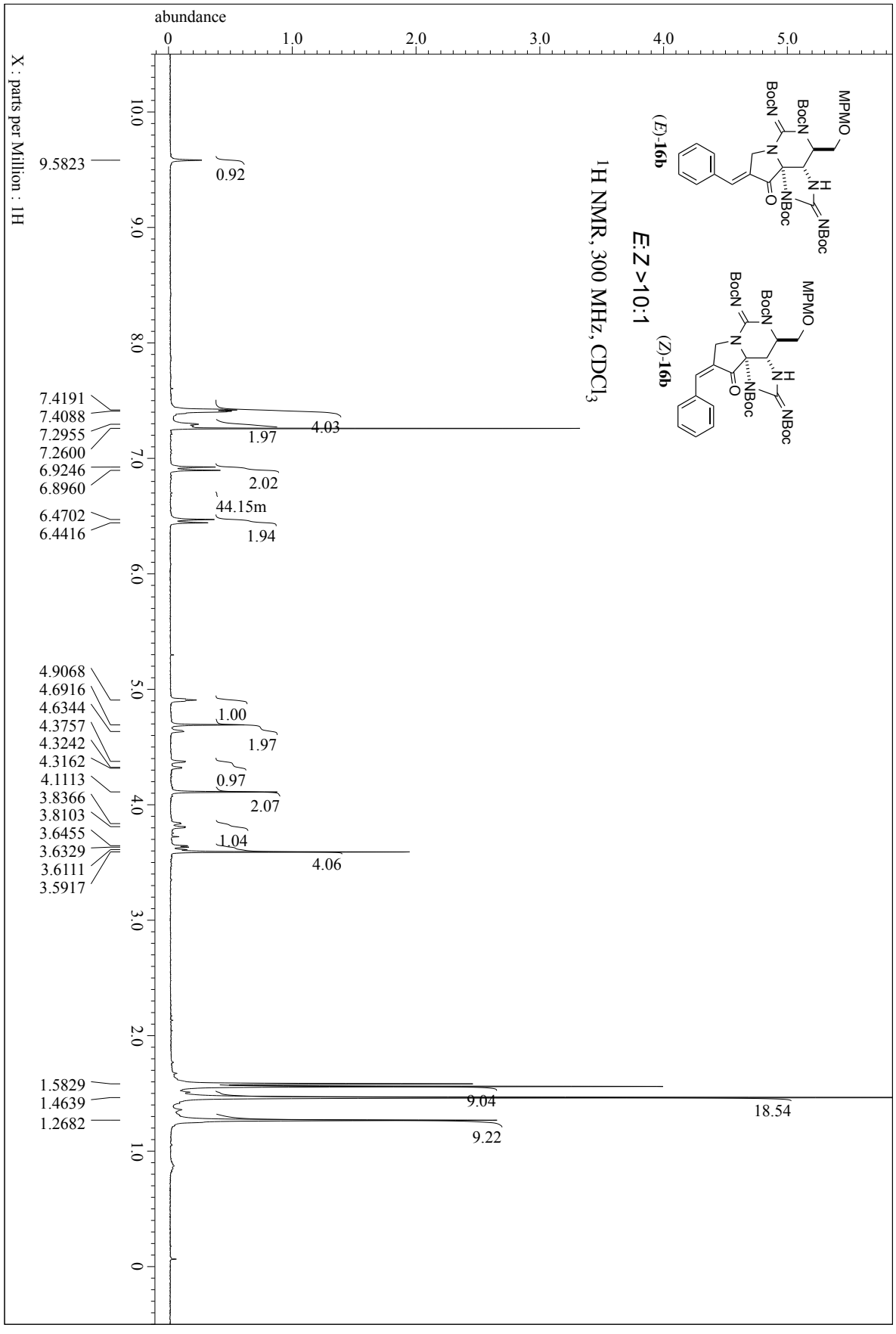

abundance
X : parts per Million : 1H
(stereoisomers ratio = 5:1)
^{1}H NMR, 300MHz, CDCl$_3$
15
MPMO
BocN
BocN
N
NBoc
O
H
N
NBoc
CO$_2$Et
9.5251
7.2600
7.0334
7.0048
6.7701
6.7415
6.4142
6.4062
6.3993
6.3066
4.9285
4.9205
4.7042
4.6424
4.6080
4.5989
4.5371
4.2177
4.1948
4.1731
4.1548
3.7965
3.7840
3.6352
1.5326
1.4502
1.3414
1.2716
1.2476
1.2247
0.1763
0.98
2.01
1.93
0.75
0.15
1.00
3.17
4.18
1.10
2.98
1.34
9.76
18.74
8.89
3.12

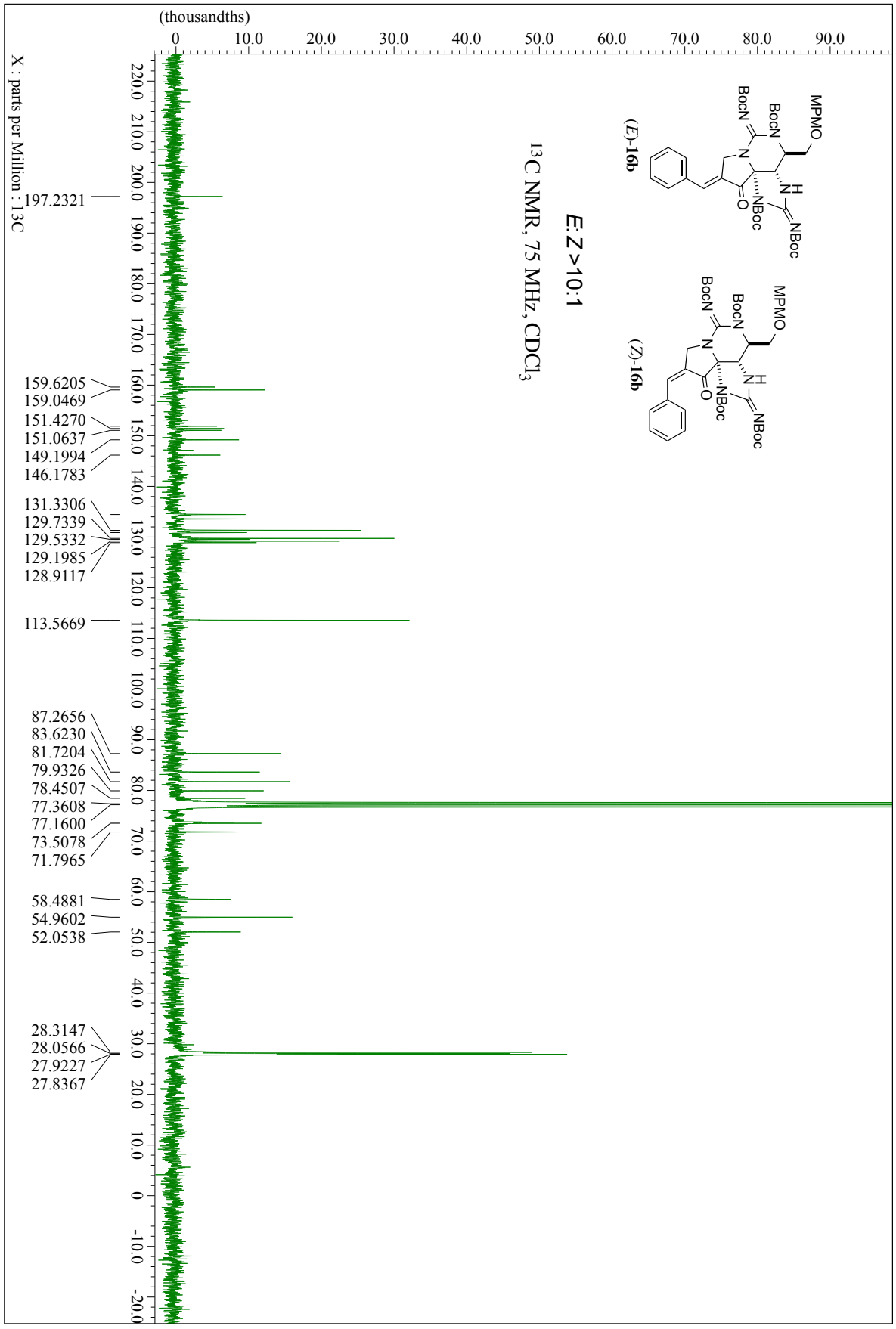

(thousandths)
0 10.0 20.0 30.0 40.0 50.0 60.0 70.0 80.0 90.0
X : parts per Million : 13C
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
197.7292
164.4677
159.4675
151.1880
151.0924
149.1229
145.9201
143.9411
130.0016
128.7874
121.0051
113.8537
88.3077
83.6708
81.8638
79.8848
77.3608
77.1600
73.5461
73.4505
71.6722
61.4614
57.8380
55.3713
55.2470
52.5892
29.8253
28.3243
28.0374
27.9323
27.7506
14.2701
(stereoisomers ratio = 5:1)
13C NMR, 75MHz, CDCl3
MPMO
BocN
BocN
N
NBoc
O
H
N
NBoc
15
CO2Et

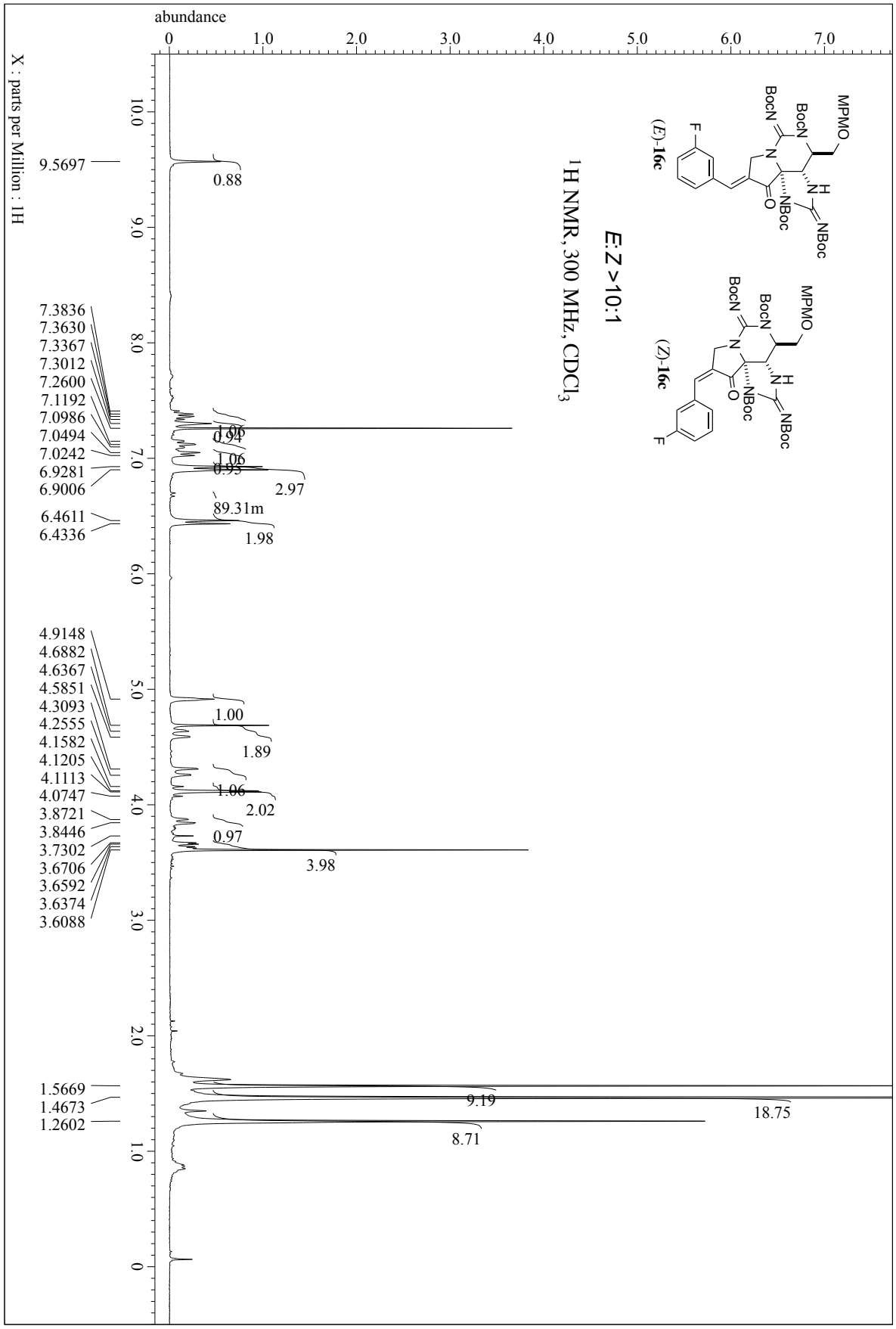

abundance
X : parts per Million : 1H
9.5842
7.3940
7.2600
7.2165
7.1981
7.1901
7.1695
6.9232
6.9026
6.4616
6.4398
4.8991
4.6861
4.6643
4.6208
4.3367
4.2932
4.1385
4.1099
3.8235
3.7983
3.7388
3.6345
3.6254
3.6093
3.5956
2.4134
1.5646
1.4661
1.2656
0.84
0.99
4.08
71.34m
1.98
79.18m
68.34m
1.97
1.00
1.00
0.98
0.94
1.96
1.07
3.98
3.12
8.85
9.19
18.39
E:Z >10:1
1H NMR, 400 MHz, CDCl3
(E)-16a
(Z)-16a
MPMO
BocN
BocN
NBoc
NBoc
Me

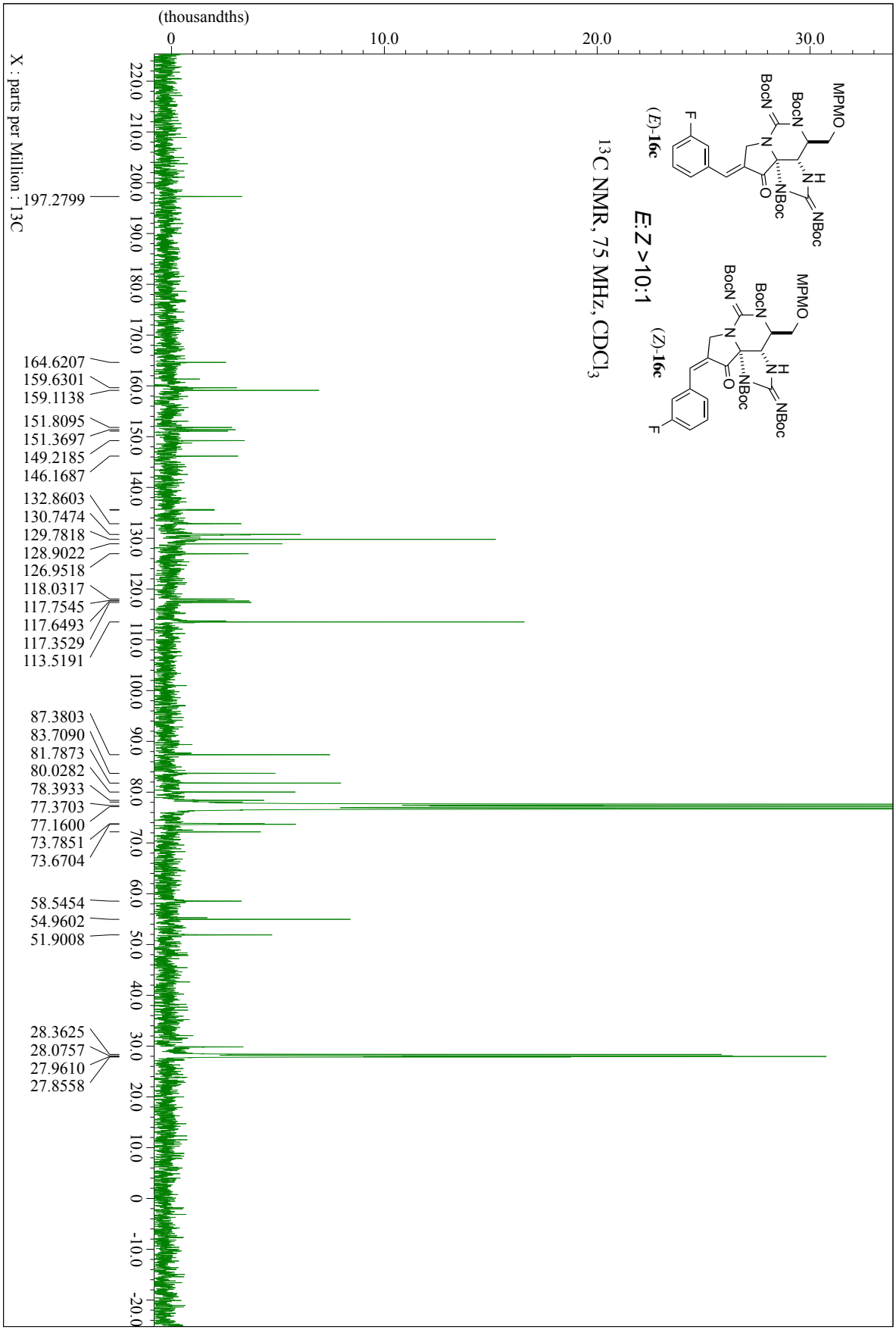

NOESY of (E)-16a
(E)-16a
MPMO
BocN
BocN
BocN
NBoc
NBoc
O
H-15
H-10
H-10
Y : parts per Million : 1H
X : parts per Million : 1H
abundance
abundance

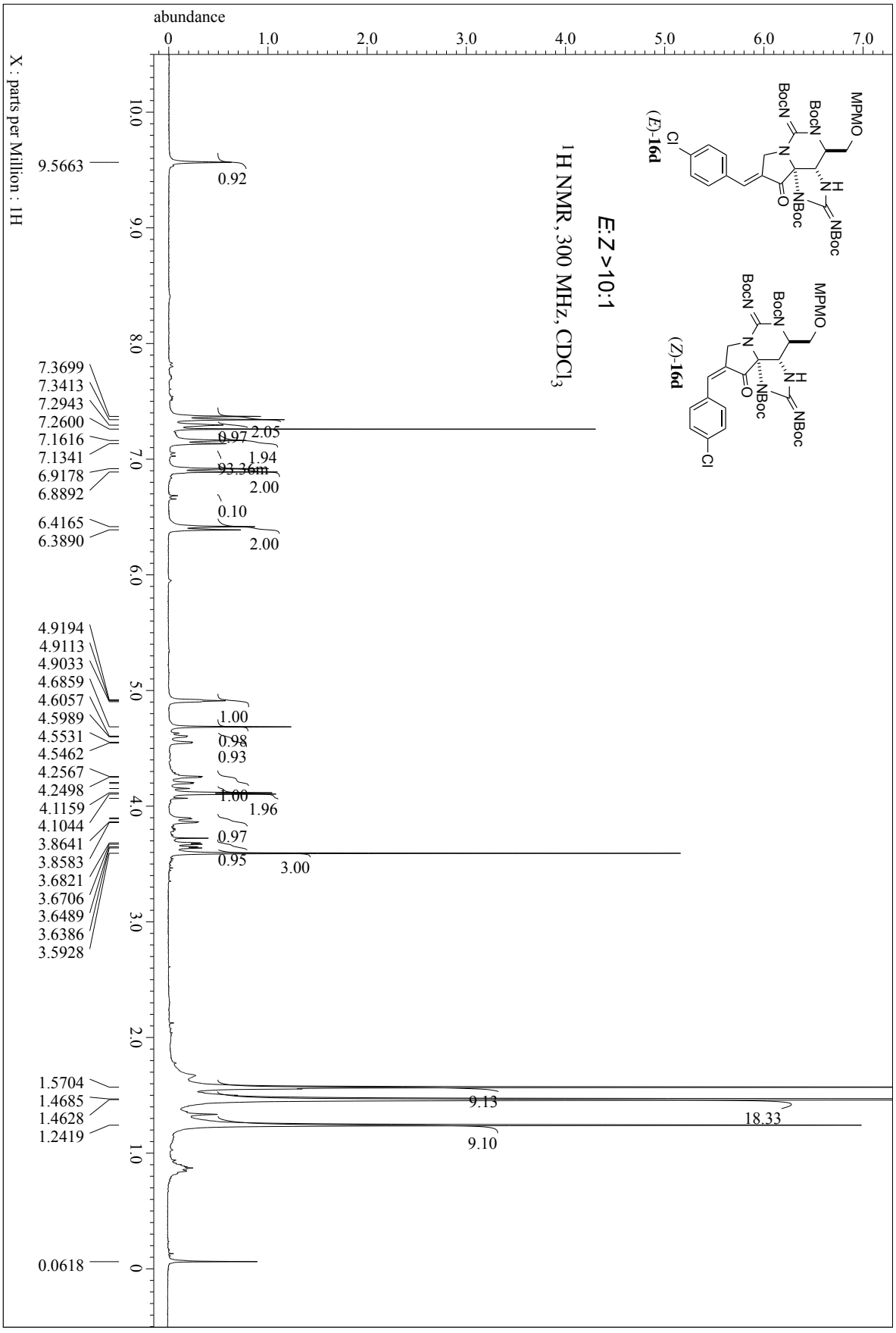

abundance
0 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.1 0.11 0.12 0.13 0.14 0.15 0.16 0.17 0.18 0.19
X : parts per Million : 13C
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
197.1527
159.6818
159.0811
151.5107
149.2414
146.2285
141.7568
131.4976
130.0197
129.7718
128.9900
113.5726
87.1808
83.6054
81.7080
79.9155
77.3602
77.1600
73.7466
73.5655
71.8206
58.5866
54.9063
52.1317
29.8399
28.3620
28.0950
27.9616
27.8757
21.7831
13C NMR, 100 MHz, CDCl3
E:Z >10:1
(E)-16a
(Z)-16a
MPMO
BocN
NBoc
Me

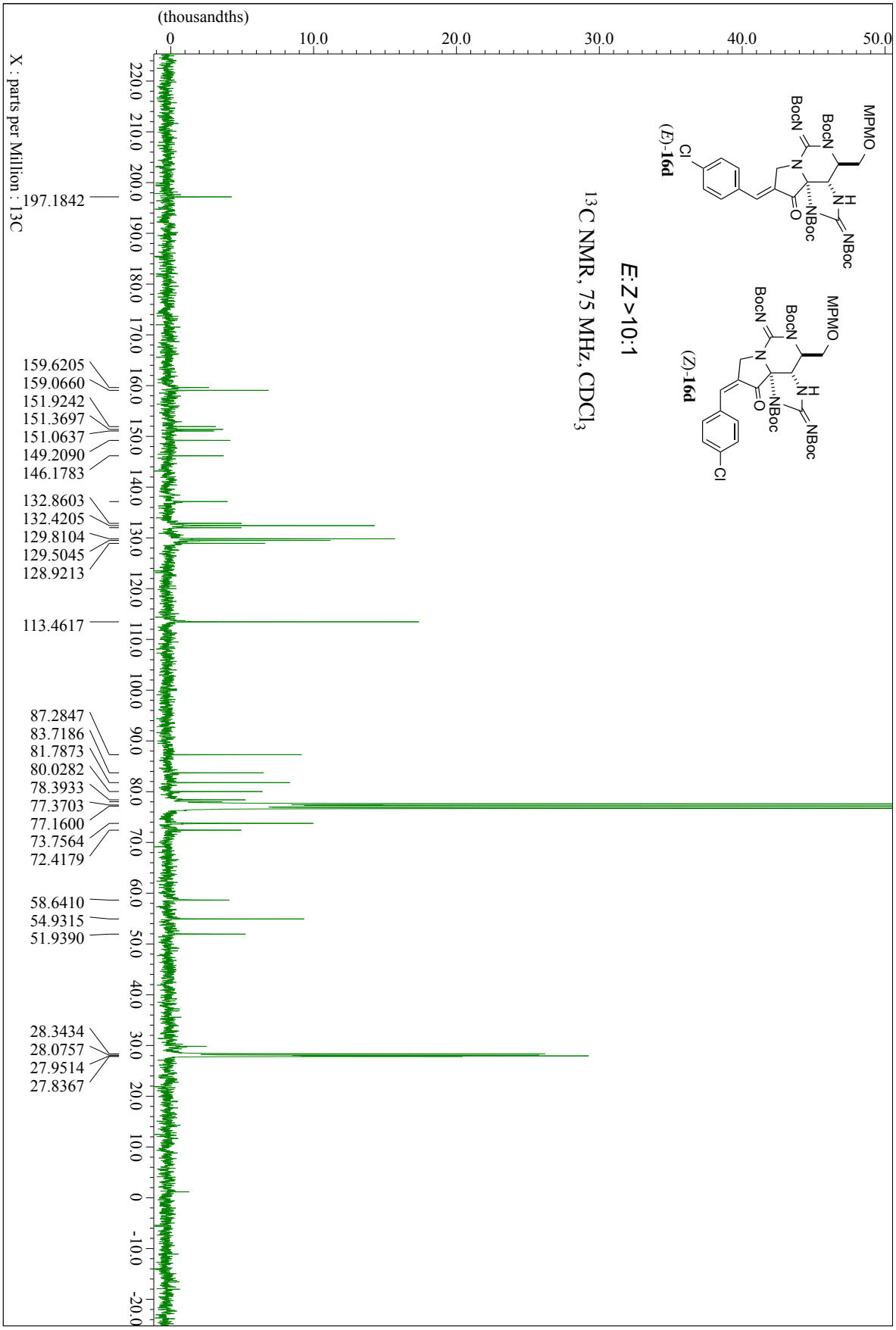

abundance
0
1.0
2.0
3.0
4.0
5.0
X : parts per Million : 1H
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
9.5823
7.4191
7.4088
7.2955
7.2600
6.9246
6.8960
6.4702
6.4416
4.9068
4.6916
4.6344
4.3757
4.3242
4.3162
4.1113
3.8366
3.8103
3.6455
3.6329
3.6111
3.5917
1.5829
1.4639
1.2682
0.92
4.03
1.97
2.02
44.15m
1.94
1.00
1.97
0.97
2.07
1.04
4.06
9.04
18.54
9.22
^{1}H NMR, 300 MHz, $CDCl_3$
E:*Z* >10:1
(*E*)-**16b**
(*Z*)-**16b**
MPMO
BocN
BocN
N
H
N
NBoc
NBoc
O

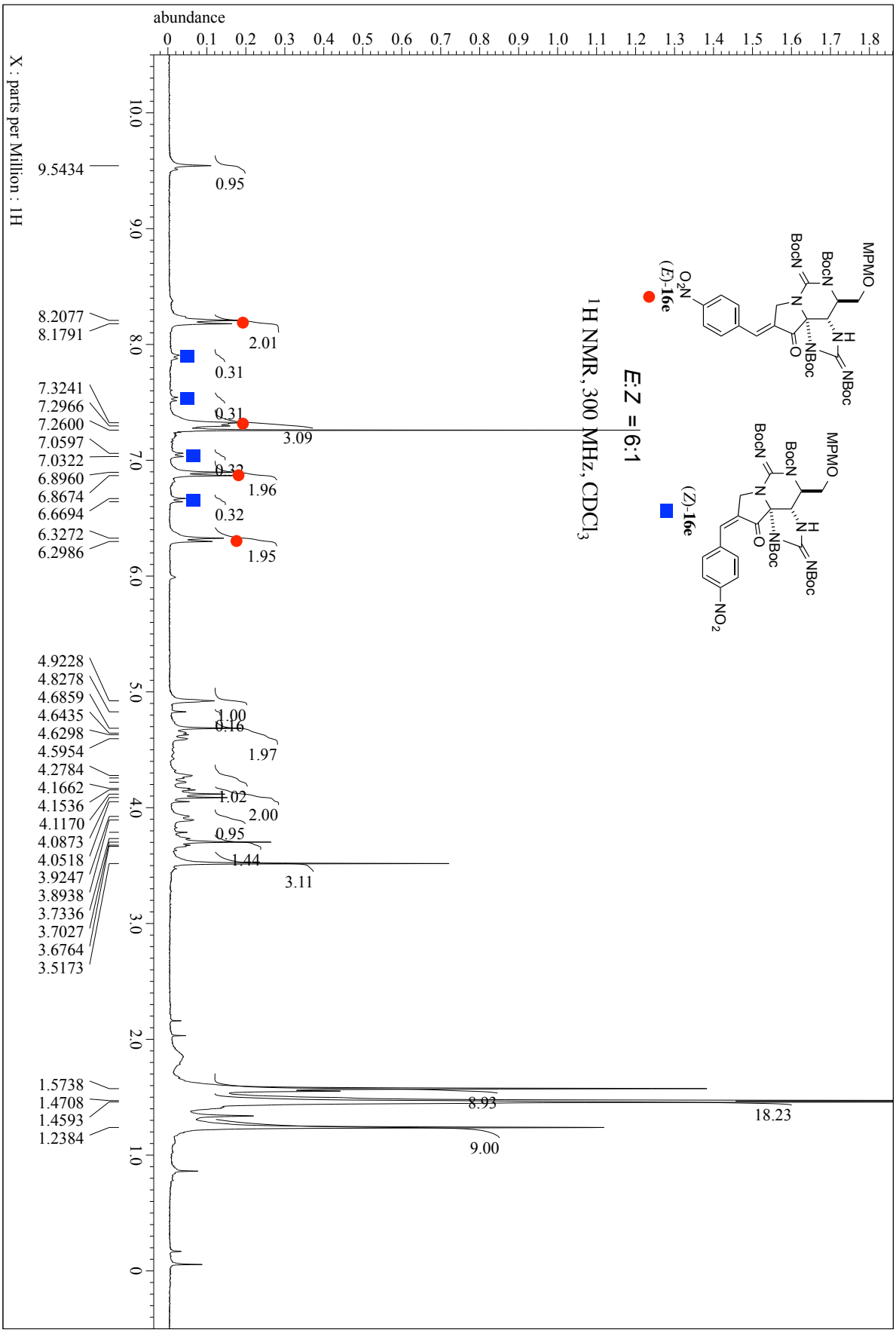

(thousandths)
0 10.0 20.0 30.0 40.0 50.0 60.0 70.0 80.0 90.0
X : parts per Million : 13C
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
197.2321
159.6205
159.0469
151.4270
151.0637
149.1994
146.1783
131.3306
129.7339
129.5332
129.1985
128.9117
113.5669
87.2656
83.6230
81.7204
79.9326
78.4507
77.3608
77.1600
73.5078
71.7965
58.4881
54.9602
52.0538
28.3147
28.0566
27.9227
27.8367
E: Z > 10:1
13C NMR, 75 MHz, CDCl3
(E)-16b
(Z)-16b
MPMO
BocN
NBoc
H
N
O

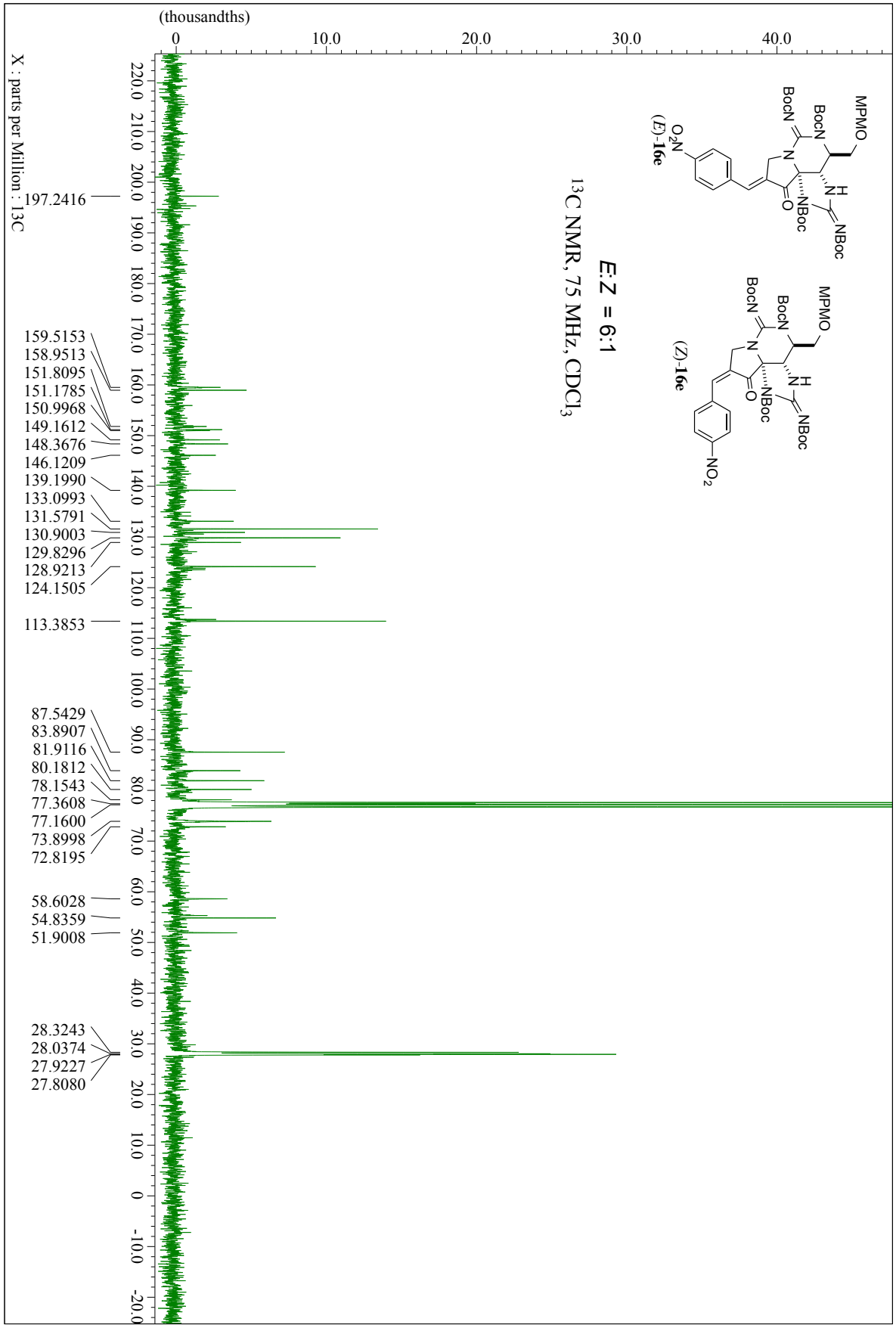

abundance
X : parts per Million : 1H
^{1}H NMR, 300 MHz, $CDCl_3$
E:*Z* >10:1
(*E*)-**16c**
(*Z*)-**16c**
MPMO
BocN
NBoc
F
9.5697
7.3836
7.3630
7.3367
7.3012
7.2600
7.1192
7.0986
7.0494
7.0242
6.9281
6.9006
6.4611
6.4336
4.9148
4.6882
4.6367
4.5851
4.3093
4.2555
4.1582
4.1205
4.1113
4.0747
3.8721
3.8446
3.7302
3.6706
3.6592
3.6374
3.6088
1.5669
1.4673
1.2602
0.88
1.06
0.94
1.06
0.95
2.97
89.31m
1.98
1.00
1.89
1.06
2.02
0.97
3.98
9.19
18.75
8.71

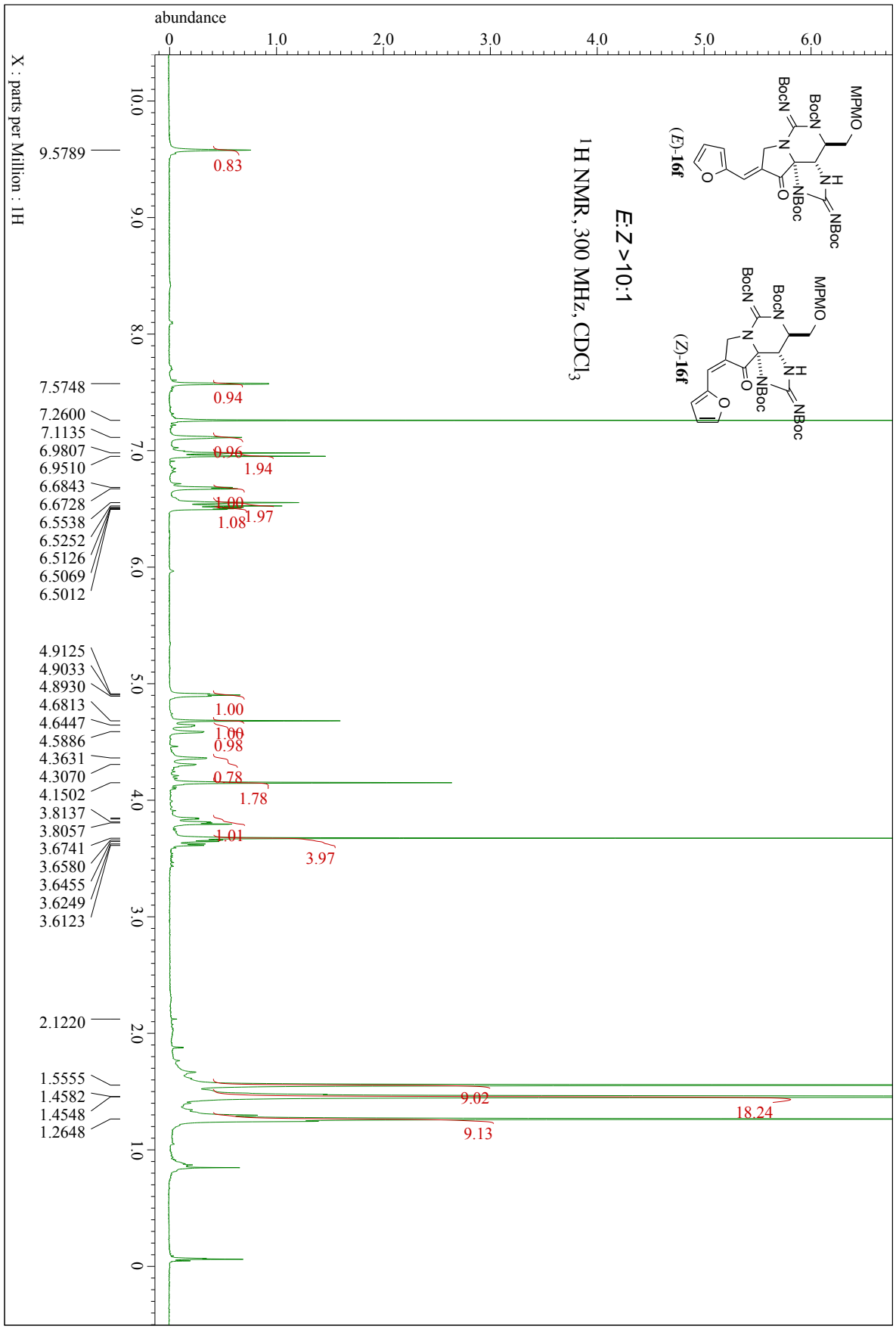

(thousandths)
0
10.0
20.0
30.0
X : parts per Million : 13C
197.2799
164.6207
159.6301
159.1138
151.8095
151.3697
149.2185
146.1687
132.8603
130.7474
129.7818
128.9022
126.9518
118.0317
117.7545
117.6493
117.3529
113.5191
87.3803
83.7090
81.7873
80.0282
78.3933
77.3703
77.1600
73.7851
73.6704
58.5454
54.9602
51.9008
28.3625
28.0757
27.9610
27.8558
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
(E)-16c
(Z)-16c
E:Z >10:1
13C NMR, 75 MHz, CDCl3
MPMO
BocN
NBoc
F
O
H
N

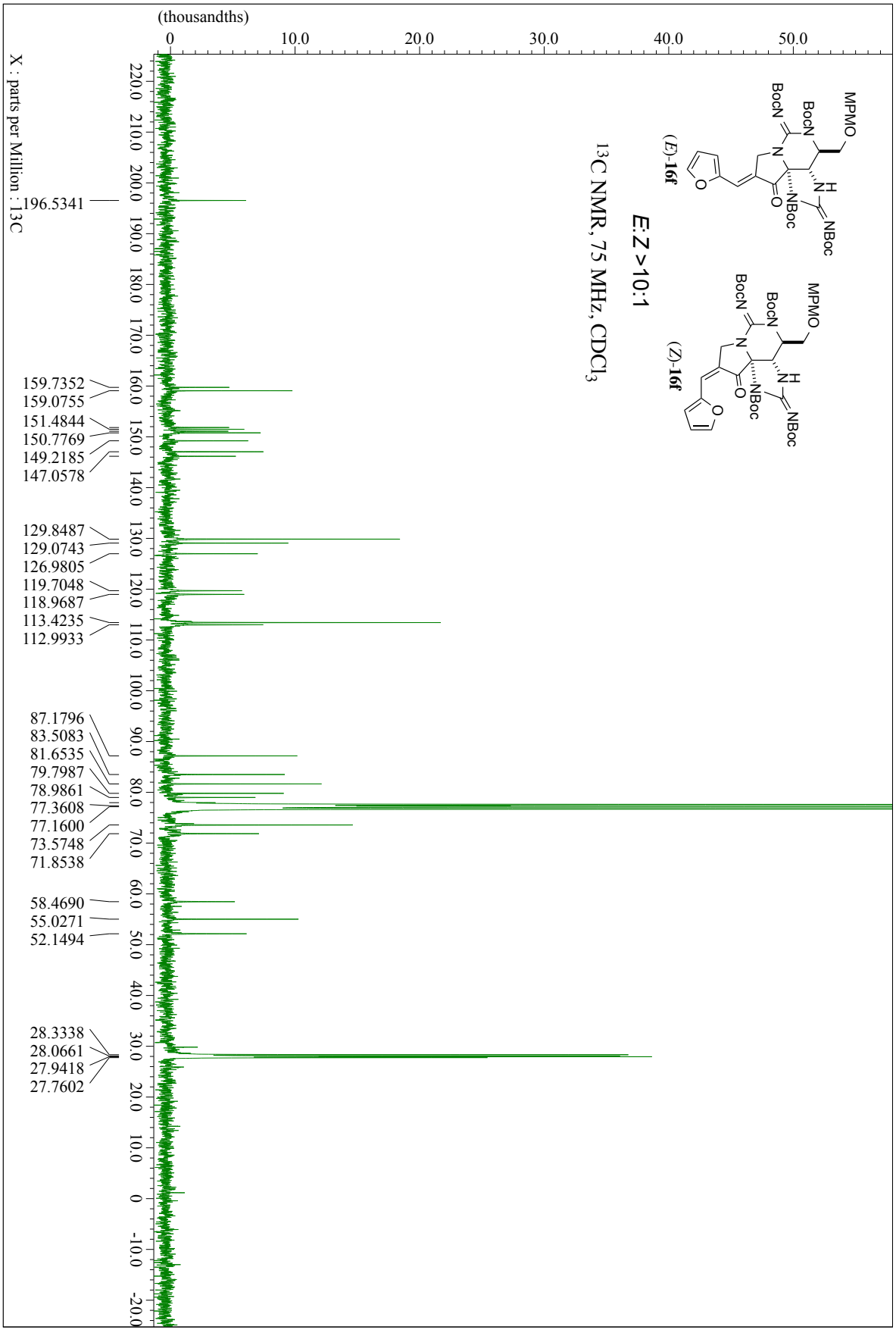

abundance
0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
X : parts per Million : 1H
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
9.5663
7.3699
7.3413
7.2943
7.2600
7.1616
7.1341
6.9178
6.8892
6.4165
6.3890
4.9194
4.9113
4.9033
4.6859
4.6057
4.5989
4.5531
4.5462
4.2567
4.2498
4.1159
4.1044
3.8641
3.8583
3.6821
3.6706
3.6489
3.6386
3.5928
1.5704
1.4685
1.4628
1.2419
0.0618
0.92
0.97
2.05
1.94
93.36m
2.00
0.10
2.00
1.00
0.98
0.93
1.00
1.96
0.97
0.95
3.00
9.13
18.33
9.10
^{1}H NMR, 300 MHz, $CDCl_3$
E:*Z* >10:1
(*E*)-**16d**
(*Z*)-**16d**
BocN
BocN
MPMO
N
H
N
NBoc
NBoc
O
Cl

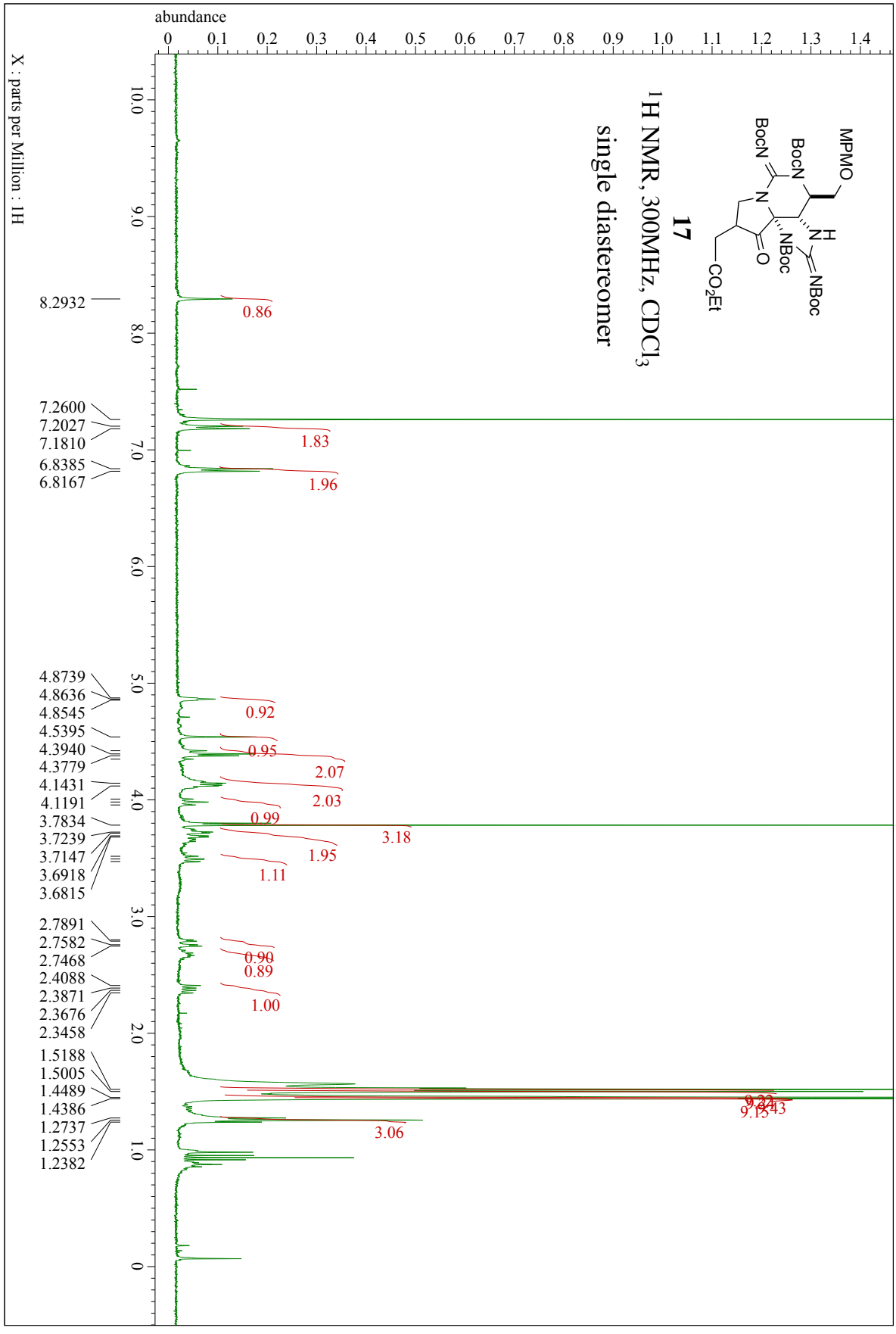

(thousandths)
0
10.0
20.0
30.0
40.0
50.0
X : parts per Million : 13C
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
-10.0
-20.0
197.1842
159.6205
159.0660
151.9242
151.3697
151.0637
149.2090
146.1783
132.8603
132.4205
129.8104
129.5045
128.9213
113.4617
87.2847
83.7186
81.7873
80.0282
78.3933
77.3703
77.1600
73.7564
72.4179
58.6410
54.9315
51.9390
28.3434
28.0757
27.9514
27.8367
^{13}C NMR, 75 MHz, $CDCl_3$
E:*Z* > 10:1
(*E*)-**16d**
(*Z*)-**16d**
MPMO
BocN
BocN
NBoc
NBoc
H
N
O
Cl

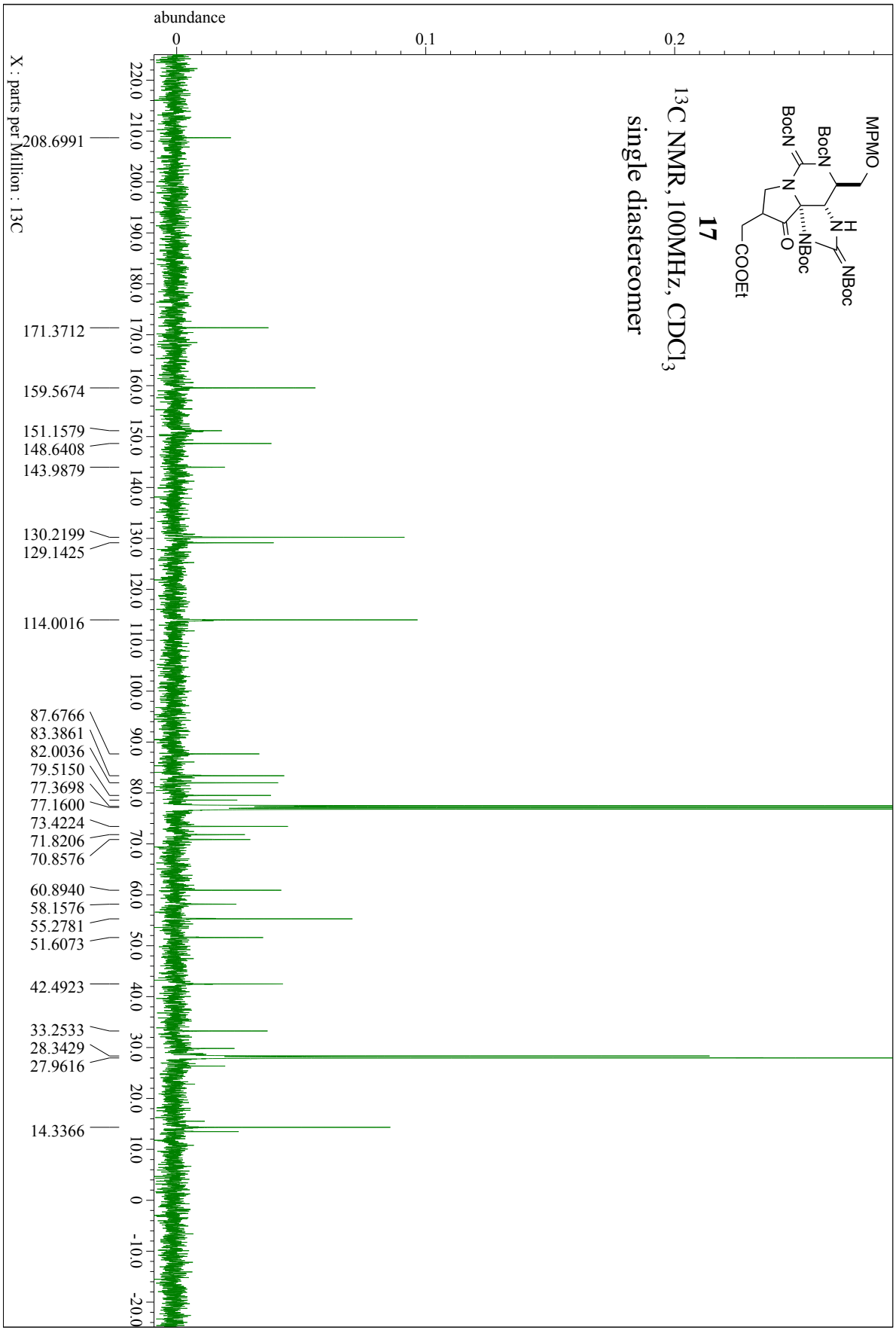

abundance
X : parts per Million : 1H
9.5434
8.2077
8.1791
7.3241
7.2966
7.2600
7.0597
7.0322
6.8960
6.8674
6.6694
6.3272
6.2986
4.9228
4.8278
4.6859
4.6435
4.6298
4.5954
4.2784
4.1662
4.1536
4.1170
4.0873
4.0518
3.9247
3.8938
3.7336
3.7027
3.6764
3.5173
1.5738
1.4708
1.4593
1.2384
0.95
2.01
0.31
0.31
3.09
0.32
1.96
0.32
1.95
1.00
0.16
1.97
1.02
2.00
0.95
1.44
3.11
8.93
18.23
9.00
^{1}H NMR, 300 MHz, $CDCl_3$
E:Z = 6:1
(E)-16e
(Z)-16e
MPMO
BocN
BocN
NBoc
NBoc
O2N
NO2

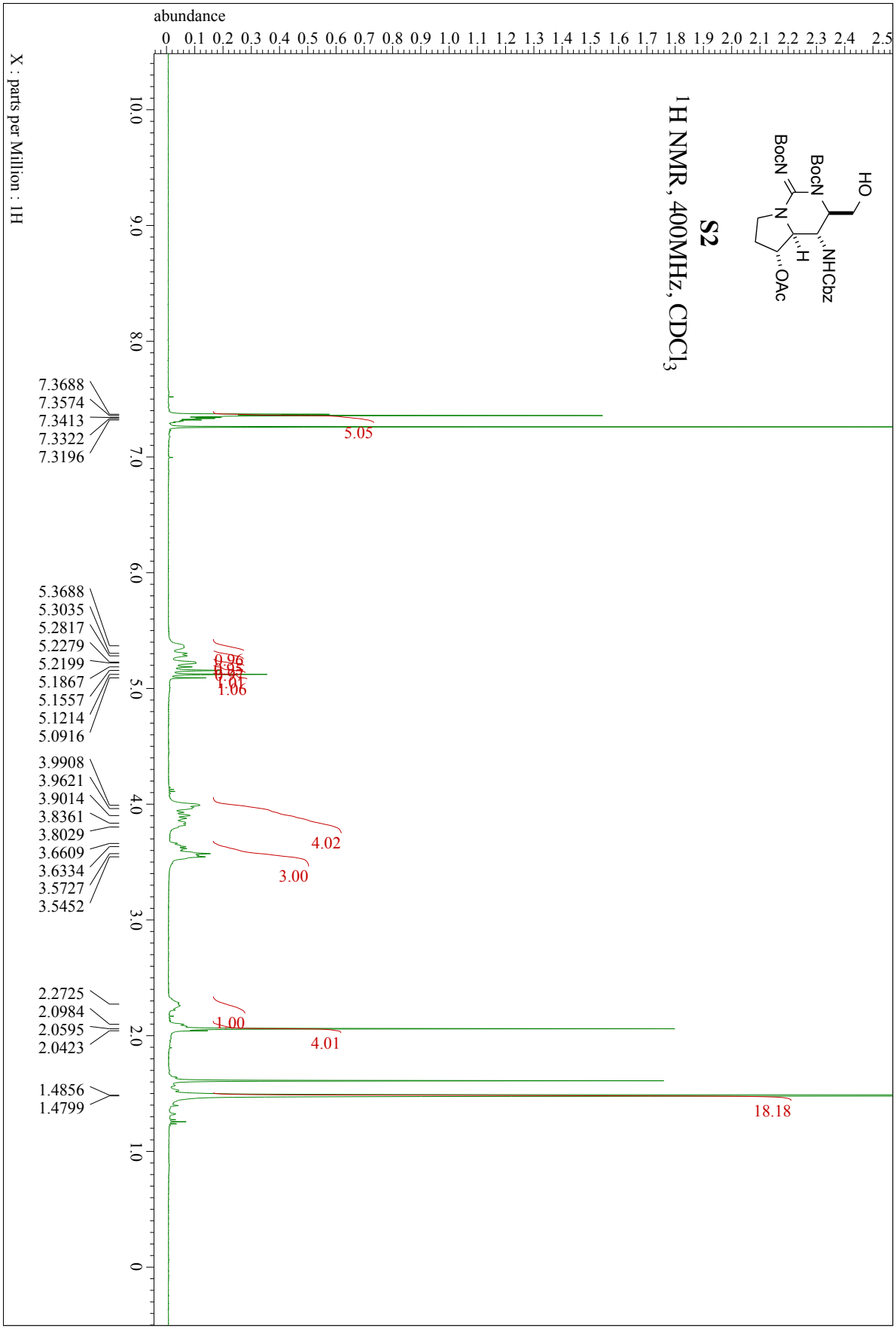

(thousandths)
0
10.0
20.0
30.0
40.0
X : parts per Million : 13C
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
197.2416
159.5153
158.9513
151.8095
151.1785
150.9968
149.1612
148.3676
146.1209
139.1990
133.0993
131.5791
130.9003
129.8296
128.9213
124.1505
113.3853
87.5429
83.8907
81.9116
80.1812
78.1543
77.3608
77.1600
73.8998
72.8195
58.6028
54.8359
51.9008
28.3243
28.0374
27.9227
27.8080
E:Z = 6:1
13C NMR, 75 MHz, CDCl3
(E)-16e
(Z)-16e
MPMO
BocN
BocN
N
NBoc
O
H
N
NBoc
O2N
NO2

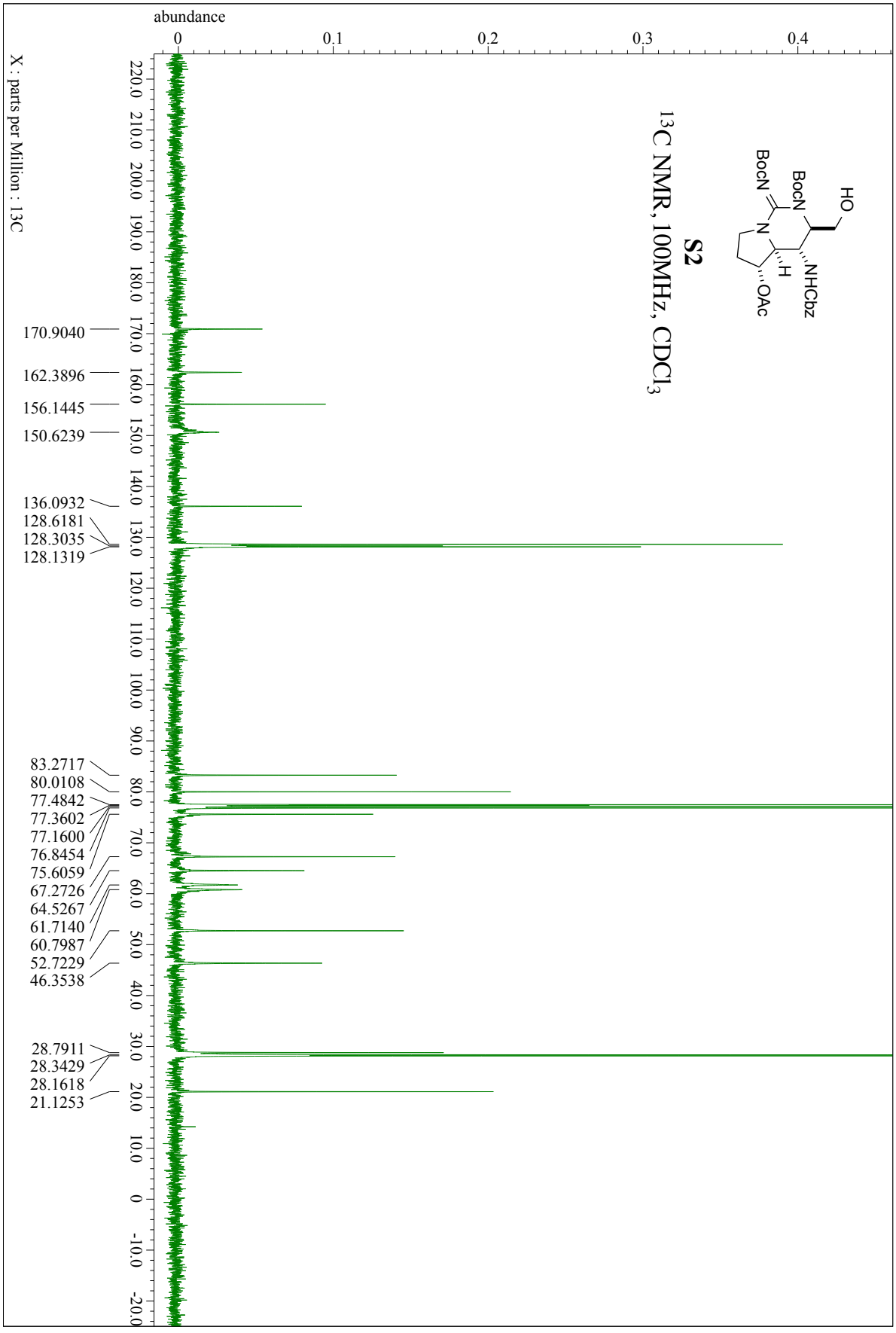

abundance
X : parts per Million : 1H
9.5789
7.5748
7.2600
7.1135
6.9807
6.9510
6.6843
6.6728
6.5538
6.5252
6.5126
6.5069
6.5012
4.9125
4.9033
4.8930
4.6813
4.6447
4.5886
4.3631
4.3070
4.1502
3.8137
3.8057
3.6741
3.6580
3.6455
3.6249
3.6123
2.1220
1.5555
1.4582
1.4548
1.2648
0.83
0.94
0.96
1.94
1.00
1.97
1.08
1.00
1.00
0.98
0.78
1.78
1.01
3.97
9.02
18.24
9.13
E:Z >10:1
1H NMR, 300 MHz, CDCl3
(E)-16f
(Z)-16f
BocN
MPMO
NBoc
O
N
H

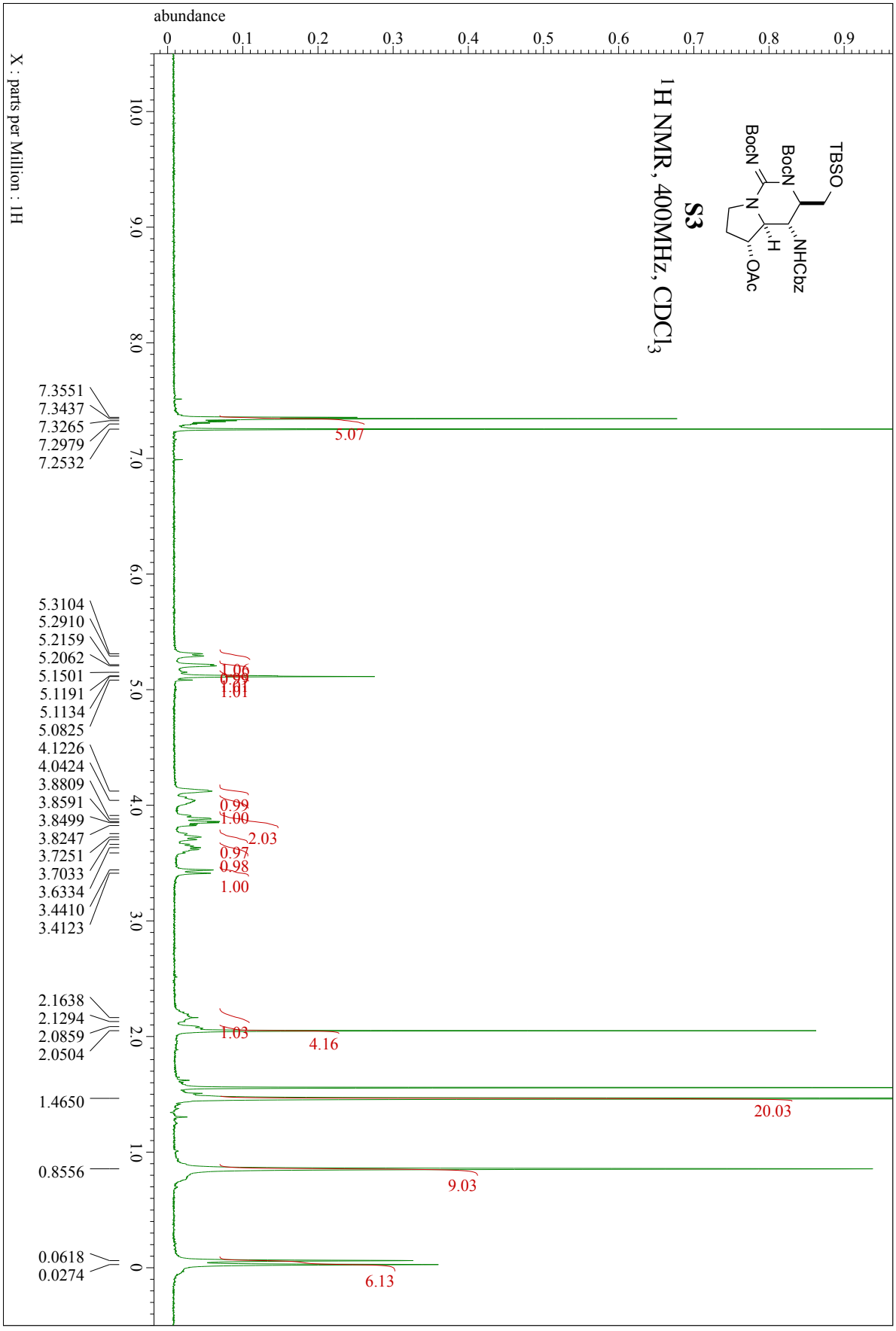

(thousandths)
0
10.0
20.0
30.0
40.0
50.0
X : parts per Million : 13C
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
-10.0
-20.0
196.5341
159.7352
159.0755
151.4844
150.7769
149.2185
147.0578
129.8487
129.0743
126.9805
119.7048
118.9687
113.4235
112.9933
87.1796
83.5083
81.6535
79.7987
78.9861
77.3608
77.1600
73.5748
71.8538
58.4690
55.0271
52.1494
28.3338
28.0661
27.9418
27.7602
13C NMR, 75 MHz, CDCl3
E:Z >10:1
(E)-16f
(Z)-16f
MPMO
BocN
BocN
NBoc
NBoc
H
N
O
O
N

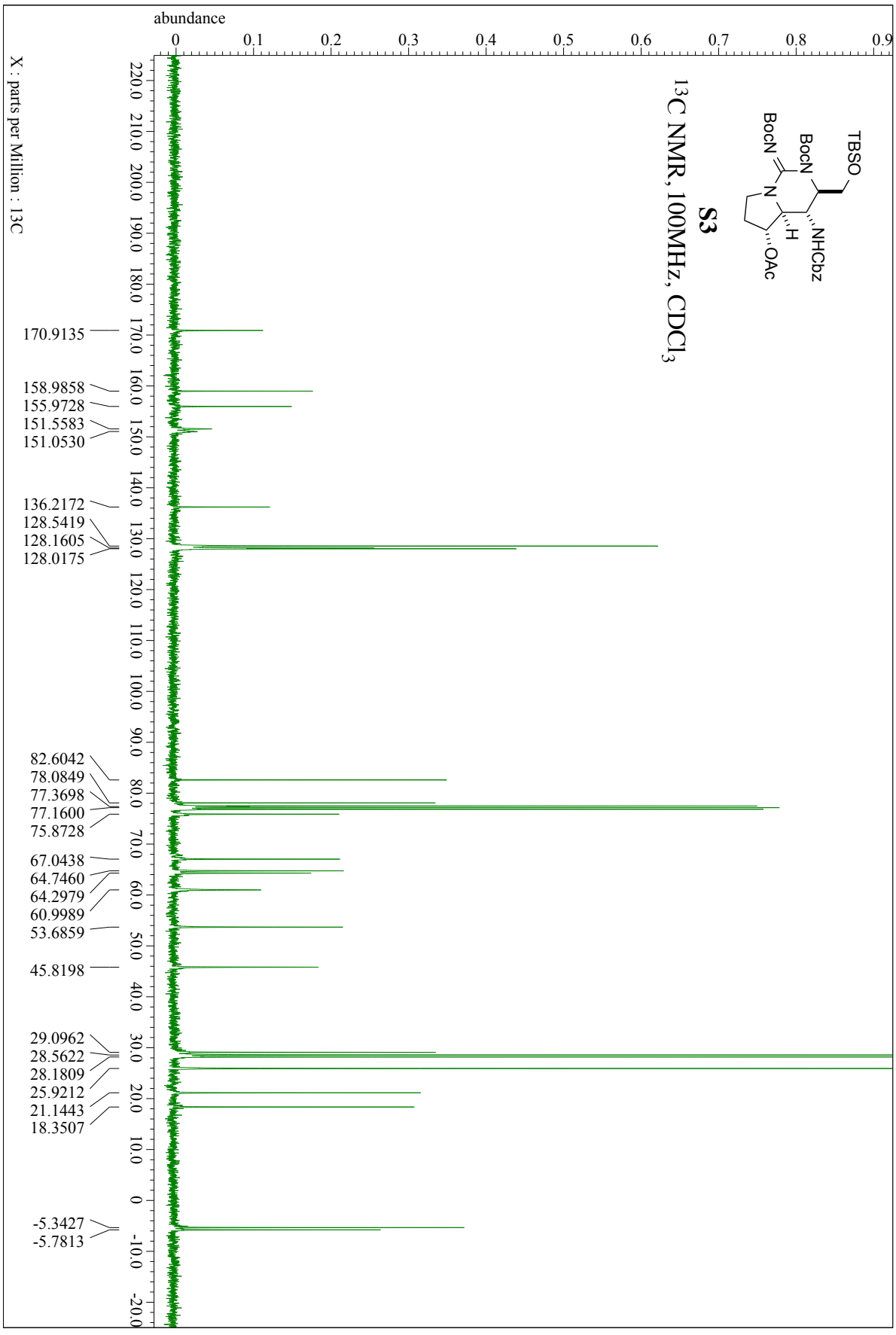

abundance
X : parts per Million : 1H
17
^{1}H NMR, 300MHz, CDCl$_3$
single diastereomer
MPMO
BocN
BocN
N
NBoc
O
H
N
NBoc
CO$_2$Et
8.2932
7.2600
7.2027
7.1810
6.8385
6.8167
4.8739
4.8636
4.8545
4.5395
4.3940
4.3779
4.1431
4.1191
3.7834
3.7239
3.7147
3.6918
3.6815
2.7891
2.7582
2.7468
2.4088
2.3871
2.3676
2.3458
1.5188
1.5005
1.4489
1.4386
1.2737
1.2553
1.2382
0.86
1.83
1.96
0.92
0.95
2.07
2.03
0.99
3.18
1.95
1.11
0.90
0.89
1.00
9.15
3.06

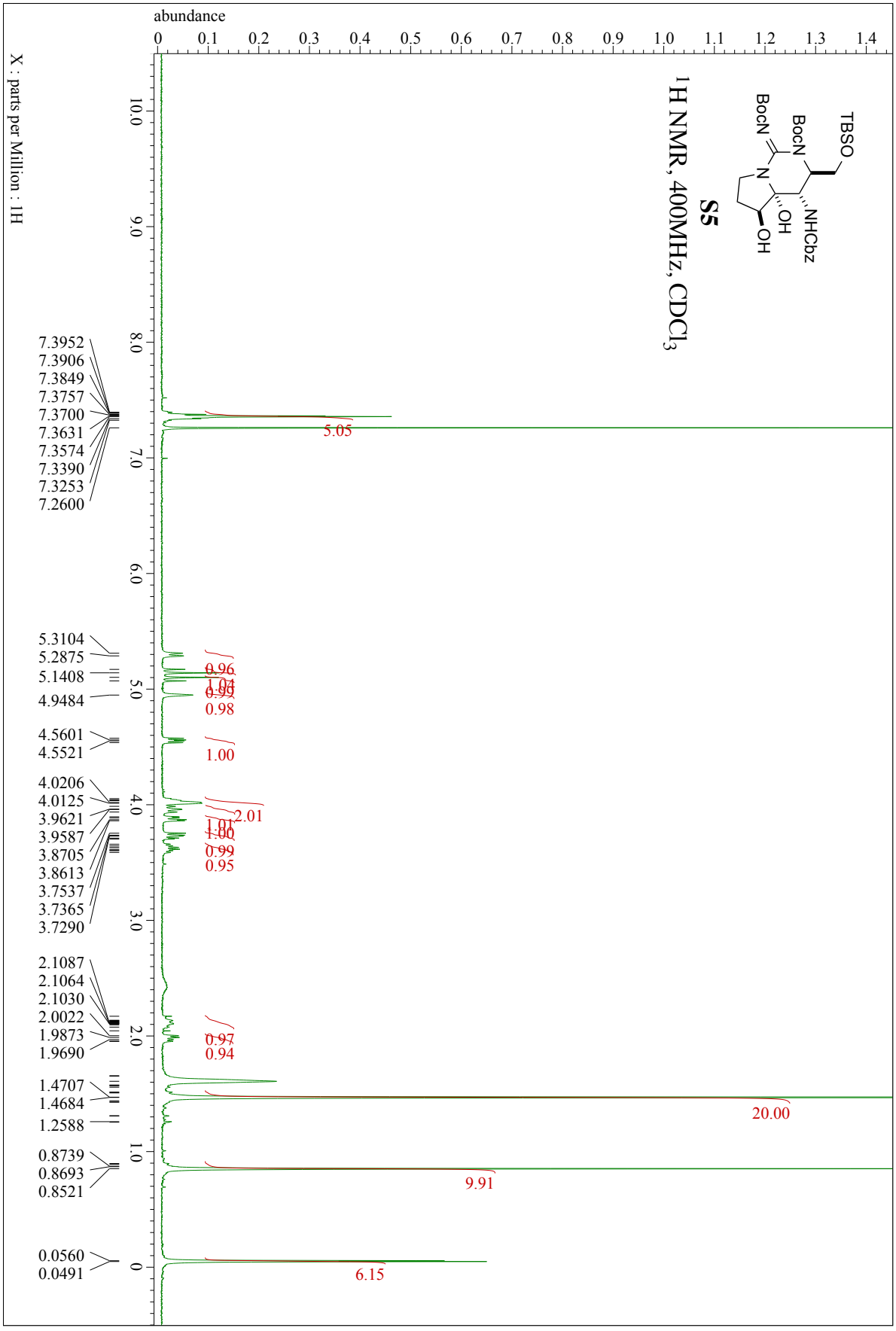

abundance
0
0.1
0.2
X : parts per Million : 13C
208.6991
171.3712
159.5674
151.1579
148.6408
143.9879
130.2199
129.1425
114.0016
87.6766
83.3861
82.0036
79.5150
77.3698
77.1600
73.4224
71.8206
70.8576
60.8940
58.1576
55.2781
51.6073
42.4923
33.2533
28.3429
27.9616
14.3366
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
^{13}C NMR, 100MHz, $CDCl_3$
single diastereomer
17
MPMO
BocN
BocN
N
NBoc
H
N
NBoc
O
COOEt

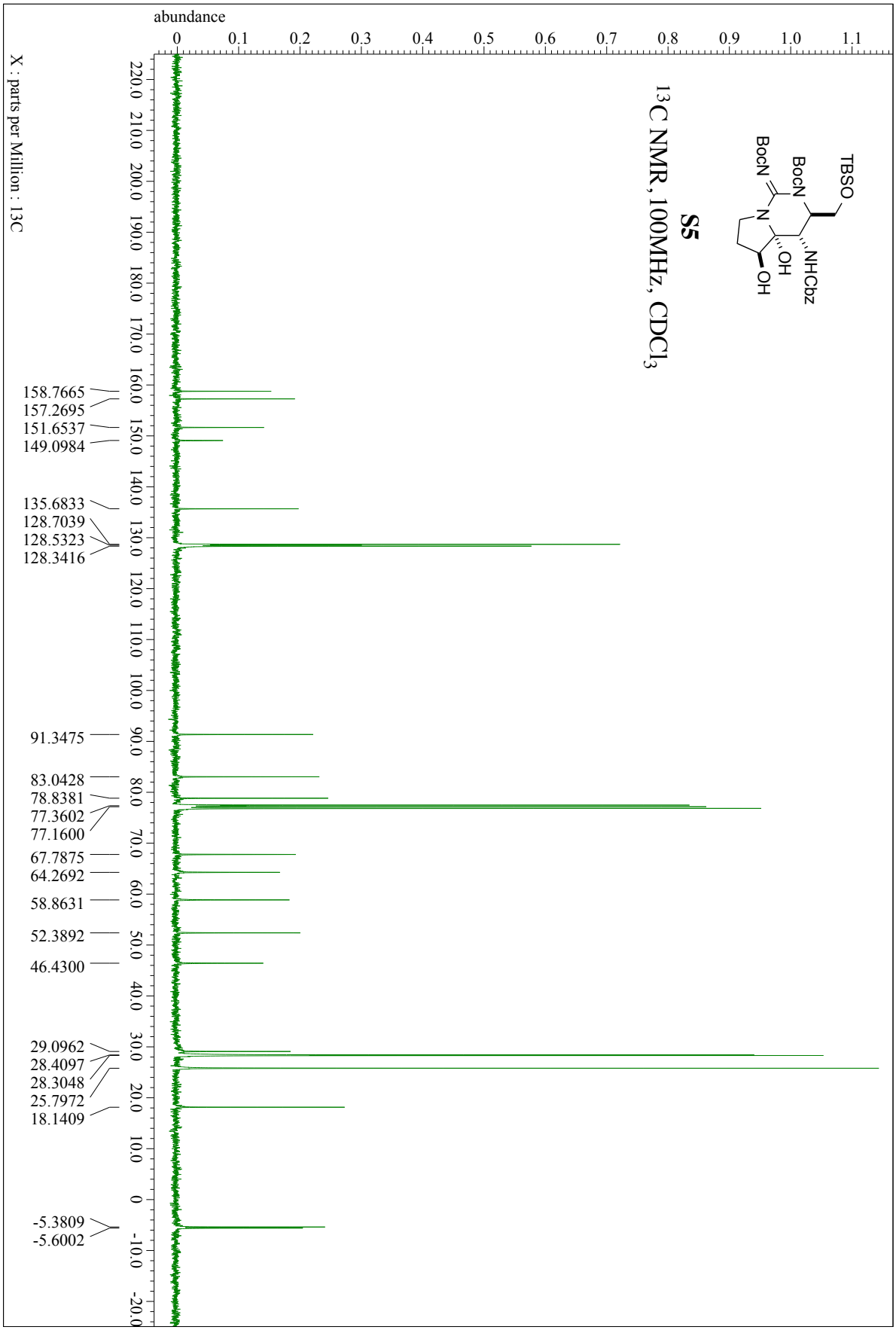

abundance
X : parts per Million : 1H
S2
1H NMR, 400MHz, CDCl3
BocN
BocN
N
H
NHCbz
OAc
HO
7.3688
7.3574
7.3413
7.3322
7.3196
5.3688
5.3035
5.2817
5.2279
5.2199
5.1867
5.1557
5.1214
5.0916
3.9908
3.9621
3.9014
3.8361
3.8029
3.6609
3.6334
3.5727
3.5452
2.2725
2.0984
2.0595
2.0423
1.4856
1.4799
5.05
1.06
4.02
3.00
1.00
4.01
18.18

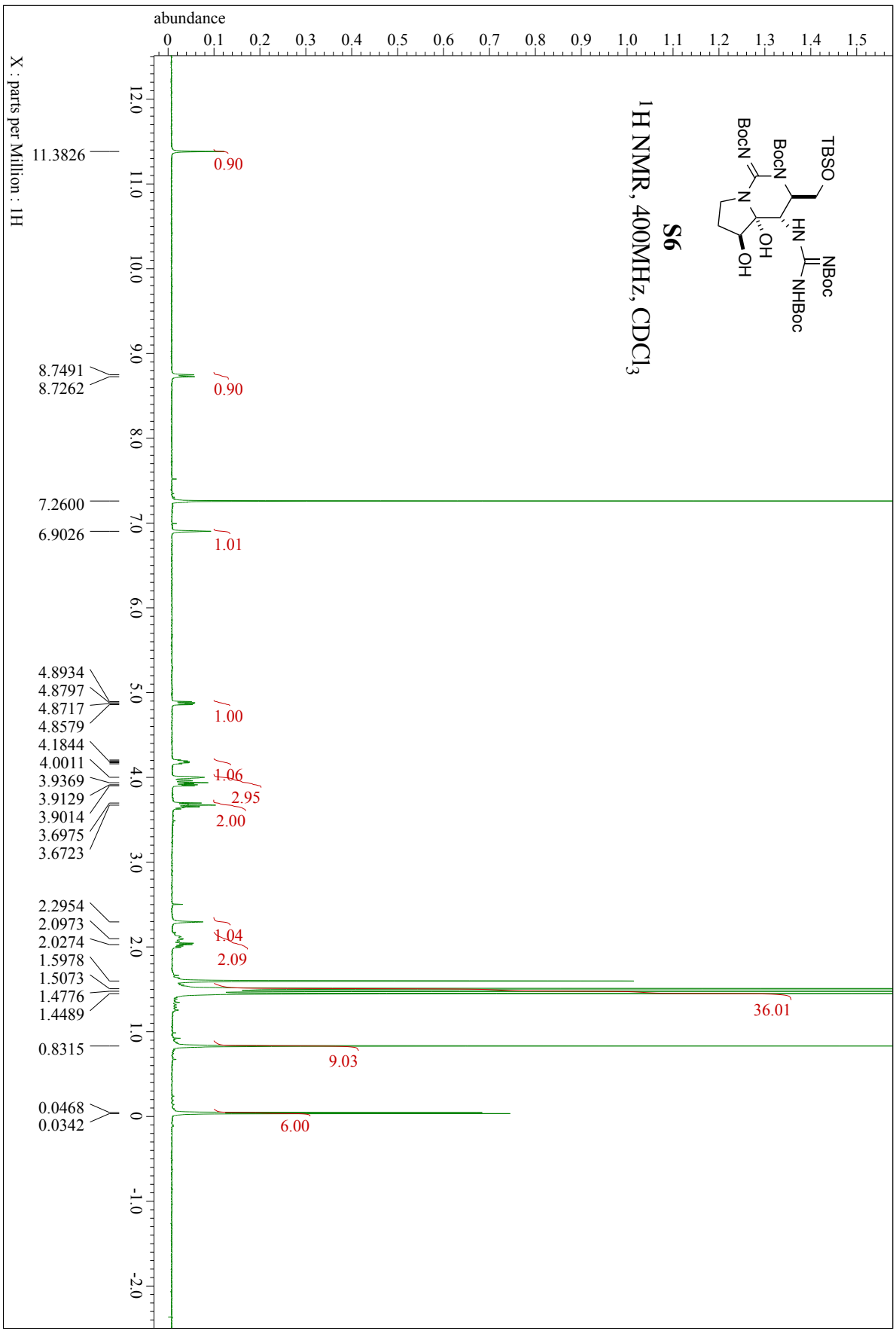

abundance
0
0.1
0.2
0.3
0.4
X : parts per Million : 13C
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
170.9040
162.3896
156.1445
150.6239
136.0932
128.6181
128.3035
128.1319
83.2717
80.0108
77.4842
77.3602
77.1600
76.8454
75.6059
67.2726
64.5267
61.7140
60.7987
52.7229
46.3538
28.7911
28.3429
28.1618
21.1253
S2
^{13}C NMR, 100MHz, CDCl$_3$
BocN
BocN
N
H
NHCbz
OAc
HO

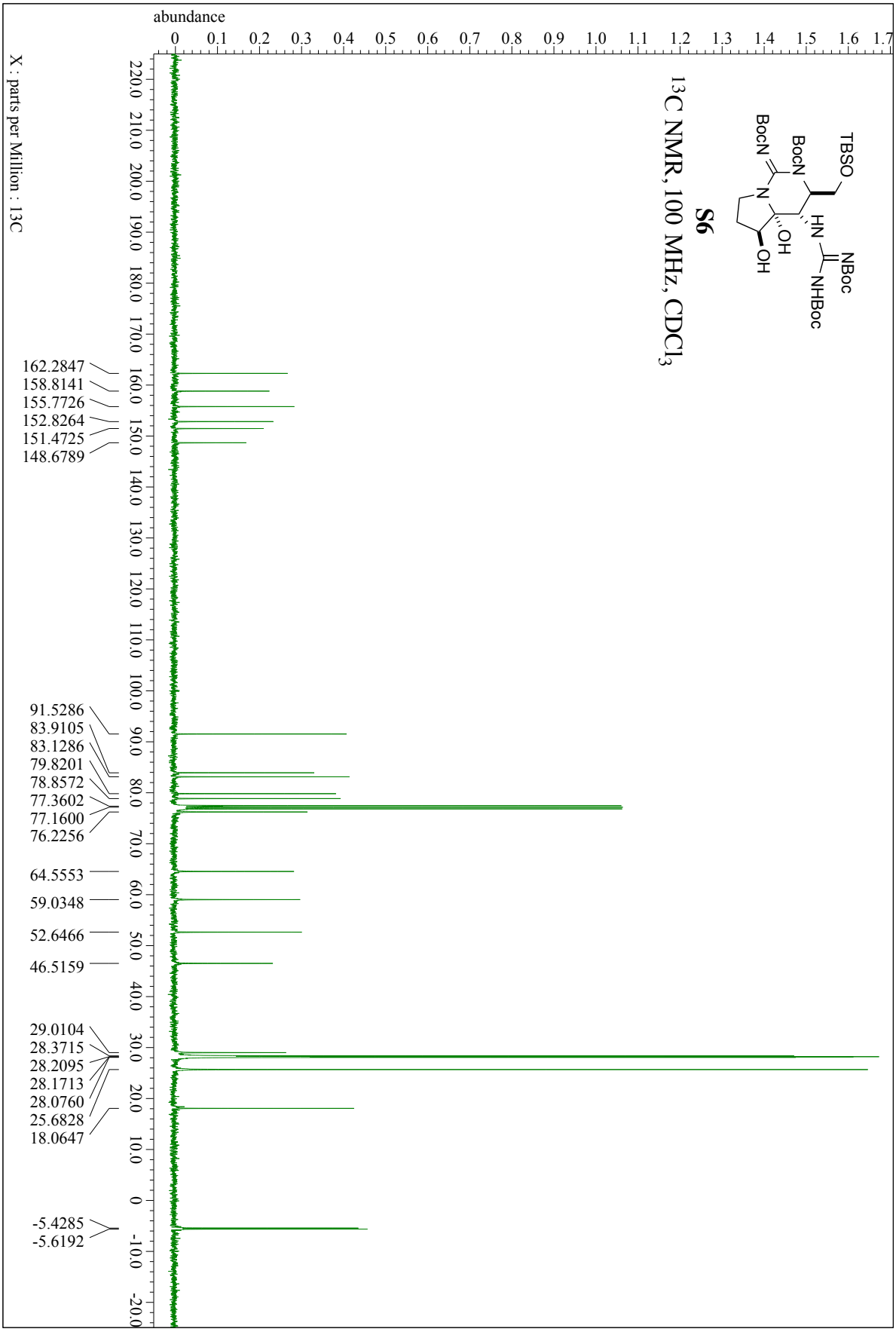

abundance
X : parts per Million : 1H
S3
^{1}H NMR, 400MHz, $CDCl_3$
BocN
BocN
TBSO
NHCbz
H
OAc
7.3551
7.3437
7.3265
7.2979
7.2532
5.3104
5.2910
5.2159
5.2062
5.1501
5.1191
5.1134
5.0825
4.1226
4.0424
3.8809
3.8591
3.8499
3.8247
3.7251
3.7033
3.6334
3.4410
3.4123
2.1638
2.1294
2.0859
2.0504
1.4650
0.8556
0.0618
0.0274
5.07
1.06
1.01
0.99
1.00
2.03
0.97
0.98
1.00
1.03
4.16
20.03
9.03
6.13

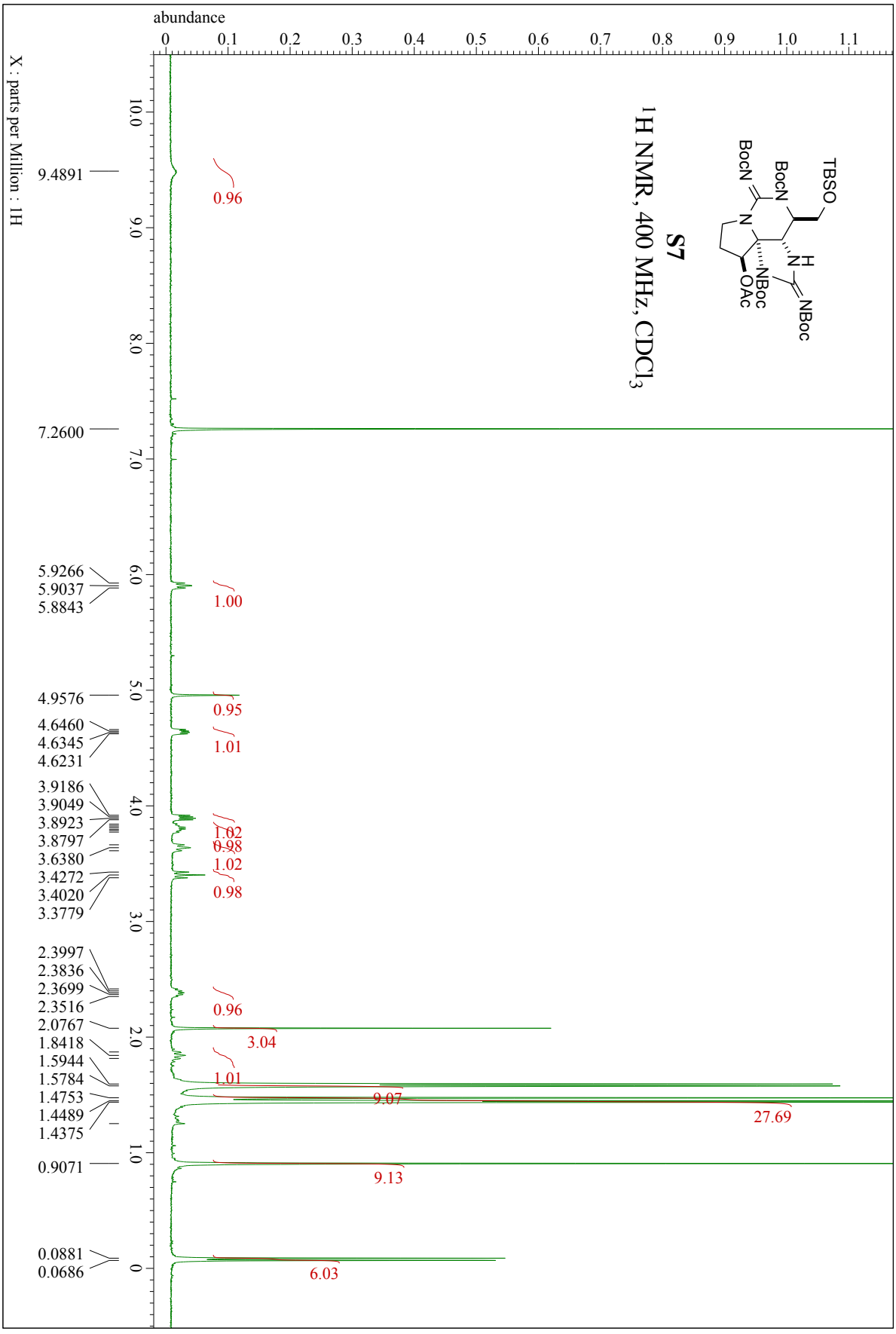

abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
X : parts per Million : 13C
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
-10.0
-20.0
170.9135
158.9858
155.9728
151.5583
151.0530
136.2172
128.5419
128.1605
128.0175
82.6042
78.0849
77.3698
77.1600
75.8728
67.0438
64.7460
64.2979
60.9989
53.6859
45.8198
29.0962
28.5622
28.1809
25.9212
21.1443
18.3507
-5.3427
-5.7813
S3
13C NMR, 100MHz, CDCl3
TBSO
BocN
BocN
N
H
NHCbz
OAc

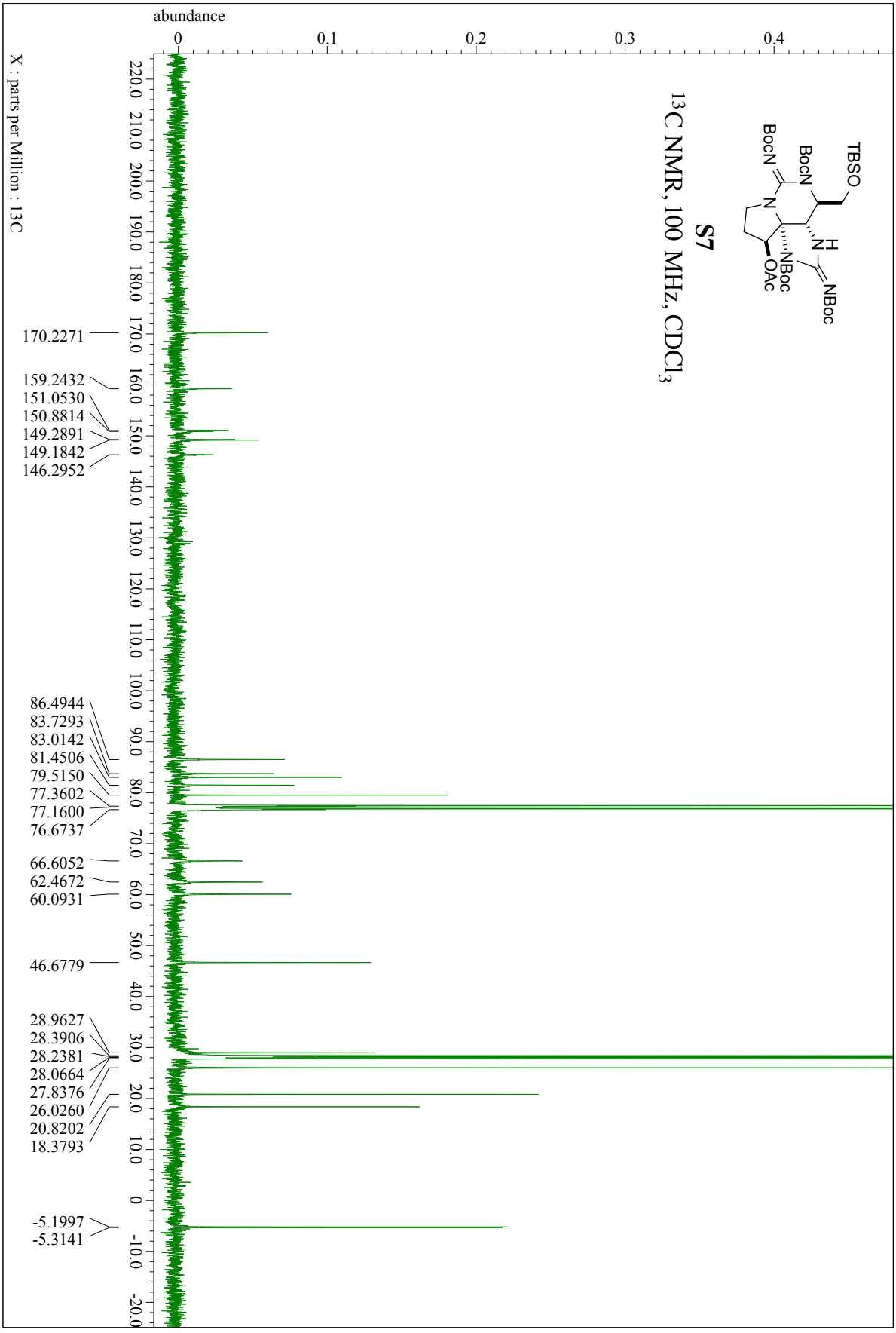

abundance
X : parts per Million : 1H
S5
1H NMR, 400MHz, CDCl3
TBSO
BocN
BocN
N
OH
OH
NHCbz
7.3952
7.3906
7.3849
7.3757
7.3700
7.3631
7.3574
7.3390
7.3253
7.2600
5.3104
5.2875
5.1408
4.9484
4.5601
4.5521
4.0206
4.0125
3.9621
3.9587
3.8705
3.8613
3.7537
3.7365
3.7290
2.1087
2.1064
2.1030
2.0022
1.9873
1.9690
1.4707
1.4684
1.2588
0.8739
0.8693
0.8521
0.0560
0.0491
5.05
0.96
1.04
0.98
1.00
2.01
1.01
0.99
0.95
0.97
0.94
20.00
9.91
6.15

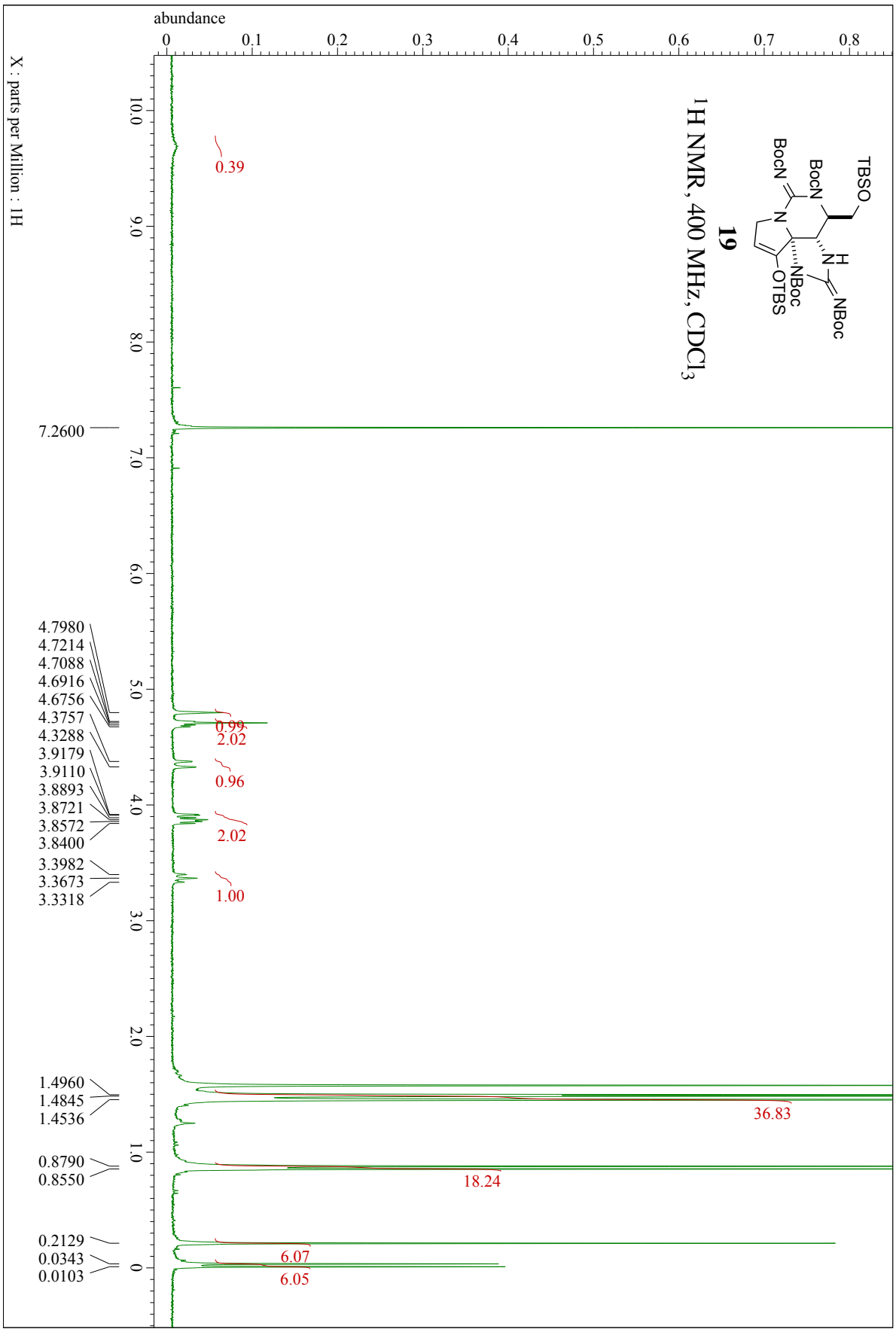

abundance
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1
X : parts per Million : 13C
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
158.7665
157.2695
151.6537
149.0984
135.6833
128.7039
128.5323
128.3416
91.3475
83.0428
78.8381
77.3602
77.1600
67.7875
64.2692
58.8631
52.3892
46.4300
29.0962
28.4097
28.3048
25.7972
18.1409
-5.3809
-5.6002
S5
13C NMR, 100MHz, CDCl3
TBSO
BocN
BocN
N
NHCbz
OH
OH

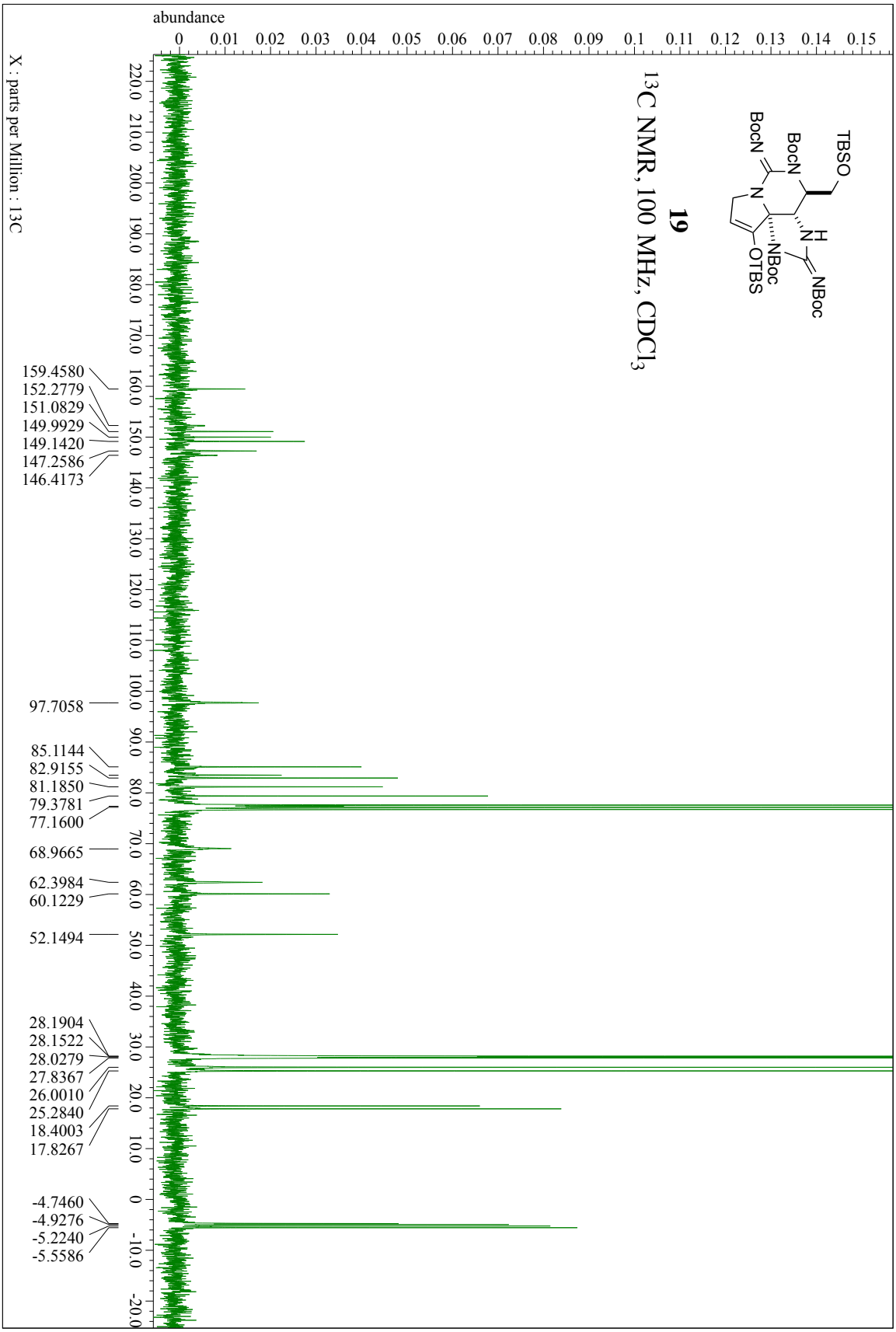

S6
^{1}H NMR, 400MHz, CDCl$_3$
abundance
X : parts per Million : 1H
TBSO
BocN
BocN
N
HN
NBoc
NHBoc
OH
OH
11.3826
8.7491
8.7262
7.2600
6.9026
4.8934
4.8797
4.8717
4.8579
4.1844
4.0011
3.9369
3.9129
3.9014
3.6975
3.6723
2.2954
2.0973
2.0274
1.5978
1.5073
1.4776
1.4489
0.8315
0.0468
0.0342
0.90
0.90
1.01
1.00
1.06
2.95
2.00
1.04
2.09
36.01
9.03
6.00

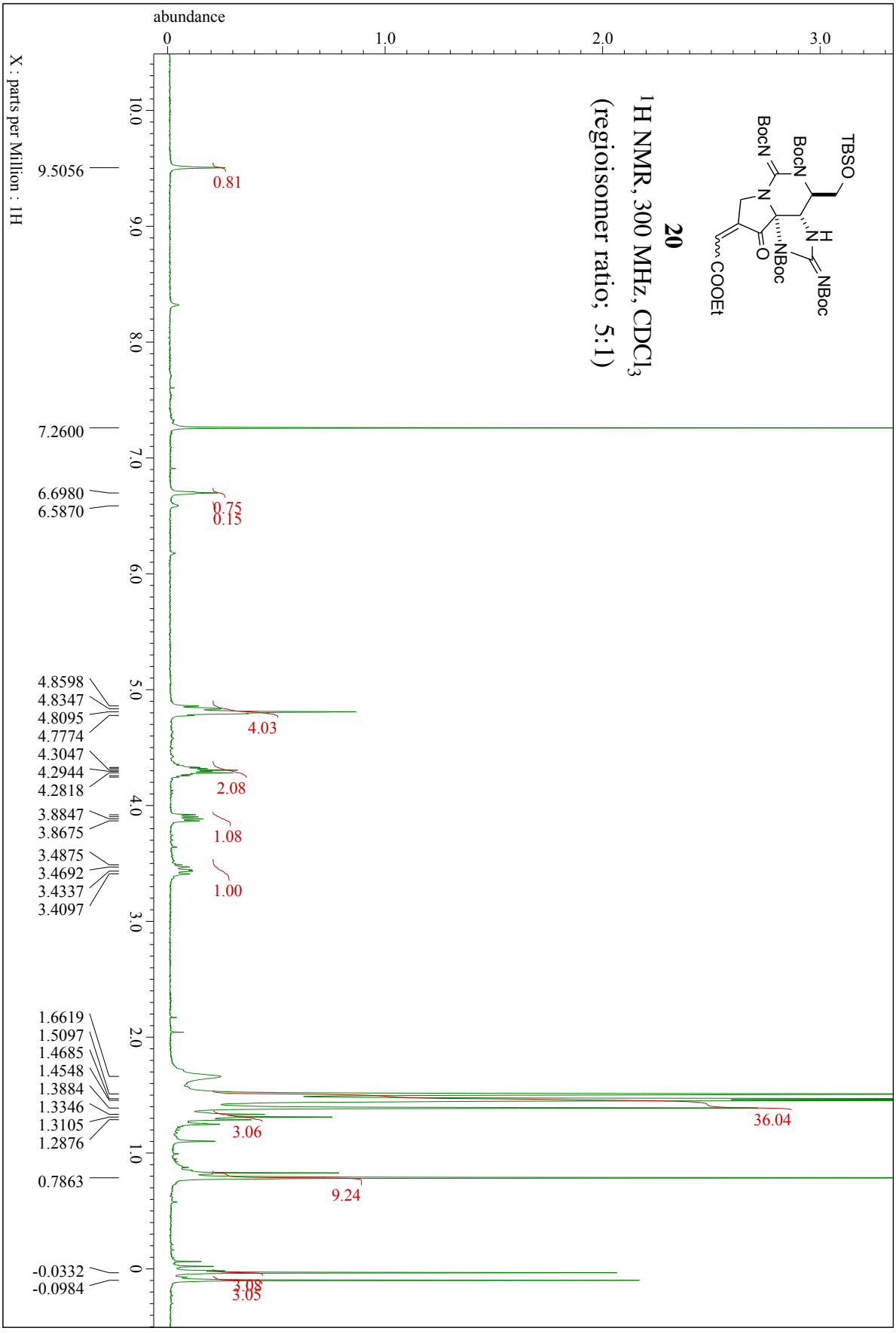

abundance
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7
X : parts per Million : 13C
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
162.2847
158.8141
155.7726
152.8264
151.4725
148.6789
91.5286
83.9105
83.1286
79.8201
78.8572
77.3602
77.1600
76.2256
64.5553
59.0348
52.6466
46.5159
29.0104
28.3715
28.2095
28.1713
28.0760
25.6828
18.0647
-5.4285
-5.6192
^{13}C NMR, 100 MHz, CDCl$_3$
S6
TBSO
BocN
BocN
N
HN
NBoc
NHBoc
OH
OH

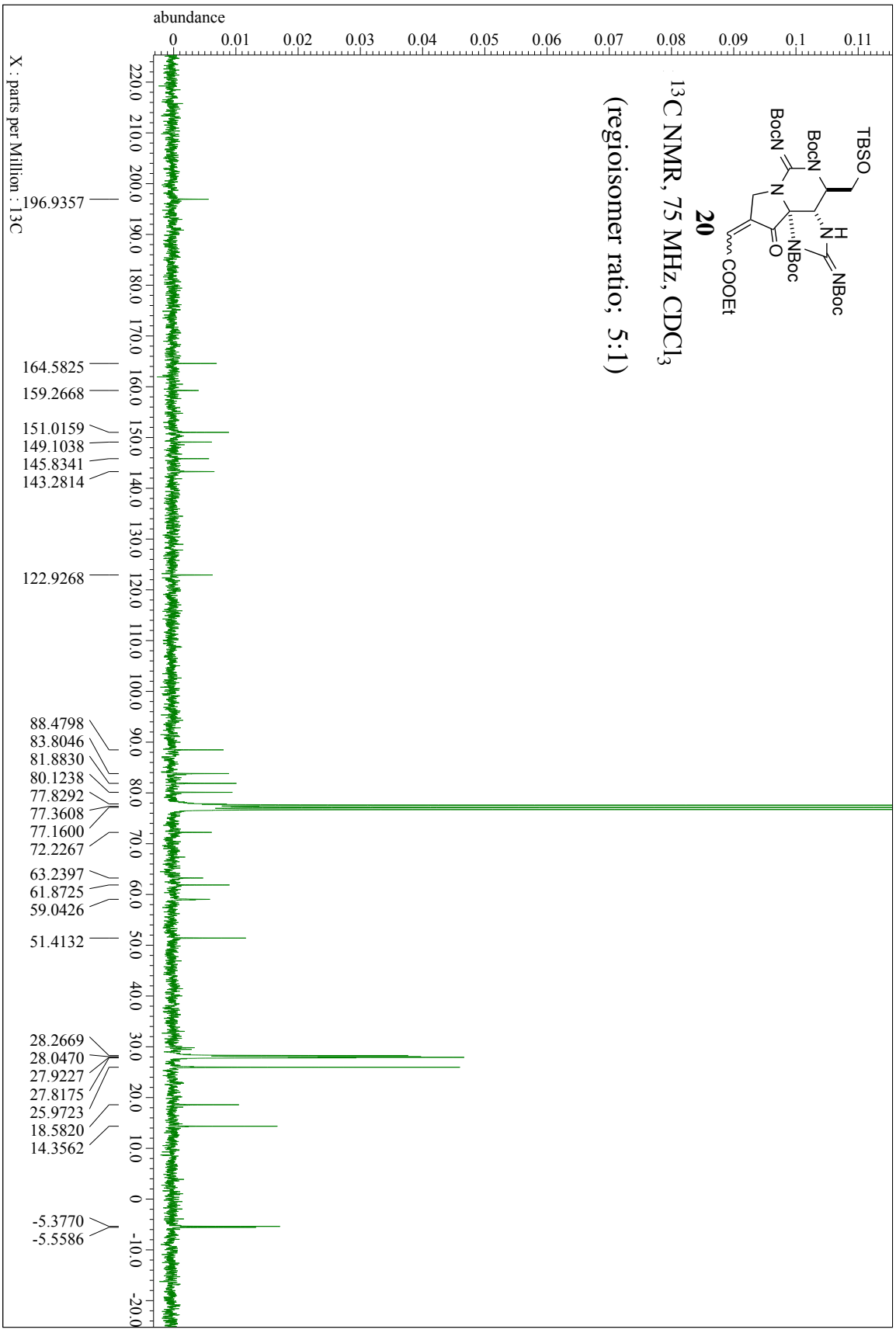

S7
^{1}H NMR, 400 MHz, $CDCl_3$
X : parts per Million : 1H
abundance
TBSO
BocN
BocN
N
H
N
NBoc
OAc
NBoc
9.4891
7.2600
5.9266
5.9037
5.8843
4.9576
4.6460
4.6345
4.6231
3.9186
3.9049
3.8923
3.8797
3.6380
3.4272
3.4020
3.3779
2.3997
2.3836
2.3699
2.3516
2.0767
1.8418
1.5944
1.5784
1.4753
1.4489
1.4375
0.9071
0.0881
0.0686
0.96
1.00
0.95
1.01
1.02
0.98
1.02
0.98
0.96
3.04
1.01
9.07
27.69
9.13
6.03

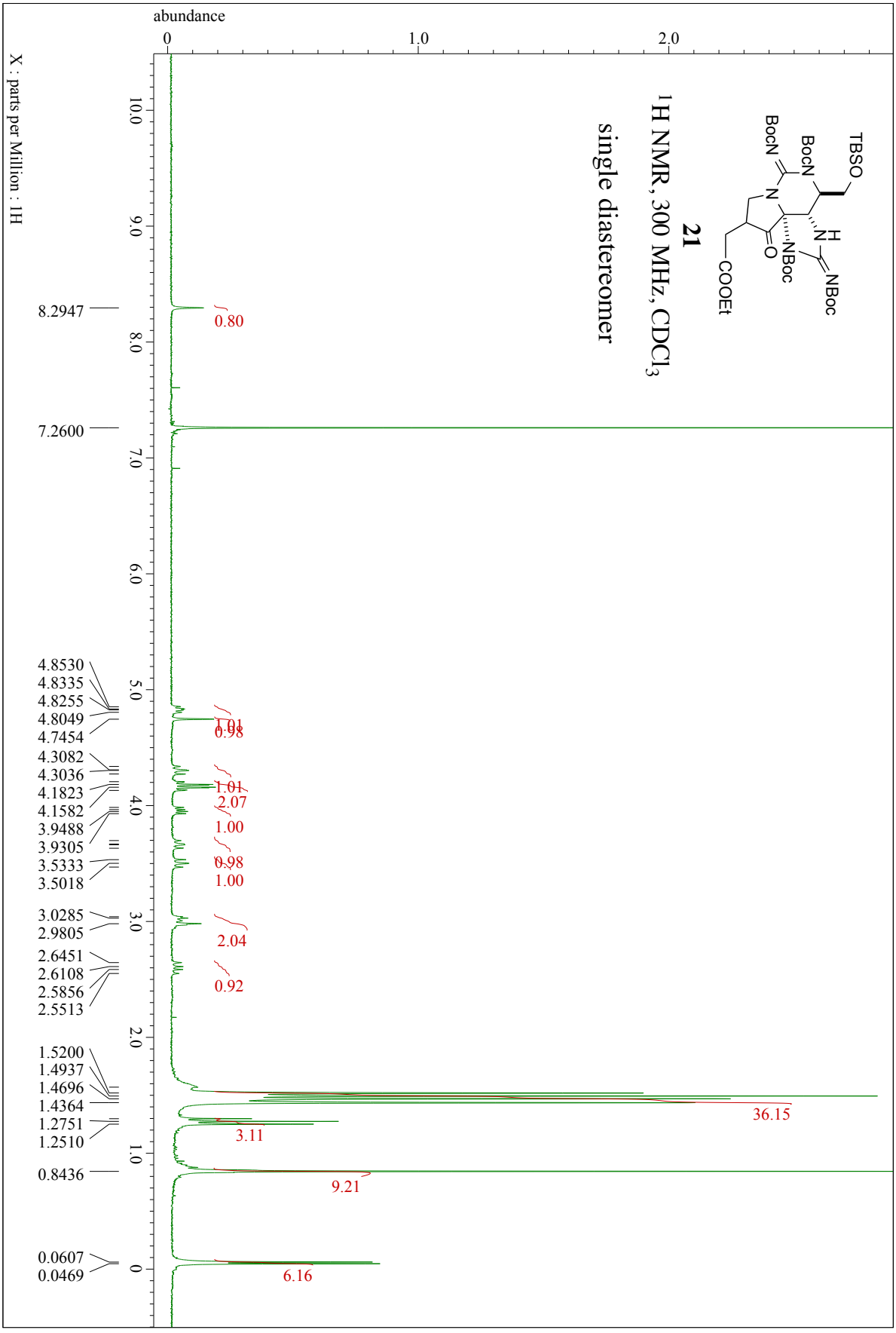

S7
^{13}C NMR, 100 MHz, $CDCl_3$
X : parts per Million : 13C
abundance
0
0.1
0.2
0.3
0.4
TBSO
BocN
BocN
N
H
N
NBoc
NBoc
OAc
170.2271
159.2432
151.0530
150.8814
149.2891
149.1842
146.2952
86.4944
83.7293
83.0142
81.4506
79.5150
77.3602
77.1600
76.6737
66.6052
62.4672
60.0931
46.6779
28.9627
28.3906
28.2381
28.0664
27.8376
26.0260
20.8202
18.3793
-5.1997
-5.3141

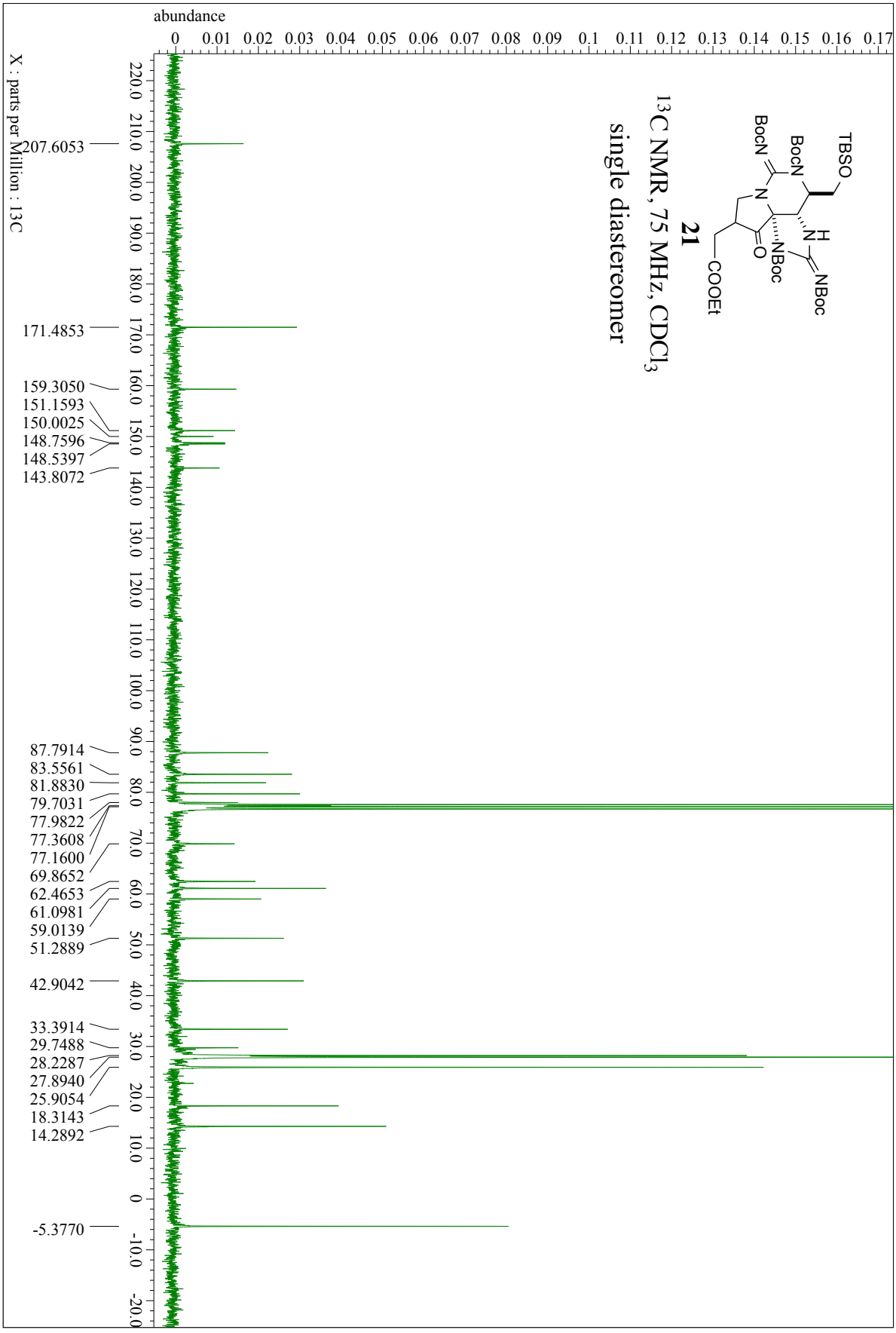

abundance
X : parts per Million : 1H
^{1}H NMR, 400 MHz, CDCl$_3$
19
TBSO
BocN
BocN
N
H
N
NBoc
OTBS
NBoc
0.39
7.2600
4.7980
4.7214
4.7088
4.6916
4.6756
4.3757
4.3288
3.9179
3.9110
3.8893
3.8721
3.8572
3.8400
3.3982
3.3673
3.3318
1.4960
1.4845
1.4536
0.8790
0.8550
0.2129
0.0343
0.0103
0.99
2.02
0.96
2.02
1.00
36.83
18.24
6.07
6.05

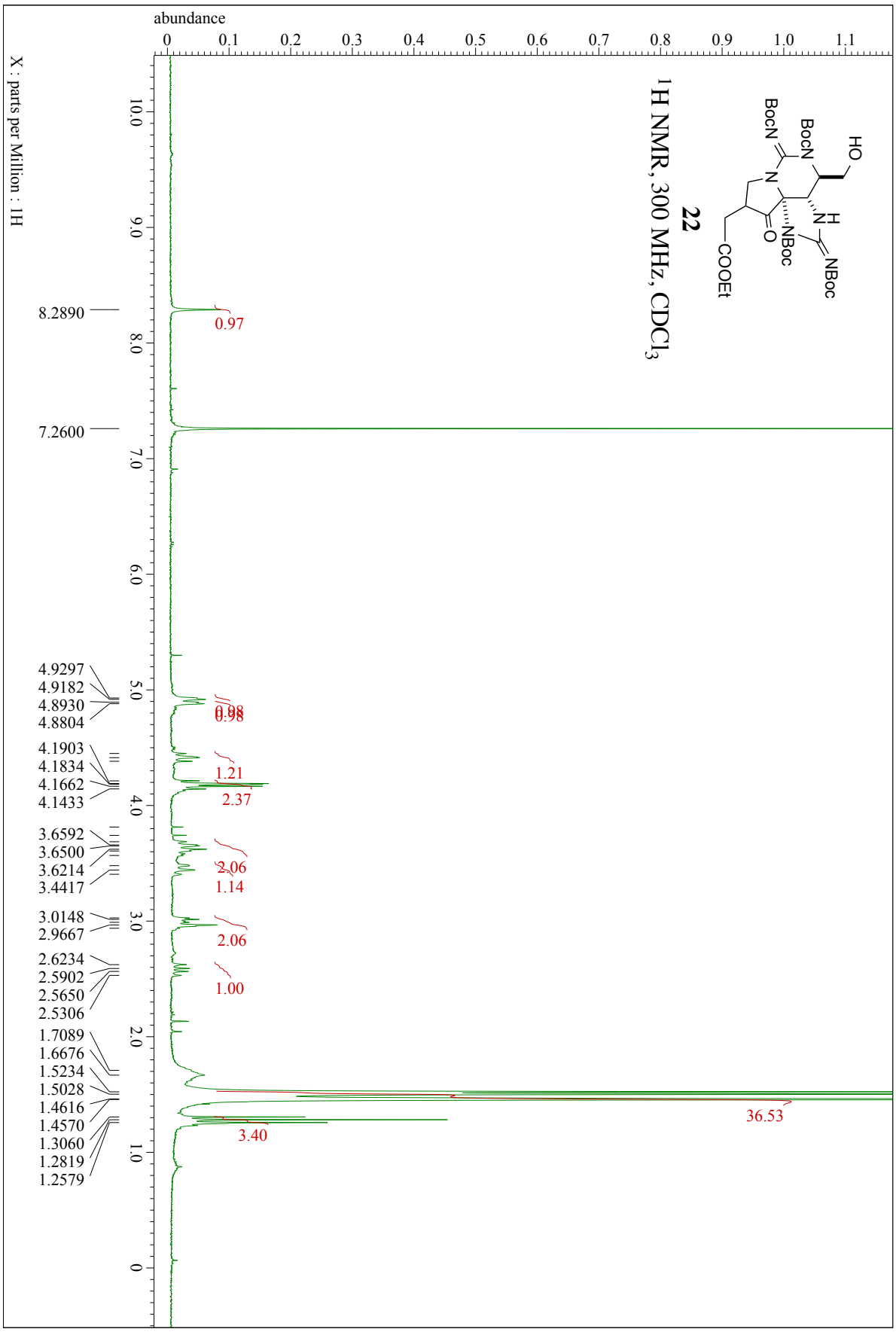

abundance
0 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.1 0.11 0.12 0.13 0.14 0.15
X : parts per Million : 13C
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
159.4580
152.2779
151.0829
149.9929
149.1420
147.2586
146.4173
97.7058
85.1144
82.9155
81.1850
79.3781
77.1600
68.9665
62.3984
60.1229
52.1494
28.1904
28.1522
28.0279
27.8367
26.0010
25.2840
18.4003
17.8267
-4.7460
-4.9276
-5.2240
-5.5586
19
13C NMR, 100 MHz, CDCl3
TBSO
BocN
BocN
N
H
N
NBoc
NBoc
OTBS

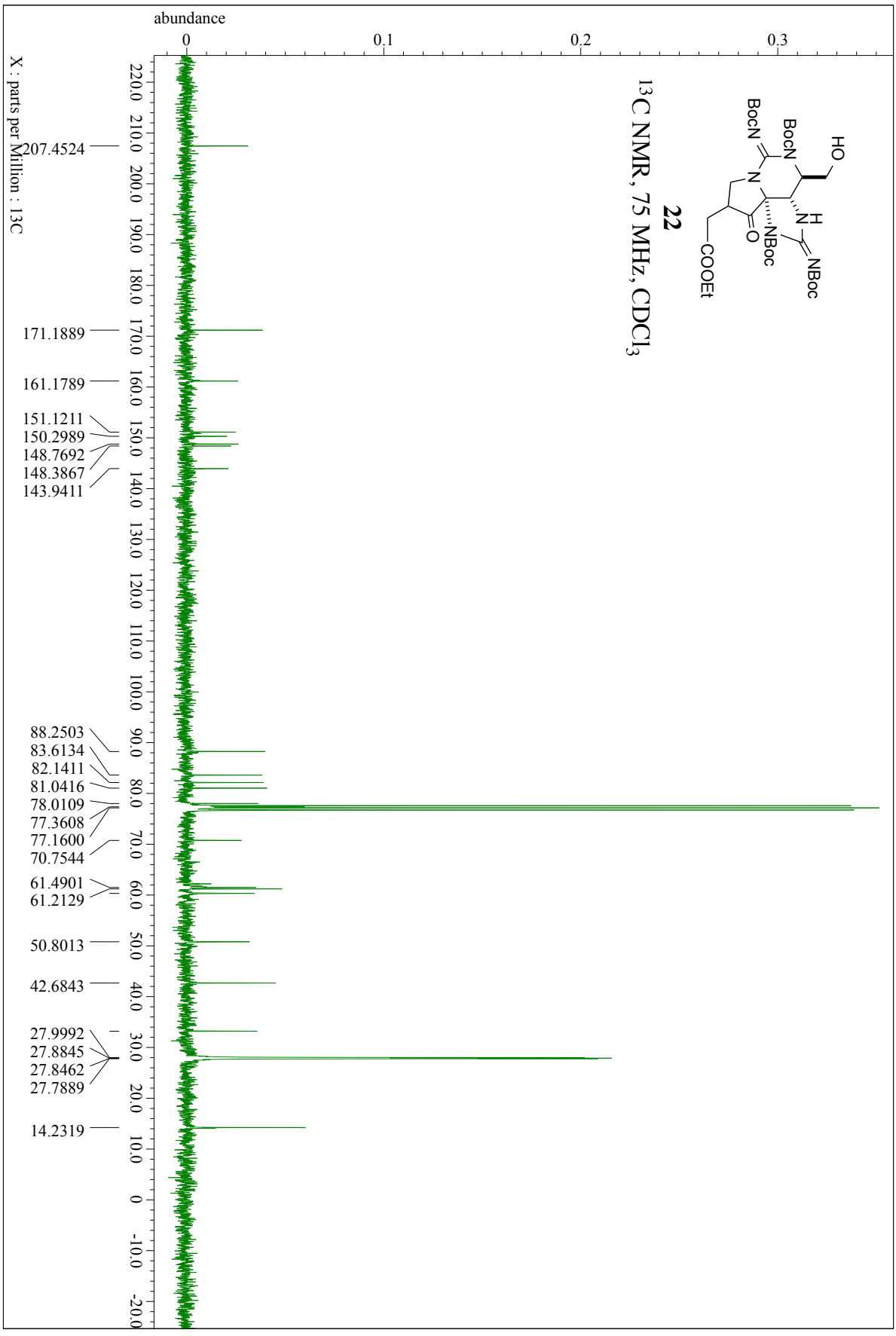

abundance
0
1.0
2.0
3.0
X : parts per Million : 1H
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
9.5056
7.2600
6.6980
6.5870
4.8598
4.8347
4.8095
4.7774
4.3047
4.2944
4.2818
3.8847
3.8675
3.4875
3.4692
3.4337
3.4097
1.6619
1.5097
1.4685
1.4548
1.3884
1.3346
1.3105
1.2876
0.7863
-0.0332
-0.0984
0.81
0.75
0.15
4.03
2.08
1.08
1.00
3.06
36.04
9.24
3.08
3.05
20
1H NMR, 300 MHz, CDCl3
(regioisomer ratio; 5:1)
TBSO
BocN
BocN
N
H
N
NBoc
O
NBoc
COOEt

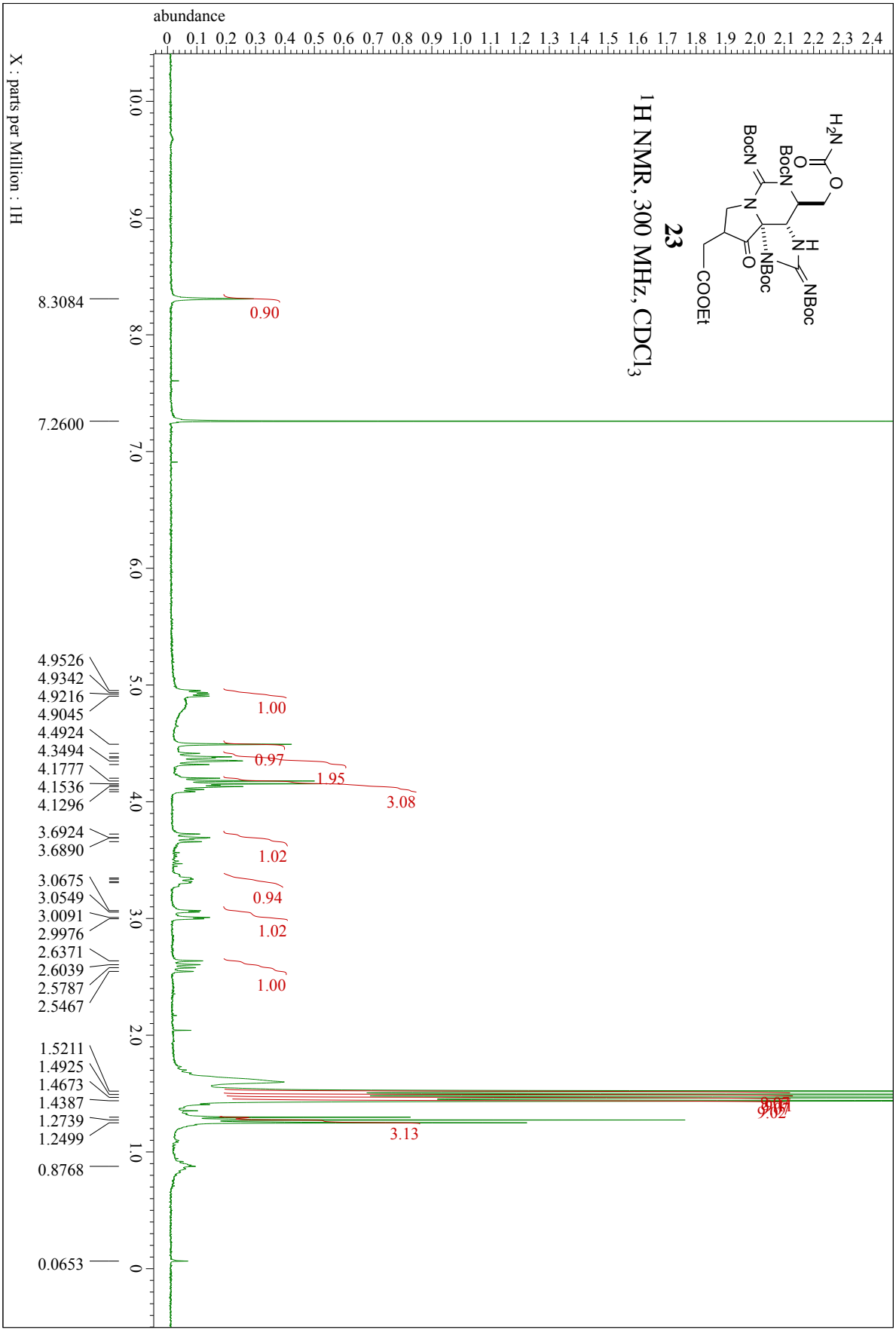

abundance
0 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.1 0.11
X : parts per Million : 13C
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
196.9357
164.5825
159.2668
151.0159
149.1038
145.8341
143.2814
122.9268
88.4798
83.8046
81.8830
80.1238
77.8292
77.3608
77.1600
72.2267
63.2397
61.8725
59.0426
51.4132
28.2669
28.0470
27.9227
27.8175
25.9723
18.5820
14.3562
-5.3770
-5.5586
^{13}C NMR, 75 MHz, $CDCl_3$
(regioisomer ratio; 5:1)
20
TBSO
BocN
BocN
N
NBoc
H
N
O
NBoc
COOEt

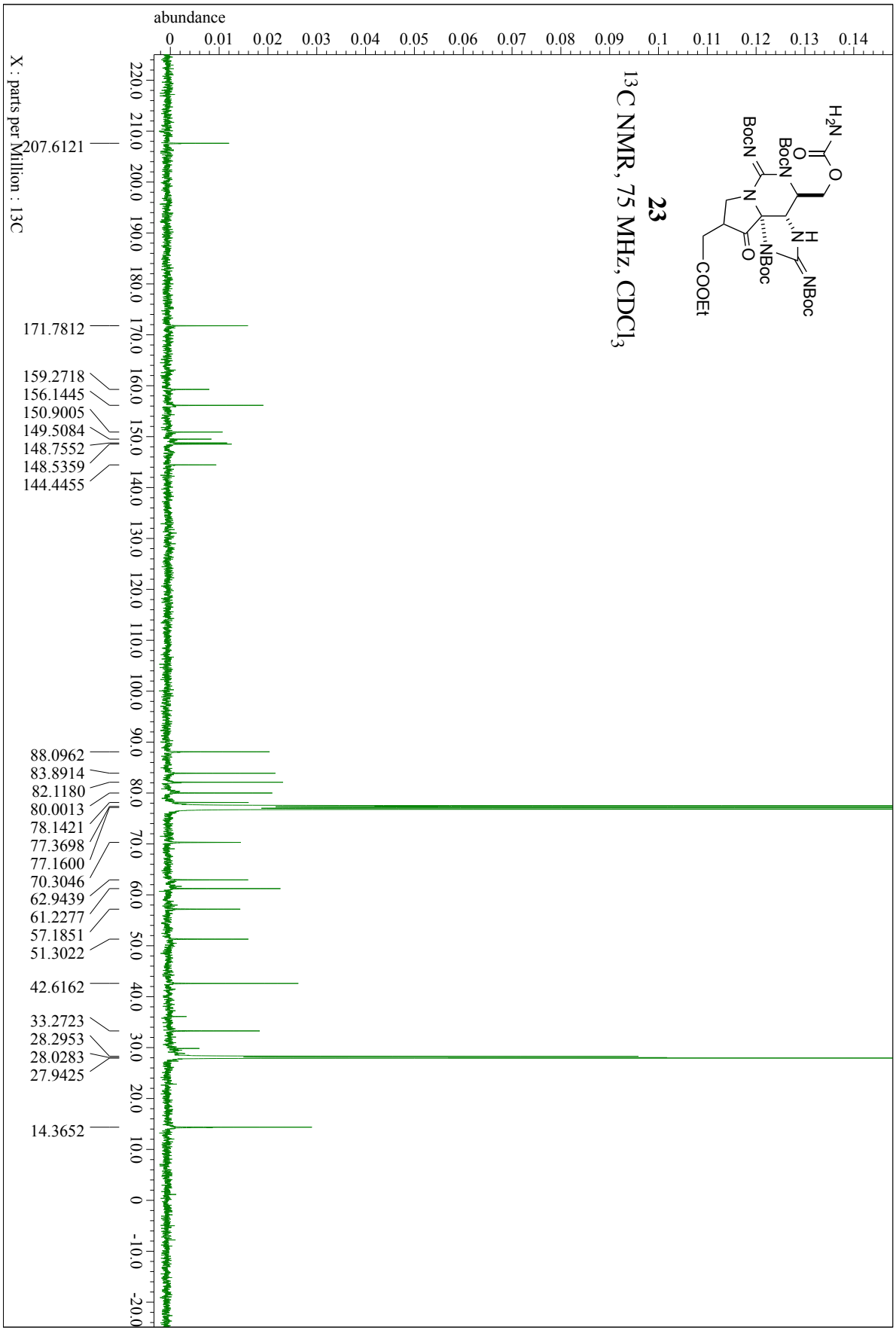

abundance
X : parts per Million : 1H
single diastereomer
21
^{1}H NMR, 300 MHz, CDCl$_3$
TBSO
BocN
BocN
N
H
N
NBoc
O
NBoc
COOEt
8.2947
7.2600
4.8530
4.8335
4.8255
4.8049
4.7454
4.3082
4.3036
4.1823
4.1582
3.9488
3.9305
3.5333
3.5018
3.0285
2.9805
2.6451
2.6108
2.5856
2.5513
1.5200
1.4937
1.4696
1.4364
1.2751
1.2510
0.8436
0.0607
0.0469
0.80
0.98
1.01
2.07
1.00
0.98
1.00
2.04
0.92
36.15
3.11
9.21
6.16

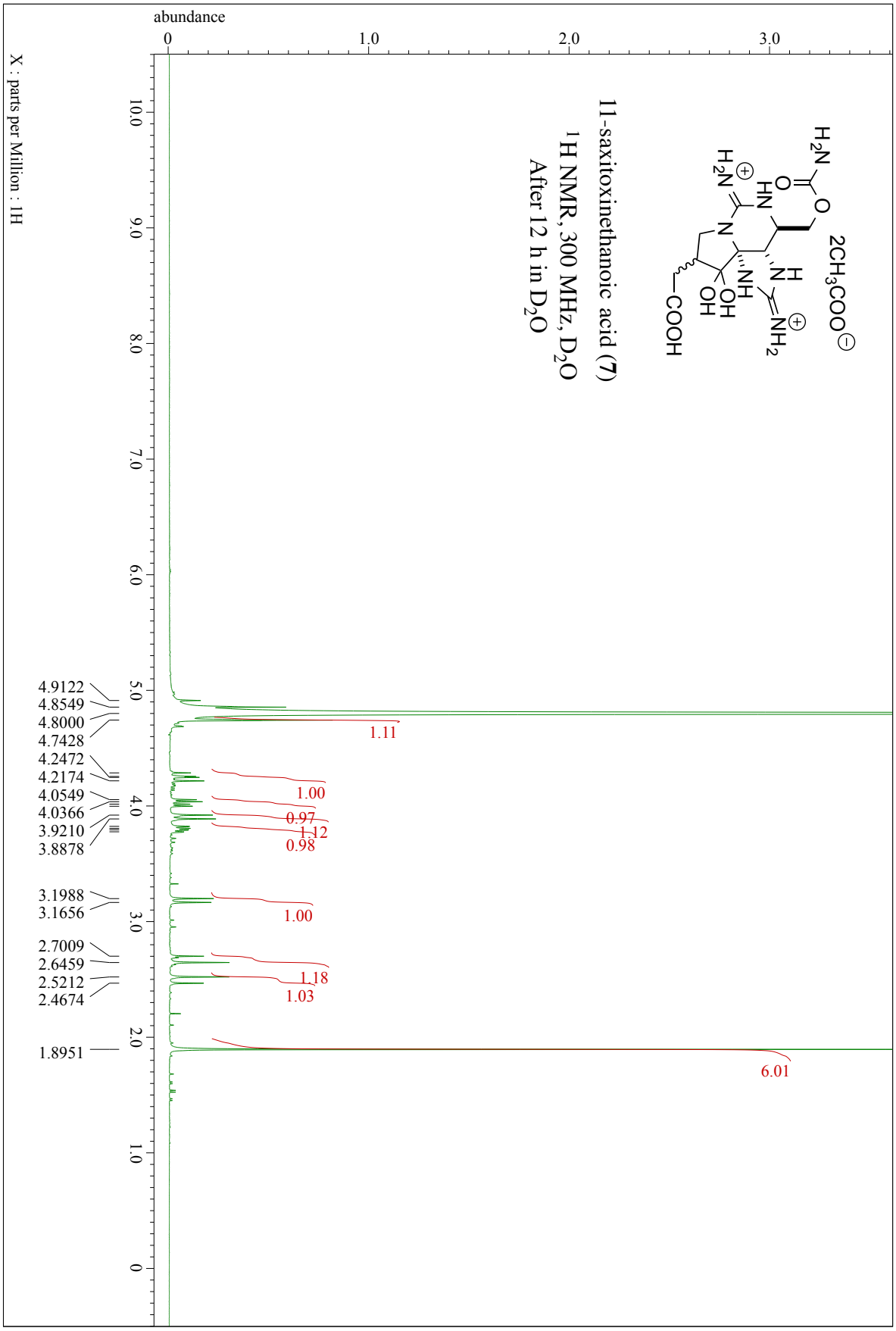

abundance
X : parts per Million : 13C
207.6053
171.4853
159.3050
151.1593
150.0025
148.7596
148.5397
143.8072
87.7914
83.5561
81.8830
79.7031
77.9822
77.3608
77.1600
69.8652
62.4653
61.0981
59.0139
51.2889
42.9042
33.3914
29.7488
28.2287
27.8940
25.9054
18.3143
14.2892
-5.3770
TBSO
BocN
BocN
N
NBoc
H
N
NBoc
O
COOEt
21
13C NMR, 75 MHz, CDCl3
single diastereomer


abundance
X : parts per Million : 1H
22
^{1}H NMR, 300 MHz, $CDCl_3$
BocN
BocN
HO
N
H
N
NBoc
O
NBoc
COOEt
8.2890
7.2600
4.9297
4.9182
4.8930
4.8804
4.1903
4.1834
4.1662
4.1433
3.6592
3.6500
3.6214
3.4417
3.0148
2.9667
2.6234
2.5902
2.5650
2.5306
1.7089
1.6676
1.5234
1.5028
1.4616
1.4570
1.3060
1.2819
1.2579
0.97
0.98
1.21
2.37
2.06
1.14
2.06
1.00
36.53
3.40

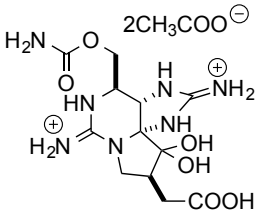

abundance
0
0.1
0.2
0.3
X : parts per Million : 13C
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
207.4524
171.1889
161.1789
151.1211
150.2989
148.7692
148.3867
143.9411
88.2503
83.6134
82.1411
81.0416
78.0109
77.3608
77.1600
70.7544
61.4901
61.2129
50.8013
42.6843
27.9992
27.8845
27.8462
27.7889
14.2319
22
13C NMR, 75 MHz, CDCl3
HO
BocN
BocN
N
H
N
NBoc
O
NBoc
COOEt


abundance
X : parts per Million : 1H
23
^{1}H NMR, 300 MHz, CDCl$_3$
8.3084
7.2600
4.9526
4.9342
4.9216
4.9045
4.4924
4.3494
4.1777
4.1536
4.1296
3.6924
3.6890
3.0675
3.0549
3.0091
2.9976
2.6371
2.6039
2.5787
2.5467
1.5211
1.4925
1.4673
1.4387
1.2739
1.2499
0.8768
0.0653
0.90
1.00
0.97
1.95
3.08
1.02
0.94
1.02
1.00
9.02
3.13

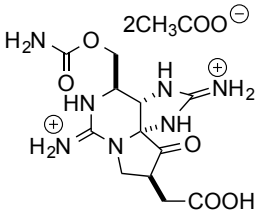

abundance
0 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09 0.1 0.11 0.12 0.13 0.14
X : parts per Million : 13C
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
207.6121
171.7812
159.2718
156.1445
150.9005
149.5084
148.7552
148.5359
144.4455
88.0962
83.8914
82.1180
80.0013
78.1421
77.3698
77.1600
70.3046
62.9439
61.2277
57.1851
51.3022
42.6162
33.2723
28.2953
28.0283
27.9425
14.3652
23
13C NMR, 75 MHz, CDCl3
H2N
O
O
BocN
O
BocN
N
H
N
NBoc
O
NBoc
COOEt


11-saxitoxinethanoic acid (7)
^{1}H NMR, 300 MHz, D_2O
After 12 h in D_2O
abundance
X : parts per Million : 1H
4.9122
4.8549
4.8000
4.7428
4.2472
4.2174
4.0549
4.0366
3.9210
3.8878
3.1988
3.1656
2.7009
2.6459
2.5212
2.4674
1.8951
1.11
1.00
0.97
1.12
0.98
1.00
1.18
1.03
6.01

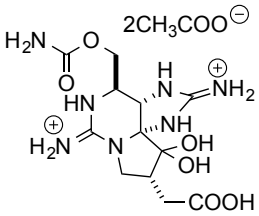
Precise assignment of 7



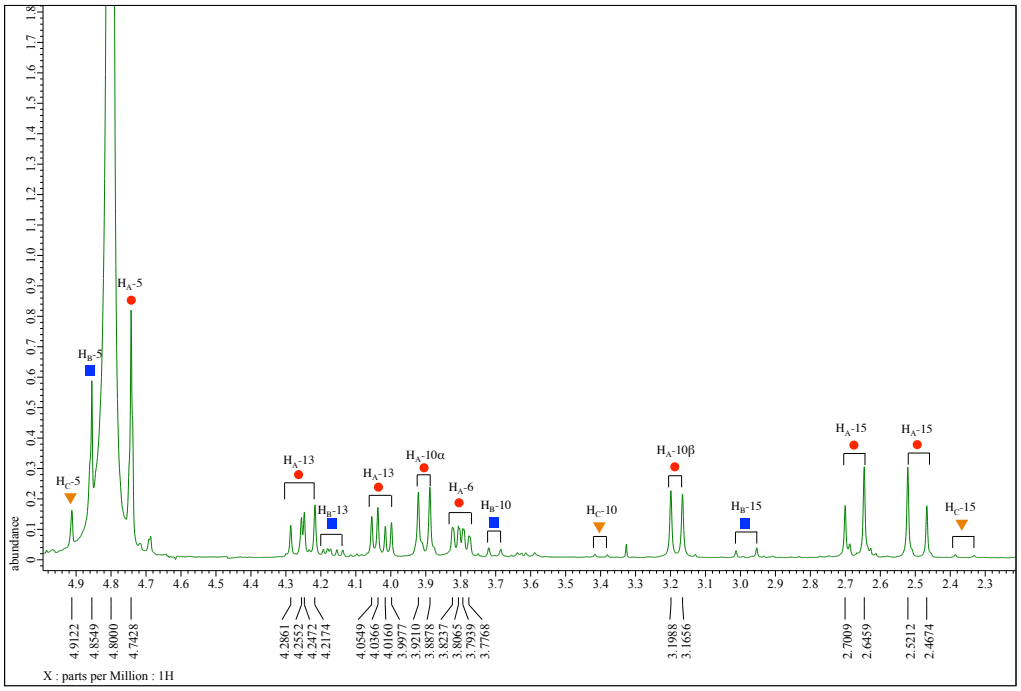
(β)-SEA

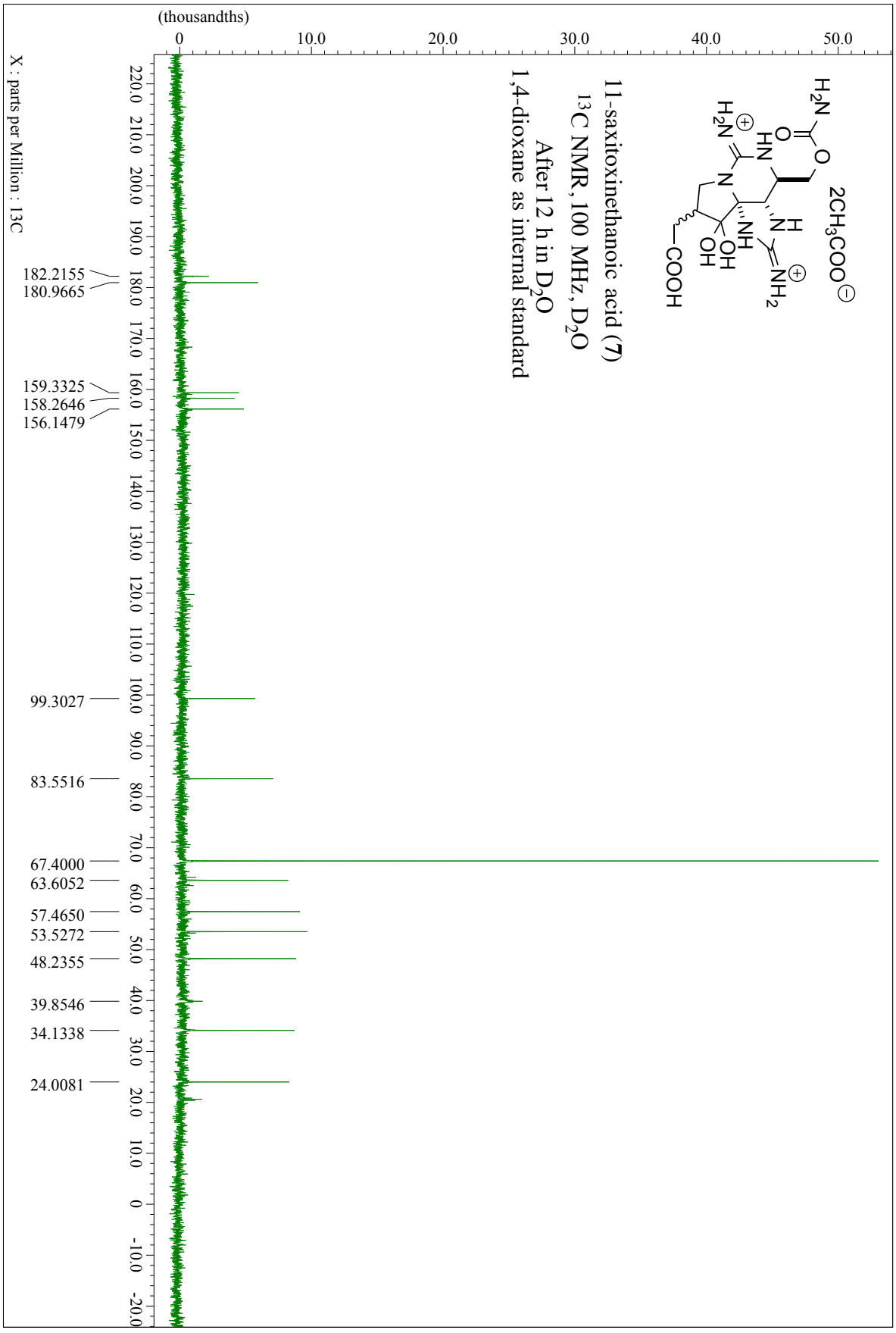


SEA (keto form)



(α)-SEA




11-saxitoxinethanoic acid (7)
13C NMR, 100 MHz, D2O
After 12 h in D2O
1,4-dioxane as internal standard
2CH3COO
X : parts per Million : 13C
(thousandths)
182.2155
180.9665
159.3325
158.2646
156.1479
99.3027
83.5516
67.4000
63.6052
57.4650
53.5272
48.2355
39.8546
34.1338
24.0081

Spectral data for synthetic and natural SEA (7)

^{1}H NMR data for synthetic and natural SEA (7).

After H-D exchange, signal of H-11 was disappeared.

	Synthetic	Natural
Position	^{1}H	^{1}H
5	4.74 (s, 1H)	4.74 (s, 1H)
6	3.80 (dd, *J* = 5.2, 8.9 Hz, 1H)	3.80 (dd, *J* = 5, 9 Hz, 1H)
10	3.90 (d, *J* = 10 Hz, 1H); 3.18 (d, *J* = 10 Hz, 1H)	3.91 (d, *J* = 10 Hz, 1H); 3.18 (d, *J* = 10 Hz, 1H)
11	----	----
13	4.25 (dd, *J* = 9.3, 11.7 Hz, 1H) 4.02 (dd, *J* = 5.5, 11.7 Hz, 1H)	4.24 (dd, *J* = 9, 12 Hz, 1H) 4.03 (dd, *J* = 5, 12 Hz, 1H)
15	2.68 (d, *J* =16.5 Hz, 1H) 2.49 (d, *J* =16.1 Hz, 1H)	2.68 (d, *J* = 16 Hz, 1H) 2.51 (d, *J* = 16 Hz, 1H)

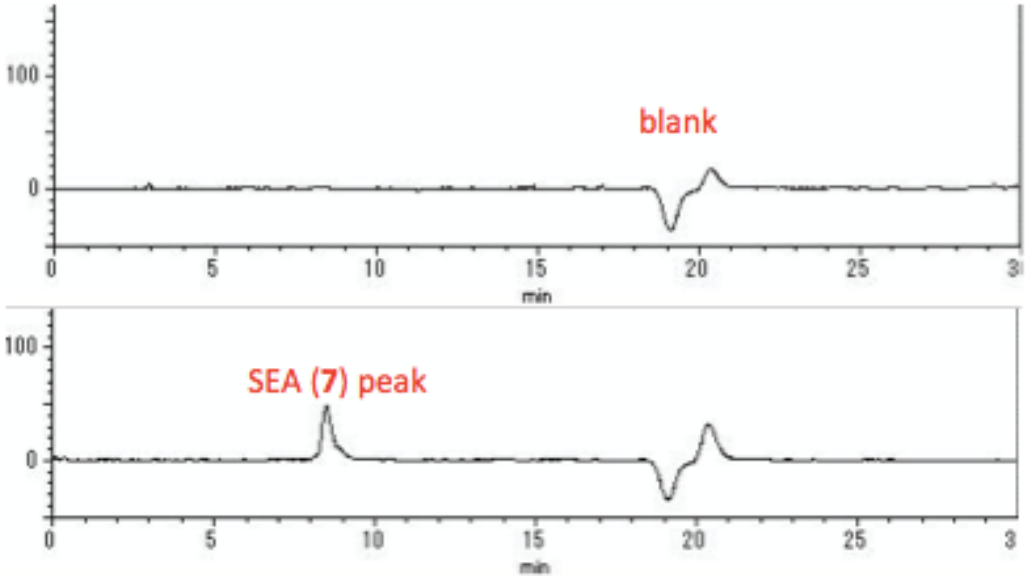
^{13}C NMR data for synthetic and natural SEA (7)

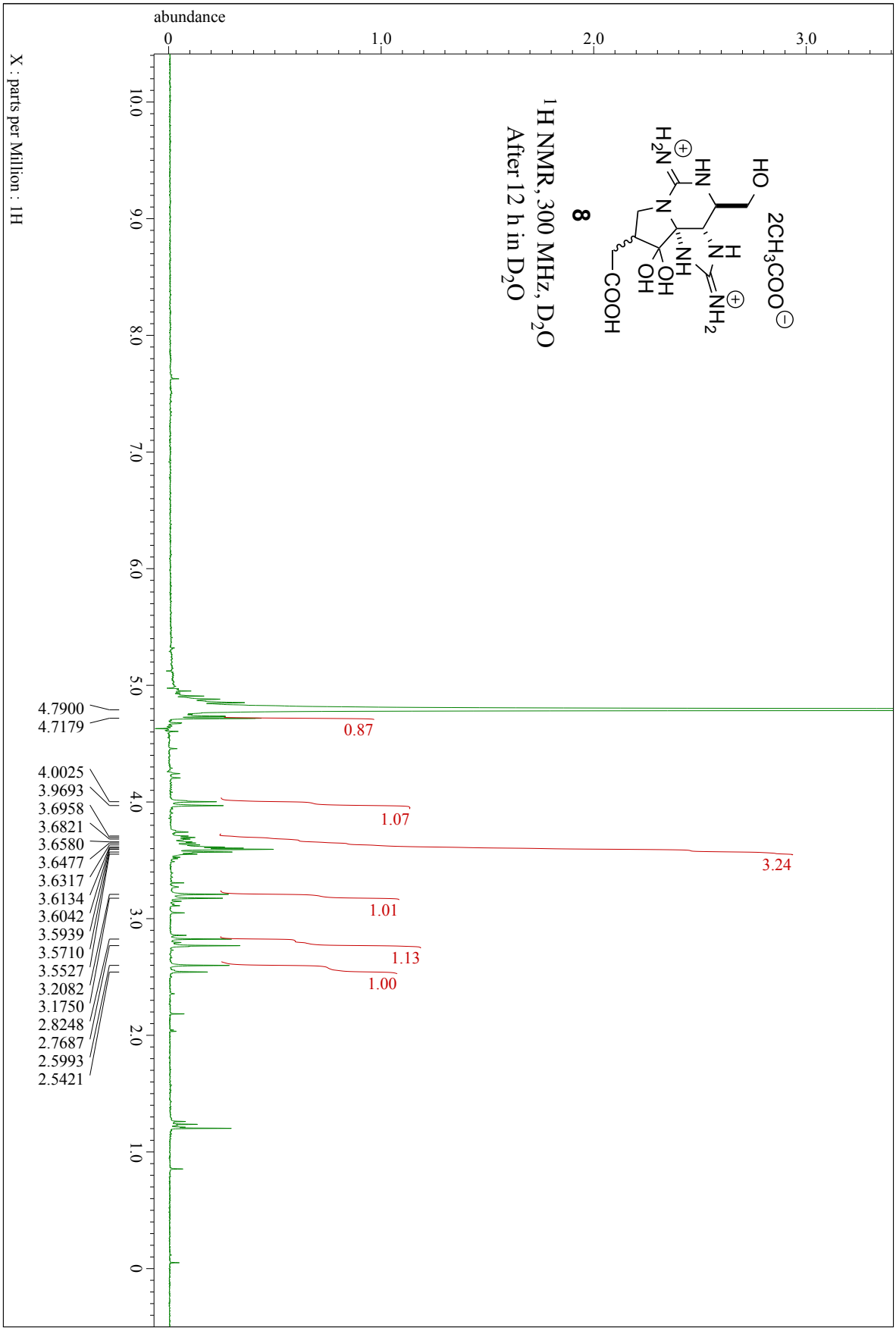
	Synthetic	Natural
Position	^{13}C NMR	^{13}C NMR
C-2	156.1	156.2
C-4	83.6	83.5
C-5	57.5	57.5
C-6	53.5	53.5
C-8	158.3	158.3
C-10	48.2	48.2
C-11	39.9	39.9
C-12	99.3	99.3
C-13	63.6	63.6
C-14	159.3	159.3
C-15	34.1	33.9
C-16*	182.2	180.6

***** The ^{13}C NMR chemical shift values of C16 were greatly influenced by pH.

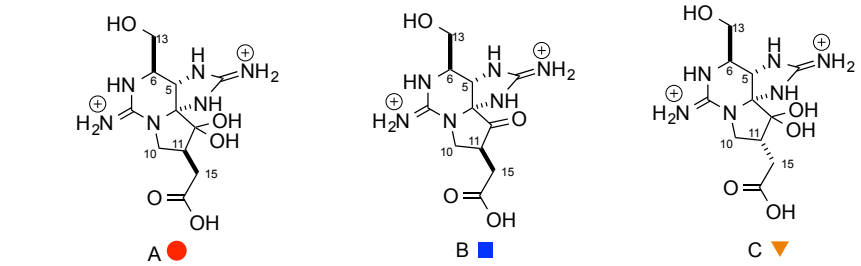
HPLC data of the SEA (7)

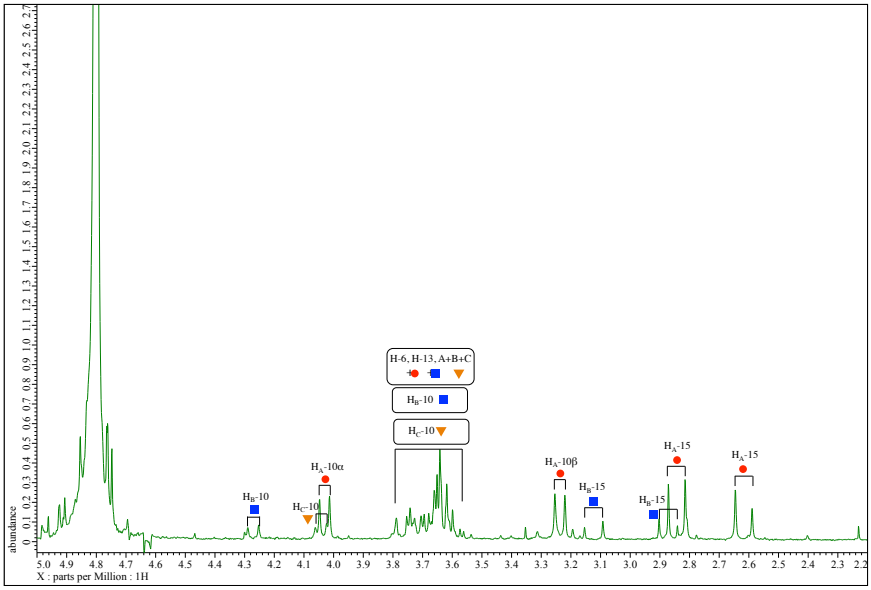
The purity of the purified SEA (**7**) was checked by using reverse phase HPLC (CH_3CN: 0.1% CH_3COOH aq. = 15: 85, Shiseido Cancel Pak AQ C18 column, Rt = 8.5 min, 214 nm UV detection).

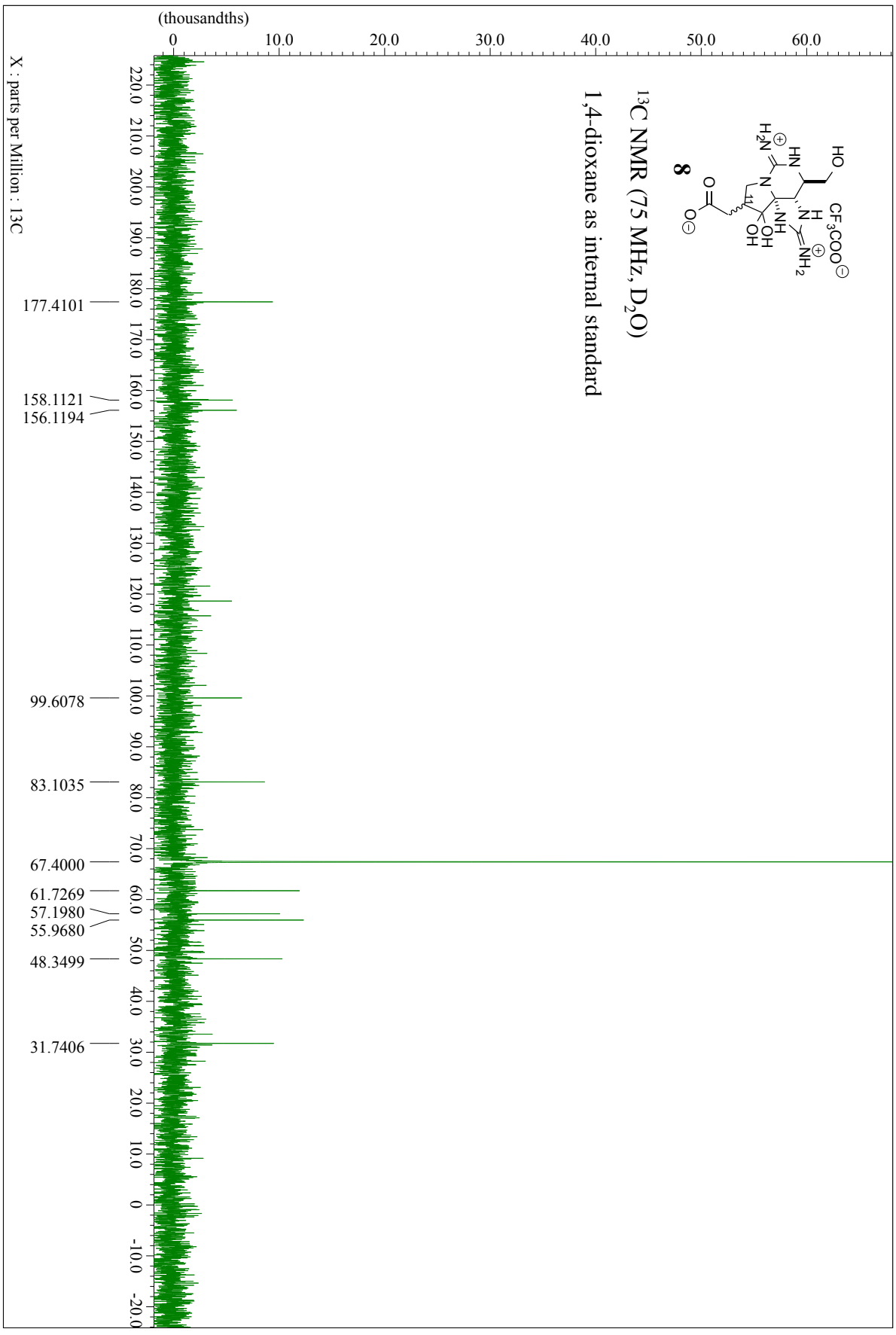


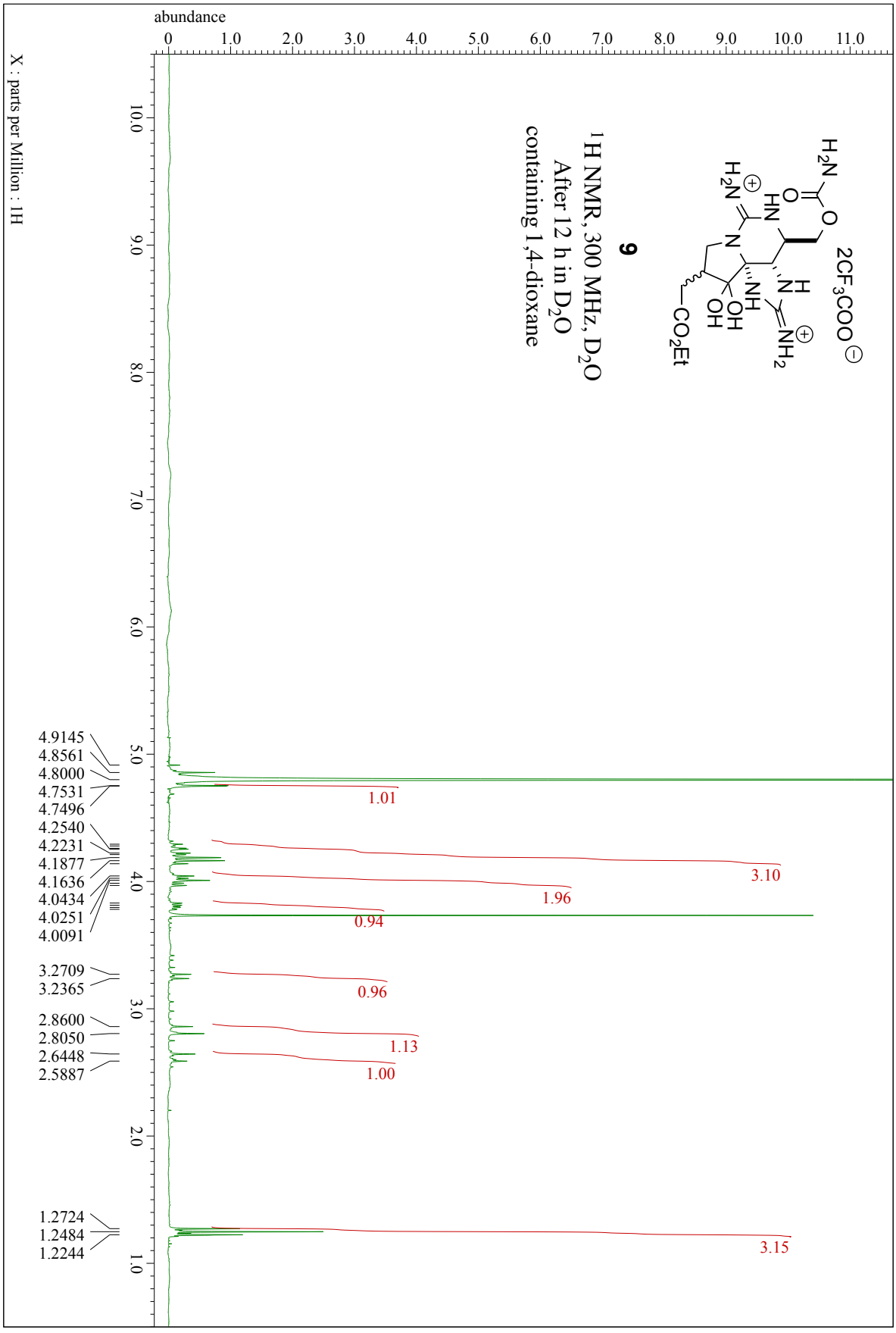

abundance
0
1.0
2.0
3.0
X : parts per Million : 1H
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
^{1}H NMR, 300 MHz, D_2O
After 12 h in D_2O
8
$2CH_3COO^{\ominus}$
4.7900
4.7179
4.0025
3.9693
3.6958
3.6821
3.6580
3.6477
3.6317
3.6134
3.6042
3.5939
3.5710
3.5527
3.2082
3.1750
2.8248
2.7687
2.5993
2.5421
0.87
1.07
3.24
1.01
1.13
1.00

Precise assignment of 8

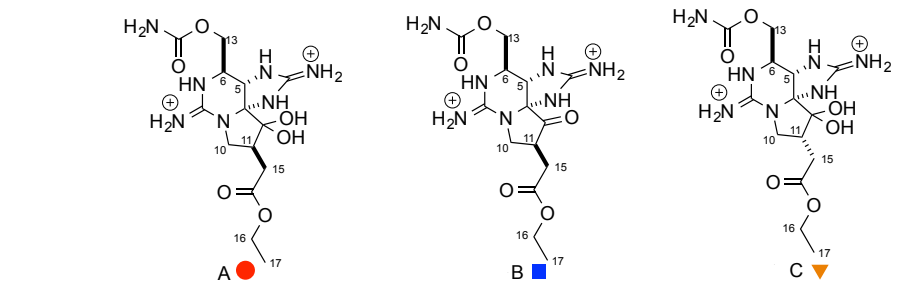


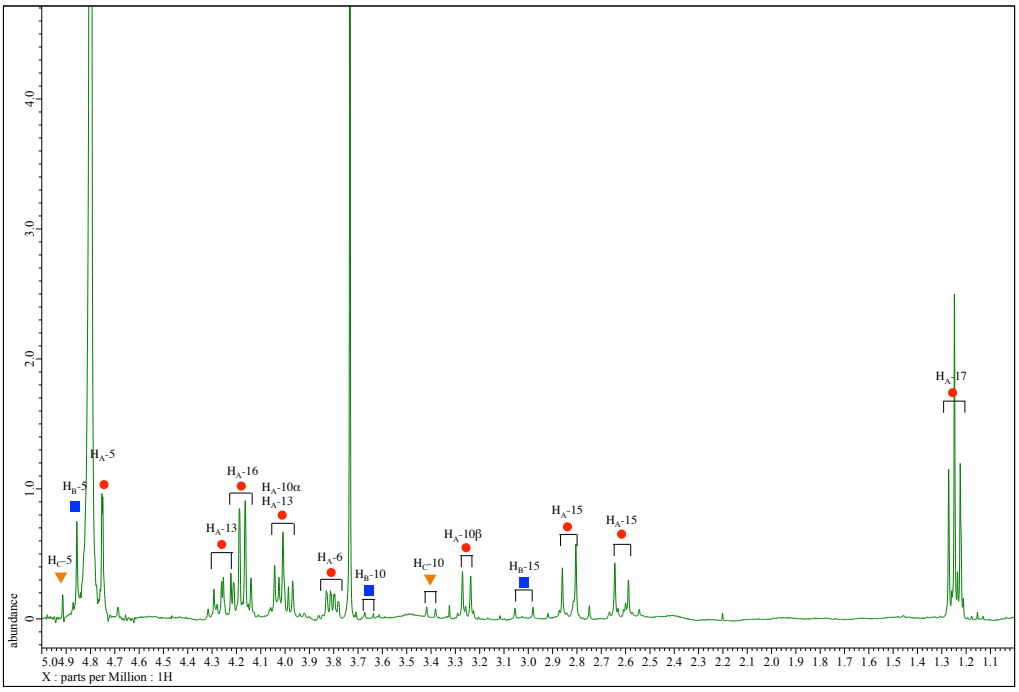


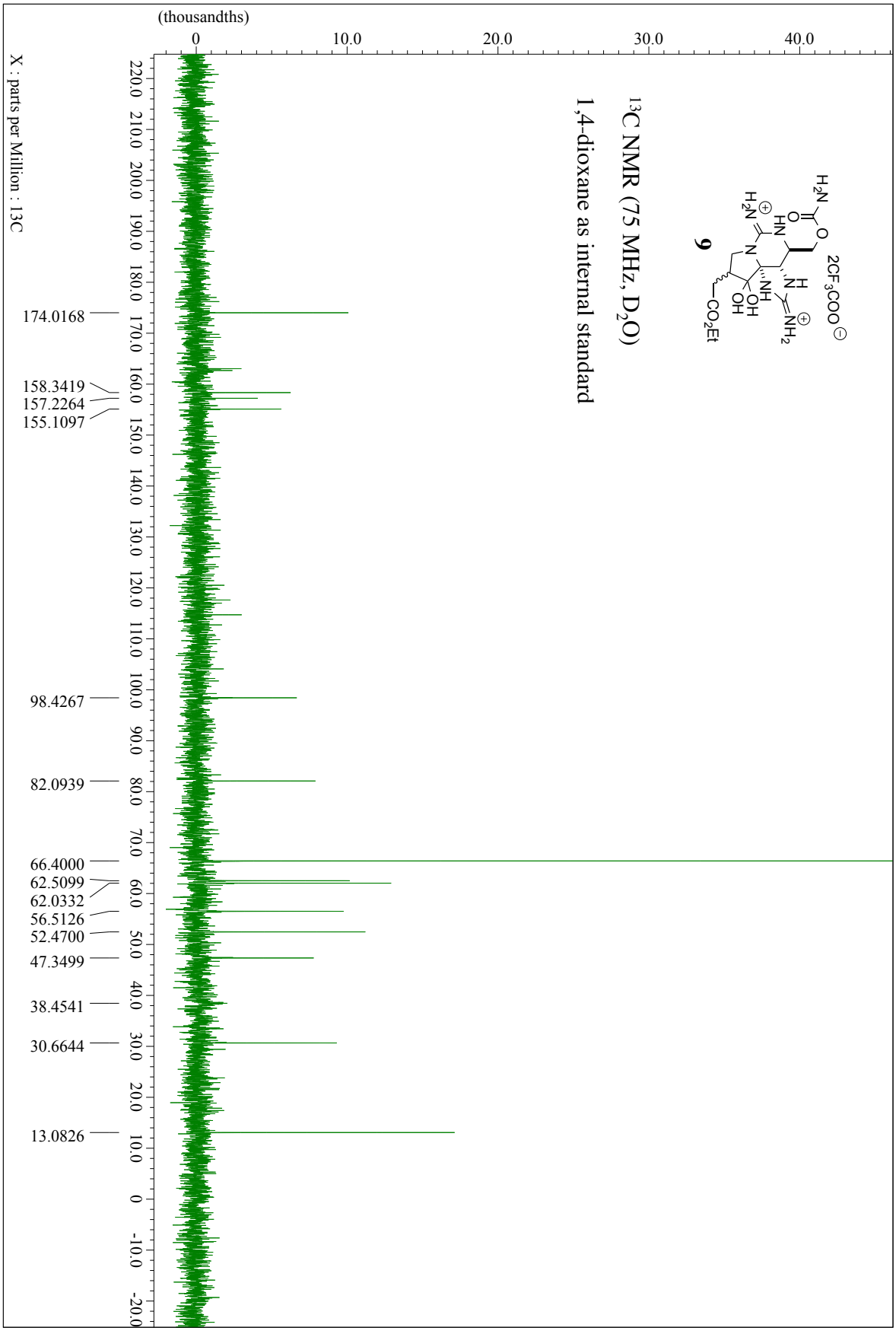

(thousandths)
0
10.0
20.0
30.0
40.0
50.0
60.0
X : parts per Million : 13C
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
177.4101
158.1121
156.1194
99.6078
83.1035
67.4000
61.7269
57.1980
55.9680
48.3499
31.7406
13C NMR (75 MHz, D2O)
1,4-dioxane as internal standard
8
HO
HN
H2N
N
NH
OH
OH
CF3COO
NH2
O
O

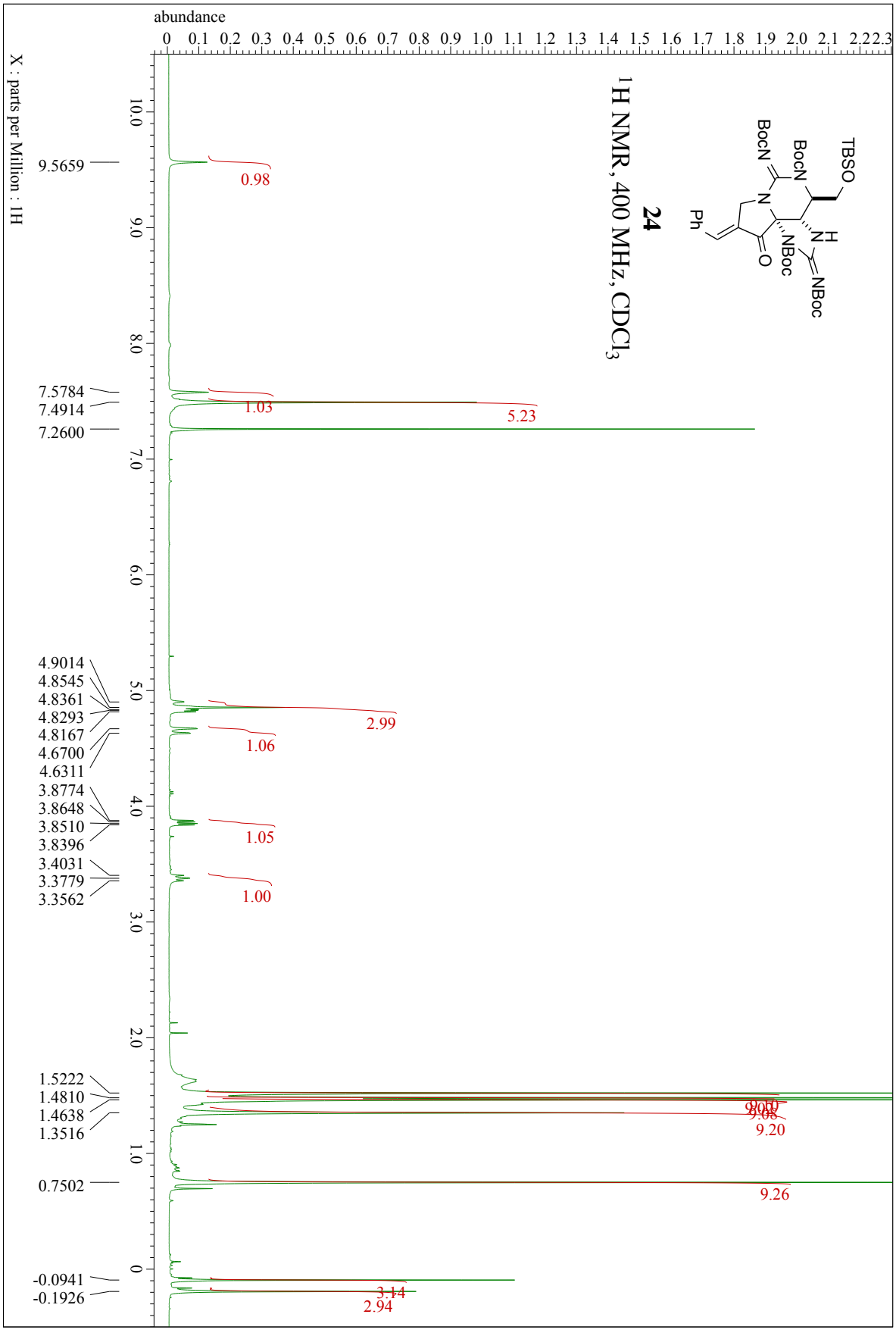

abundance
X : parts per Million : 1H
9
^{1}H NMR, 300 MHz, D_2O
After 12 h in D_2O
containing 1,4-dioxane
$2CF_3COO^-$
4.9145
4.8561
4.8000
4.7531
4.7496
4.2540
4.2231
4.1877
4.1636
4.0434
4.0251
4.0091
3.2709
3.2365
2.8600
2.8050
2.6448
2.5887
1.2724
1.2484
1.2244
1.01
3.10
1.96
0.94
0.96
1.13
1.00
3.15

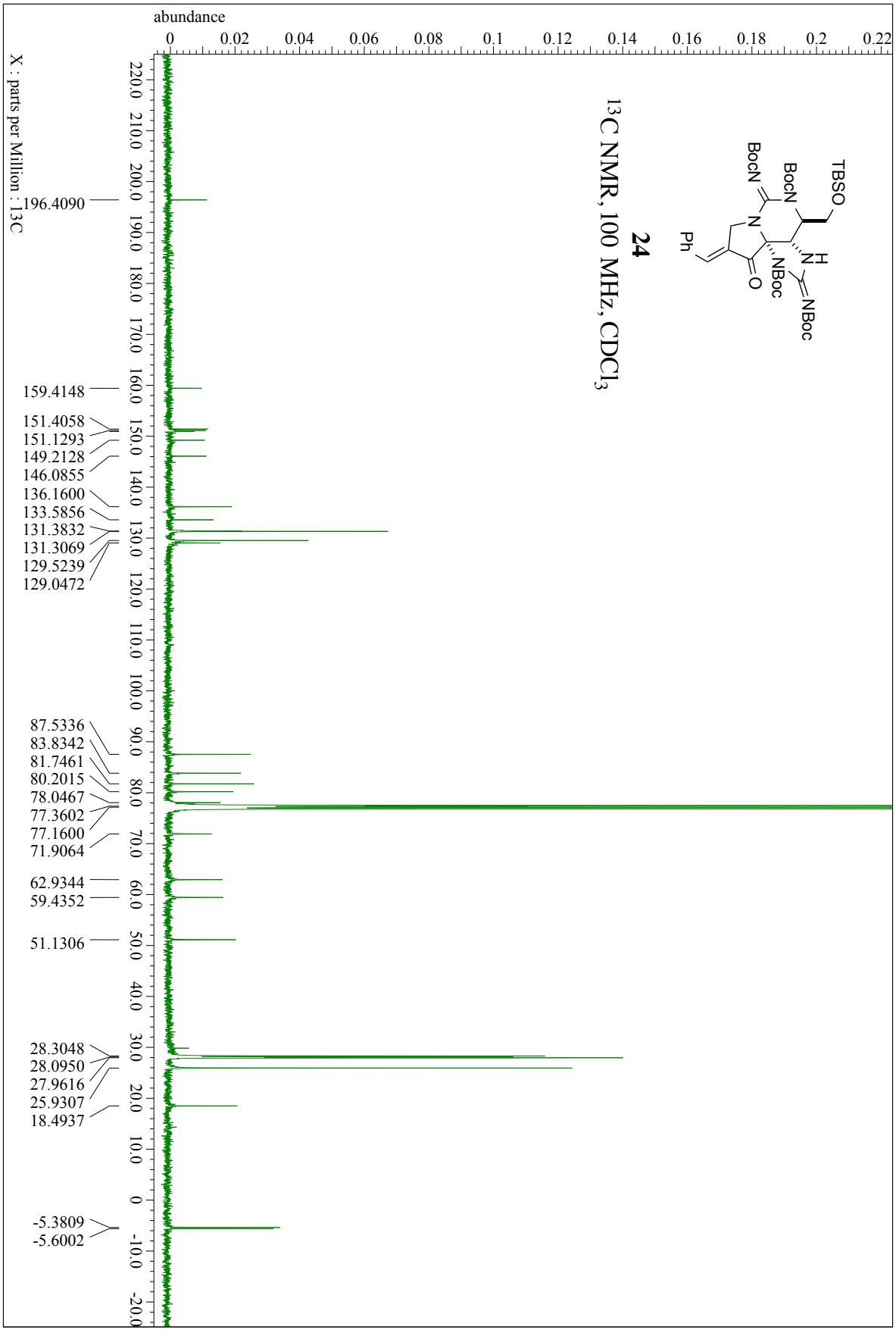
Precise assignment of 9

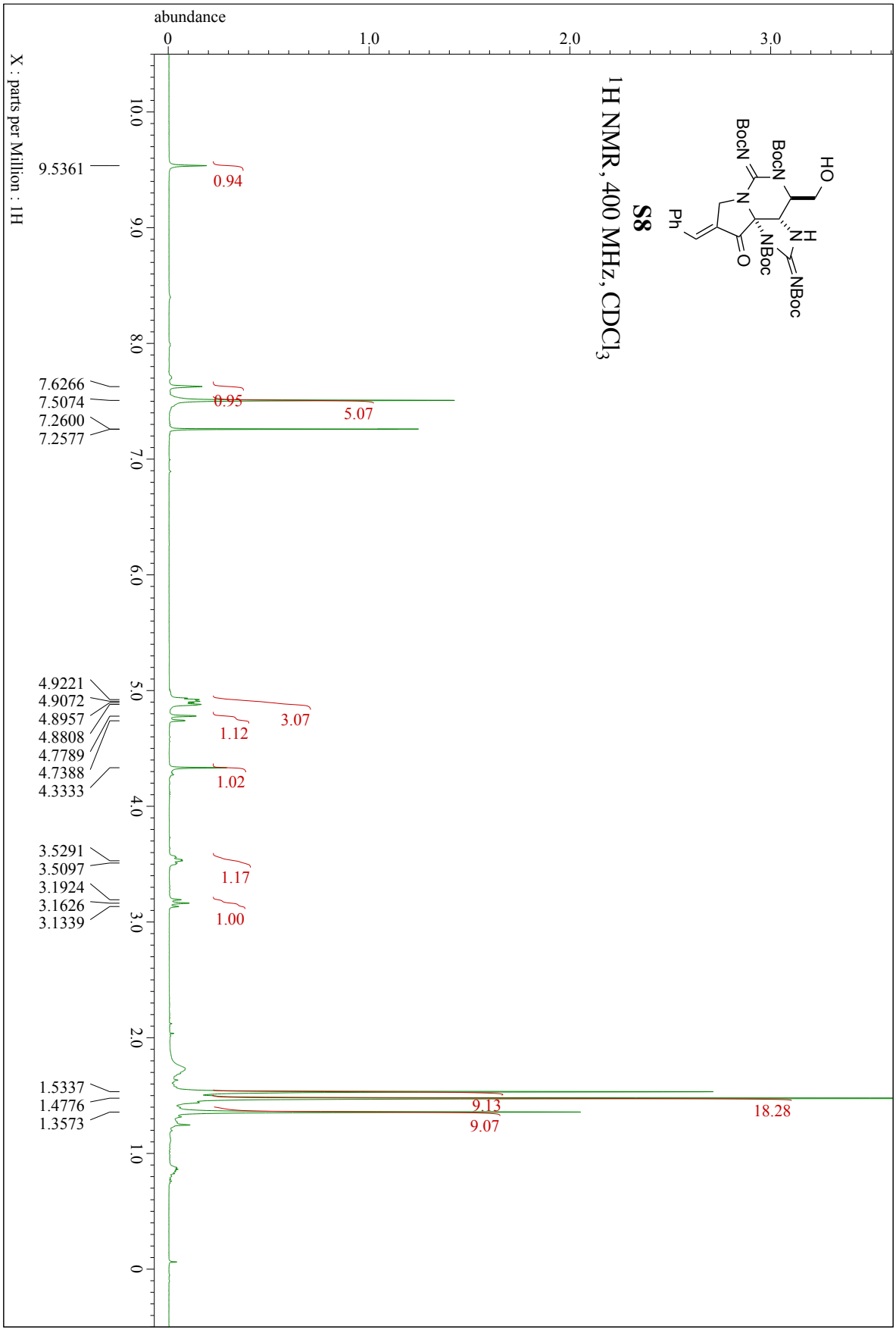


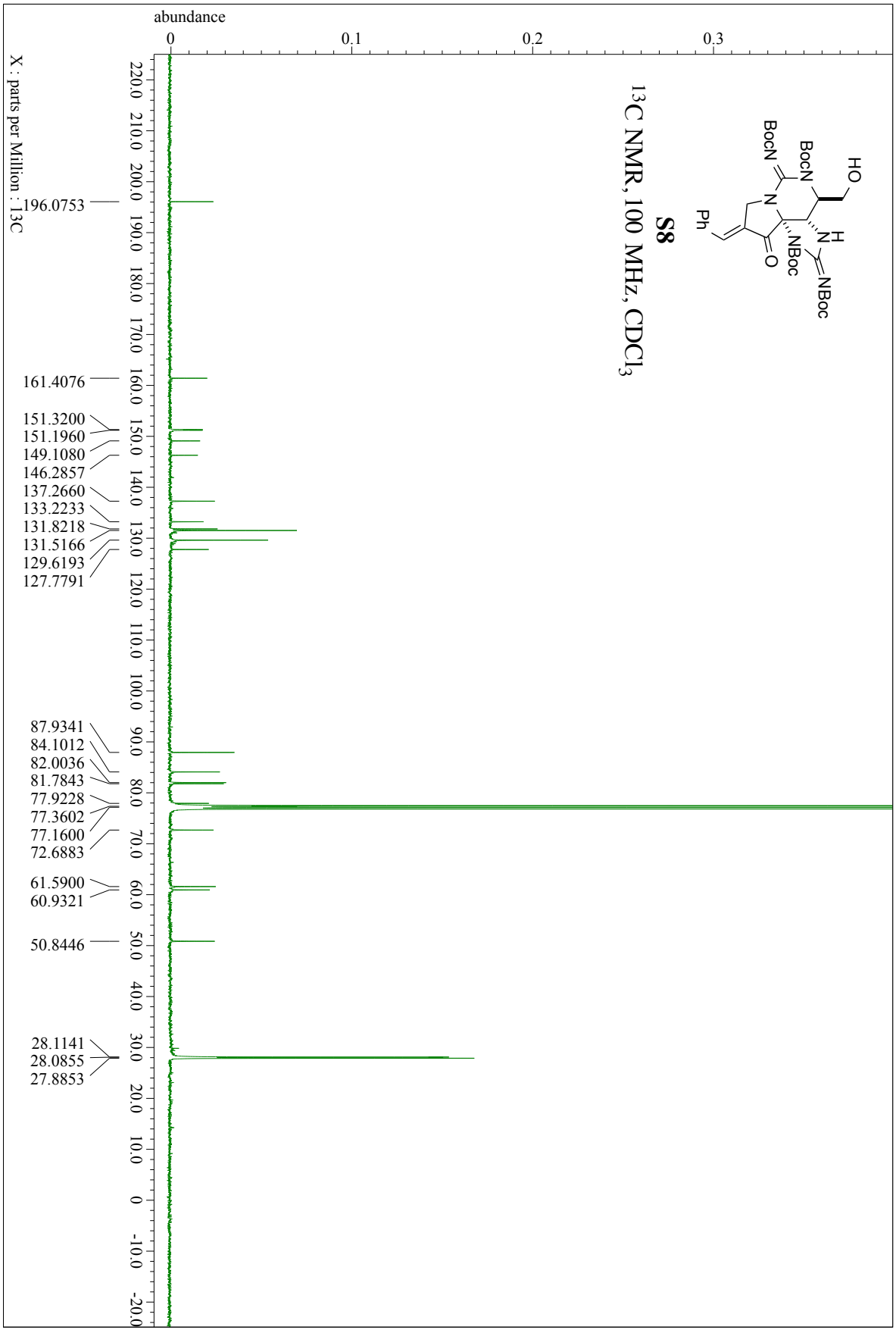


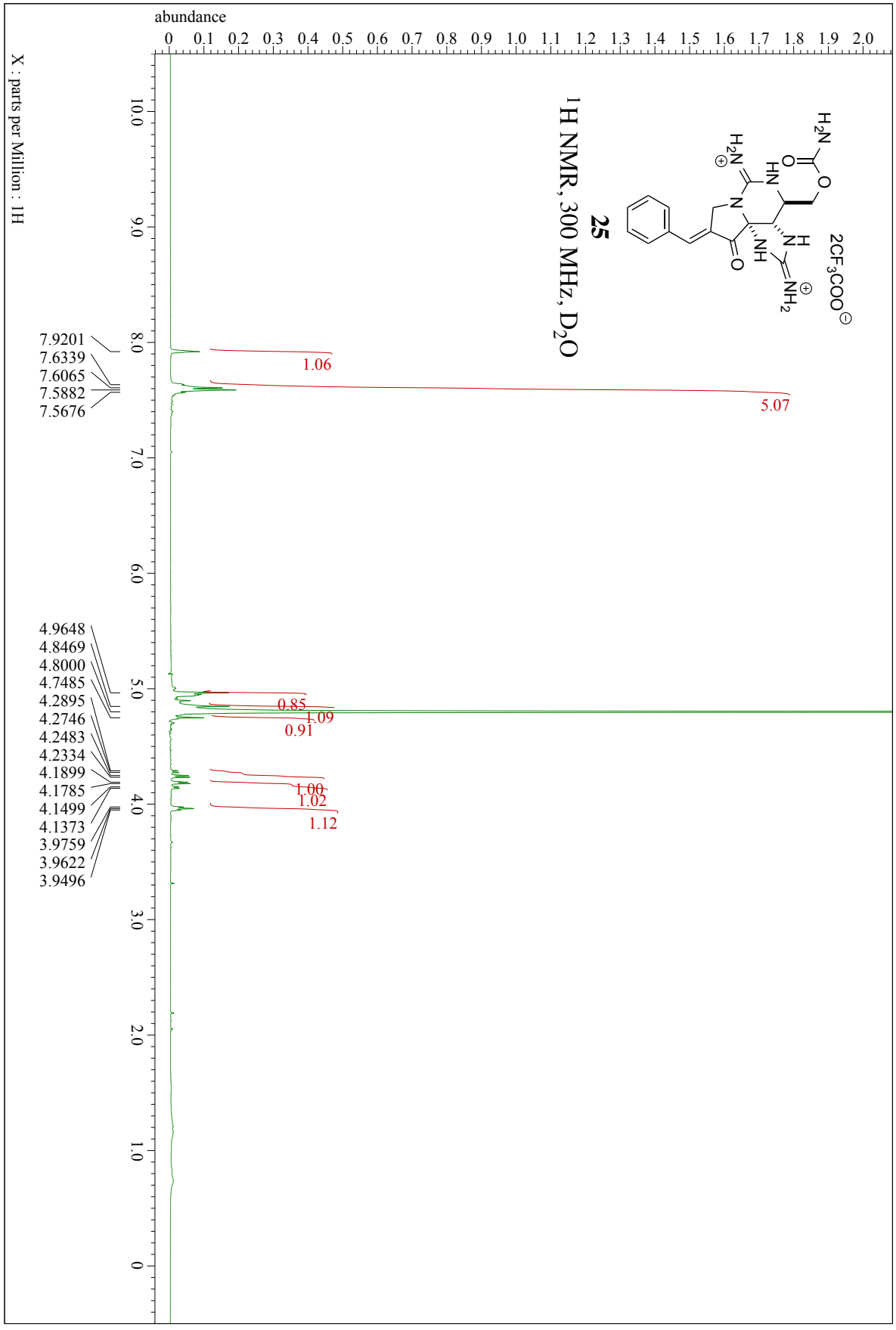

(thousandths)
0
10.0
20.0
30.0
40.0
X : parts per Million : 13C
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
174.0168
158.3419
157.2264
155.1097
98.4267
82.0939
66.4000
62.5099
62.0332
56.5126
52.4700
47.3499
38.4541
30.6644
13.0826
^{13}C NMR (75 MHz, D_2O)
1,4-dioxane as internal standard
9
$2CF_3COO^-$

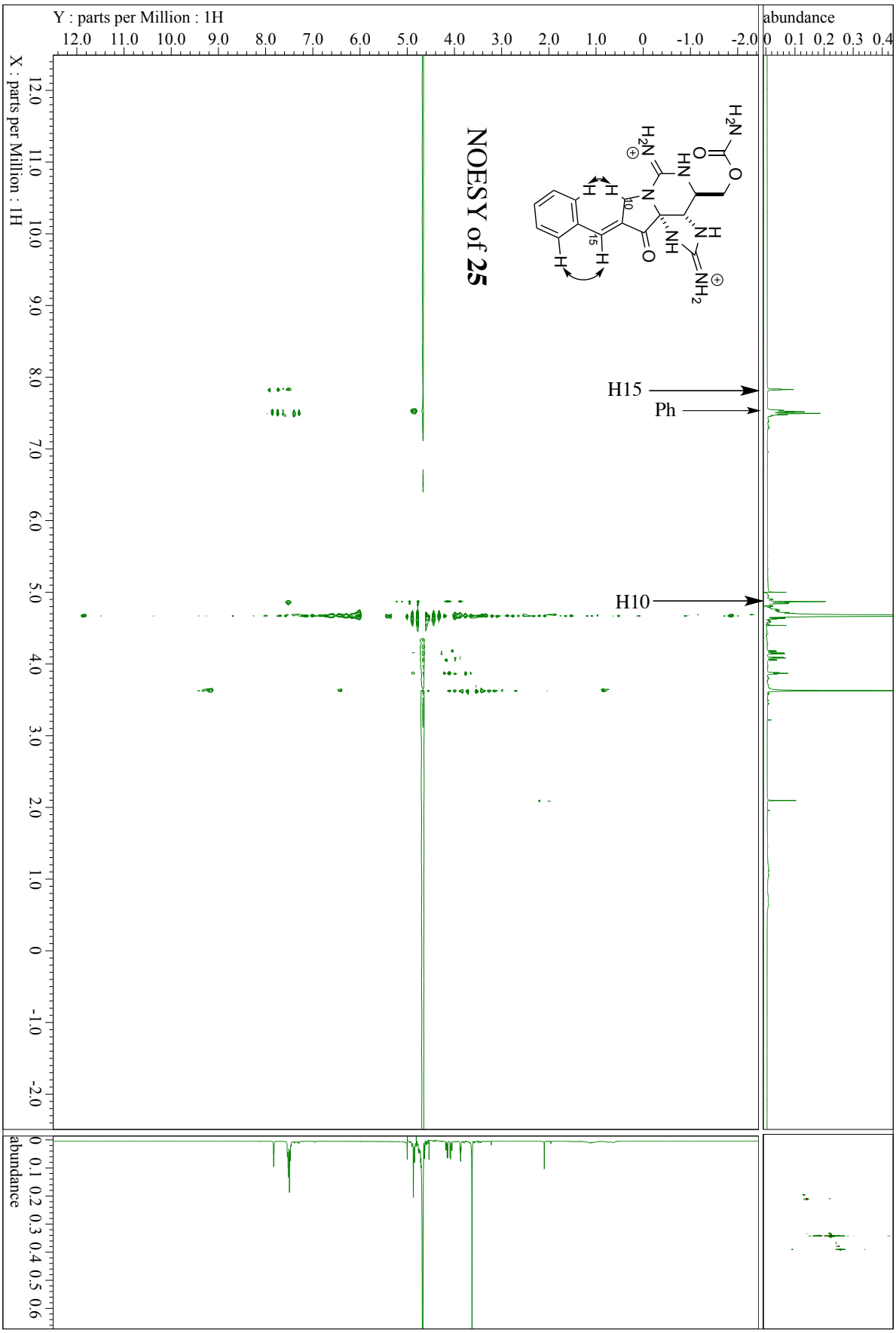

abundance
X : parts per Million : 1H
24
^{1}H NMR, 400 MHz, $CDCl_3$
TBSO
BocN
BocN
N
Ph
NBoc
O
H
N
NBoc
9.5659
7.5784
7.4914
7.2600
4.9014
4.8545
4.8361
4.8293
4.8167
4.6700
4.6311
3.8774
3.8648
3.8510
3.8396
3.4031
3.3779
3.3562
1.5222
1.4810
1.4638
1.3516
0.7502
-0.0941
-0.1926
0.98
1.03
5.23
2.99
1.06
1.05
1.00
9.20
9.26
3.14
2.94

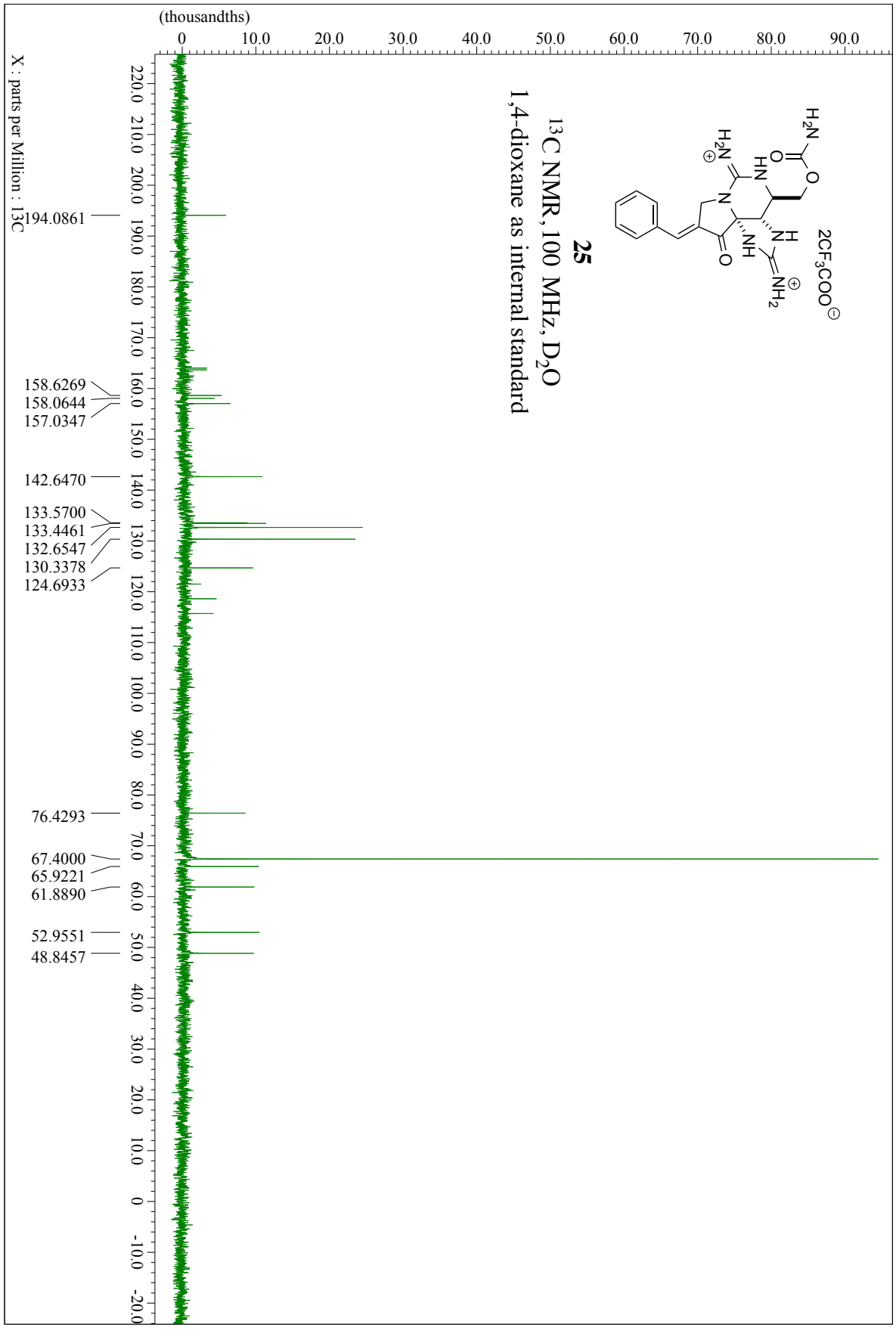

abundance
0 0.02 0.04 0.06 0.08 0.1 0.12 0.14 0.16 0.18 0.2 0.22
X : parts per Million : 13C
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
196.4090
159.4148
151.4058
151.1293
149.2128
146.0855
136.1600
133.5856
131.3832
131.3069
129.5239
129.0472
87.5336
83.8342
81.7461
80.2015
78.0467
77.3602
77.1600
71.9064
62.9344
59.4352
51.1306
28.3048
28.0950
27.9616
25.9307
18.4937
-5.3809
-5.6002
24
13C NMR, 100 MHz, CDCl3
TBSO
BocN
BocN
N
Ph
O
NBoc
H
N
NBoc


abundance
0
1.0
2.0
3.0
X : parts per Million : 1H
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
9.5361
7.6266
7.5074
7.2600
7.2577
4.9221
4.9072
4.8957
4.8808
4.7789
4.7388
4.3333
3.5291
3.5097
3.1924
3.1626
3.1339
1.5337
1.4776
1.3573
0.94
0.95
5.07
3.07
1.12
1.02
1.17
1.00
9.13
9.07
18.28
^{1}H NMR, 400 MHz, $CDCl_3$
S8
BocN
BocN
HO
N
Ph
NBoc
O
H
N
NBoc


abundance
0
0.1
0.2
0.3
X : parts per Million : 13C
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
196.0753
161.4076
151.3200
151.1960
149.1080
146.2857
137.2660
133.2233
131.8218
131.5166
129.6193
127.7791
87.9341
84.1012
82.0036
81.7843
77.9228
77.3602
77.1600
72.6883
61.5900
60.9321
50.8446
28.1141
28.0855
27.8853
S8
^{13}C NMR, 100 MHz, CDCl$_3$
HO
BocN
BocN
N
Ph
O
NBoc
H
N
NBoc


abundance
X : parts per Million : 1H
25
1H NMR, 300 MHz, D2O
2CF3COO⊖
7.9201
7.6339
7.6065
7.5882
7.5676
4.9648
4.8469
4.8000
4.7485
4.2895
4.2746
4.2483
4.2334
4.1899
4.1785
4.1499
4.1373
3.9759
3.9622
3.9496
1.06
5.07
0.85
1.09
0.91
1.00
1.02
1.12


NOESY of 25
Y : parts per Million : 1H
X : parts per Million : 1H
abundance
H15
Ph
H10


25
13C NMR, 100 MHz, D2O
1,4-dioxane as internal standard
2CF3COO⊖
X : parts per Million : 13C
194.0861
158.6269
158.0644
157.0347
142.6470
133.5700
133.4461
132.6547
130.3378
124.6933
76.4293
67.4000
65.9221
61.8890
52.9551
48.8457