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

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

Abstract: 11-Saxitoxinethanoic acid (SEA) is a member of the saxitoxin family of paralytic shellfish poisons, but unusually contains a C-C bond at the C11 position. Herein, we reported a total synthesis of SEA. The key to our synthesis lies in a Mukaiyama-aldol condensation reaction of silyl enol ether with glyoxylate in the presence of an anhydrous fluoride reagent, $[Bu_4N][Ph_3SnF_2]$, which directly constructs the crucial C-C bond at the C11 position in SEA. The Na_VCh-inhibitory activity of SEA and its derivatives was evaluated by means of cell-based assay. SEA showed an IC_{50} value of 47±12 nM, being approximately twice as potent as decarbamoyl-STX (dcSTX).

Saxitoxin (**1**, STX, Figure 1), which was first isolated as a paralytic shellfish poison,[1] is an inhibitor of voltage-gated sodium channels (Na_VCh).[2] So far, more than 50 analogs have been discovered,[3] and they have attracted considerable interest from synthetic chemists.[1c,d,4] Among the STX analogs, only zetekitoxin AB (**6**, ZTX)[5] and 11-saxitoxinethanoic acid (**7**, SEA)[6] contain a C-C bond at the C11 position. It is extremely difficult to understand how this C-C bond arises, in terms of proposed biosynthetic pathways for STXs.[7]

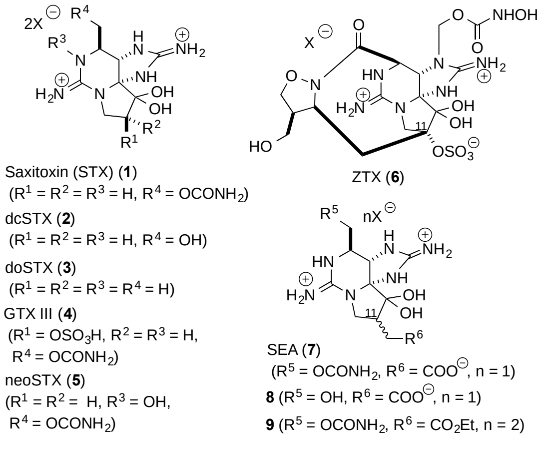
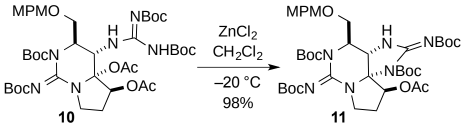


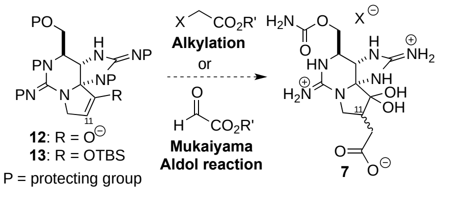
Figure 1 Structures of saxitoxin (**1**) and its derivatives **2-5**, zetekitoxin AB (**6**, ZTX), 11-saxitoxinethanoic acid (**7**, SEA) and its derivatives **8** and **9**.

We are interested in developing subtype-selective Na_VCh inhibitors, and in this work we focused on the synthesis of SEA (**7**) and its analogs as candidate Na_VCh modulators.[8] SEA (**7**) was originally isolated from xanthid crab *Atergatis floridus* in 1995,[6] and it contains a saxitoxin core with an acetic acid group at the C11 position; the natural product is a 9:1 mixture of stereoisomers. The toxicity of SEA (**7**) was reported as 830 mouse units per μmol on i.p. injection into mice, which corresponds to approximately one-third of the toxicity of STX (**1**).[3,6] In this communication, we describe the synthesis of SEA (**7**)[9] and its derivatives **8** and **9**. The Na_VCh-inhibitory activity of these new STX derivatives in cell-based assay is also reported.



Scheme 1. Synthesis of fully protected saxitoxinol **11** in our group.

We have recently developed a synthesis of fully protected saxitoxinol **11**[4g] by utilizing neighboring acyl group-assisted construction of the 5-membered cyclic guanidine structure in STXs under mild conditions (Scheme 1). Compound **11** is a key intermediate for the synthesis of STX and its derivatives, which have highly polar nature due to the two guanidine groups. We have employed **11** in syntheses of dcSTX (**2**), GTX III (**4**), and artificial STX derivatives.[4g,8b] Here, we envisaged application of **11** to the synthesis of SEA (**7**) through C-C bond formation at the C11 position.



Scheme 2 Synthetic strategies to SEA (**7**).

Regarding synthetic approaches to SEA (**7**), there are two possibilities to construct the C-C bond at the C11 position (Scheme 2), i.e., direct alkylation of the enolate **12** with halides in the presence of base, and Mukaiyama-aldol reaction of the silyl enol ether **13** with glyoxylate.

We initially investigated the alkylation strategy. However, the conversions were extremely low, and only trace amounts of the corresponding alkylation product were obtained.

Then, the Mukaiyama aldol reaction was investigated for construction of the C-C bond at the C11 position. The silyl enol ether **14** was synthesized from the fully protected saxitoxinol **11** in three steps, i.e., (i) hydrolysis of acetate with

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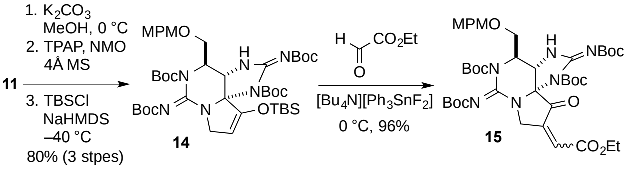
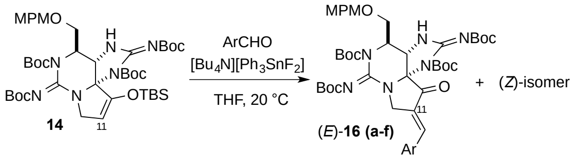
Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate)) potassiumcarbonate, (ii) oxidation of the resulting alcohol by means of Ley oxidation,[10] and (iii) silyl enol ether formation from the resulting ketone with TBSCl in the presence of NaHMDS (Scheme 3). With the silyl enol ether **14** in hand, the Mukaiyama aldol reaction was investigated with ethyl glyoxylate under various conditions. At first, Lewis acid-promoted conditions with $TiCl_4$ or $BF_3 \cdot Et_2O$ were tested,[11] but substrate **14** decomposed to generate mostly Boc-deprotected compounds, and no aldol reaction products were obtained. Next, fluoride anion-promoted reaction conditions were investigated. In the case of Bu_4NF,[12] no reaction occurred. On the other hand, in the case of $[Bu_4N][Ph_3SnF_2]$,[13] which is an anhydrous fluoride anion reagent, the condensation product **15** was obtained in 96% yield as a mixture of stereoisomers of the double bond (5:1).



Scheme 3 Mukaiyama aldol reaction of **14** with ethyl glyoxylate.

Since the Mukaiyama aldol condensation reaction appears to be a powerful tool for constructing the C-C bond at C11 in STXs, the scope of the reaction was investigated. Thus, various aromatic aldehydes were subjected to reaction with **14**, and the corresponding aldol condensation adducts (**16a-f**) were obtained in 45–80% yields (Table 1).

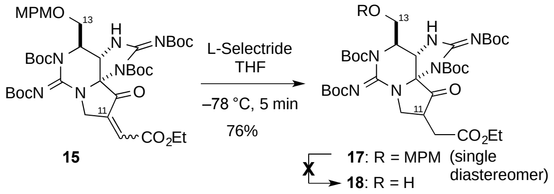
Table 1. Substrate scope of the Mukaiyama aldol condensation reaction of **14** with aromatic aldehydes.



entry	Ar	time(h)	product	E/Z^b	yield(%)
1	4-Me-C_6H_4	48	**16a**	>10:1	45
2	C_6H_5	24	**16b**	>10:1	60
3	3-F-C_6H_4	24	**16c**	>10:1	63
4	4-Cl-C_6H_4	24	**16d**	>10:1	65
5[a]	4-NO_2-C_6H_4	2	**16e**	6:1	80
6[a]	2-furyl	2	**16f**	>10:1	80

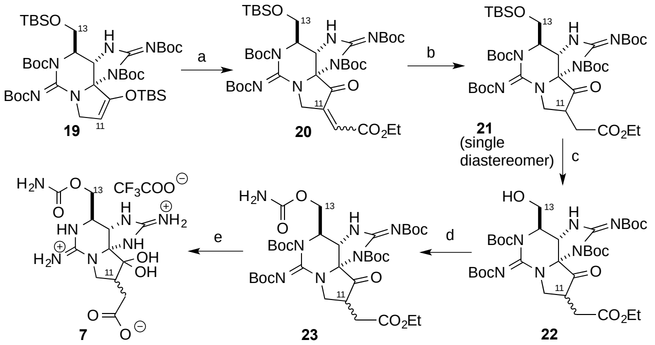
[a]Reaction was carried out at 0 °C. [b]Ratios at C11 were determined by ^1H NMR.[14]

After construction of the crucial C-C bond at the C11 position of SEA (**7**), the double bond in **15** had to be reduced, followed by deprotection of the MPM group at the C13 position. For the reduction, after extensive investigation,[15] L-selectride was found to be quite effective, giving **17** in 76% yield as a single diastereomer (Scheme 4).[17] Unfortunately, subsequent deprotection of MPM group at the C13 failed under all the conditions we investigated, e.g., NBS-Et_3B,[4g] DDQ or CAN.[18] Finally, we decided to change the protecting group from MPM to TBS ether at an earlier stage.



Scheme 4 Investigation of the reduction at C11 and deprotection of the MPM group at C13.

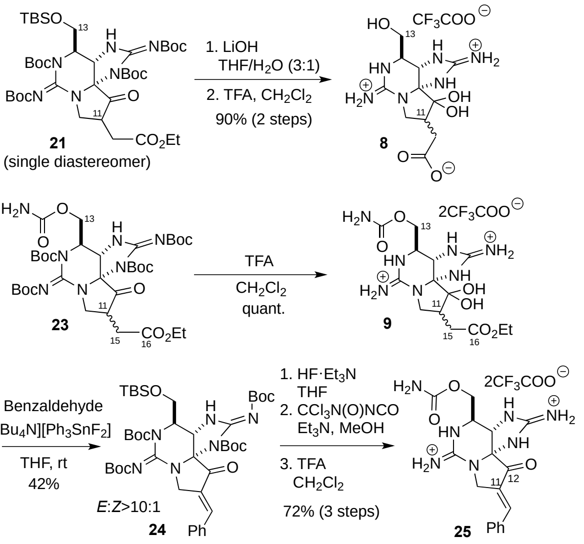
Thus, silyl enol ether **19** with TBS ether at the C13 position was synthesized by following a similar procedure to that used for **14**,[19] and the Mukaiyama aldol condensation reaction with ethyl glyoxylate was examined in the presence of $[Bu_4N][Ph_3SnF_2]$. Under these conditions, aldol condensation adduct **20** was obtained in 85% yield. Interestingly, the TBS ether at C13 remained intact under these conditions (Scheme 5). After reduction of the double bond with L-selectride, deprotection of the silyl ether in **21** at C13 took place smoothly on treatment with $HF \cdot Et_3N$ complex to give **22** in 87% yield.[20] The resulting hydroxyl group was further converted to a carbamoyl group by reaction with trichloroisocyanate followed by hydrolysis with triethylamine in methanol to give **23** in 68% yield. Finally, 11-saxitoxinethanoic acid (**7**) was obtained by further hydrolysis of the ethyl ester with lithium hydroxide and deprotection of all four Boc groups with TFA, in 90% yield.[21] The stereochemistry at C11 of synthetic **7** was found to be a mixture of ca. 9:1 ratio, which is identical with that of the natural product reported by Onoue.[6]



Scheme 5 Synthesis of SEA (**7**). Reagents and conditions: a) ethyl glyoxylate, $[Bu_4N][Ph_3SnF_2]$, THF, 0 °C, 85%; b) L-Selectride, THF, –78 °C, 76%; c) $HF \cdot Et_3N$, THF/Et_3N (5:1), rt, 87%; d) $CCl_3C(O)NCO$, CH_2Cl_2, 0 °C, then Et_3N, MeOH, rt, 68%; e) LiOH, THF/H_2O (3:1), 0 °C; then, TFA, CH_2Cl_2, rt, 90%. L-Selectride = lithium tri-sec-butyl(hydrido)borate(1-), TFA = trifluoroacetic acid.

The inhibitory activities towards Na_VCh of SEA (**7**) and its synthetic derivatives decarbamoyl-11-saxitoxinethanoic acid (**8**, dcSEA), 11-saxitoxinethanoic ethyl ester (**9**, SEE), which were obtained from **21** and **23**, respectively (Scheme 6), were evaluated in a cell-based assay. In addition, 11-benzyliden-saxitoxin (**25**, 11-benzylidenSTX), synthesized from **19** via **24** (Scheme 6), was also tested.[22] Specifically, the Na_VCh-inhibitory activity of ligands was evaluated in terms of cytotoxicity to mouse neuroblastoma Neuro-2a cells, which express Na_VCh.[23] In this cell-based assay, Neuro-2a is treated with a sodium channel activator, veratridine, in the presence of ouabain, an inhibitor of Na^+/K^+ ATPase. This blocks sodium ion efflux, and decreases the cell viability. Na_VCh inhibition by tetrodotoxin (TTX), STX and related compounds antagonizes this effect, and rescues the cells in a dose-dependent manner.[23e,8] The inhibitory activities of **7**, **8**, **9** and **25** were calculated from the cell viability in the above assay, and the results are summarized in Table 2. SEA (**7**), dcSEA (**8**), SEE (**9**), and 11-benzylidenSTX (**25**) showed a concentration-dependent Na_VCh-inhibitory effect, and their IC_{50} values were determined to be 47±12 nM, 5.7±3.1 μM, 185±74 nM, and 16±6.9 nM,[24] respectively (the IC_{50} values of synthetic dcSTX (**2**)[4g] and TTX, used as controls, were 89±36 nM and 5.0±1.6 nM, respectively). Thus, SEA (**7**) was twice as potent as dcSTX (**2**) on its Na_VCh-

inhibitory activity. In the case of dcSEA (**8**), the inhibitory activity was markedly decreased, and it was approximately hundred times less potent than dcSTX (**2**). SEE (**9**) showed about half weaker inhibitory activity than dcSTX (**2**). Interestingly, 11-benzylidenSTX (**25**) showed the same level inhibitory activity with dcSTX (**2**), although hydrated form of ketone at C12 in STXs is suggested to be important for their Na$_V$Ch-inhibitory activity.[25] Further structure-activity relationship studies are under way to examine the inhibitory activity of other STX derivatives having a C-C bond at the C11 position.



Scheme 6 Synthesis of dcSEA (**8**), SEE (**9**) and (**25**).

Table 2 Na$_V$Ch-inhibitory activity of SEA (**7**) and its derivatives dcSEA (**8**), SEE (**9**) and 11-benzylidenSTX (**25**) in a cell-based assay with Neuro-2a cells.

Compound	IC$_{50}$ (mean ± SD)	n
SEA (**7**)	47±12 nM	3
dcSEA (**8**)	5.7±3.1 μM	3
SEE (**9**)	185±74 nM	4
11-benzylidenSTX (**25**)	16±6.9 nM[24]	5
dcSTX (**2**)[4g]	89±36 nM	3
TTX	5.0±1.6 nM	6

In conclusion, a total synthesis of SEA (**7**) has been achieved from the silyl enol ether **19** in 35% overall yield. The synthesis features a Mukaiyama aldol condensation reaction to construct the C-C bond at the C11 position of STX. The derivatives (**8**, **9,** and **25**) were similarly synthesized. In a cell-based assay, SEA (**7**) showed approximately twice more potent Na$_V$Ch-inhibitory activity than dcSTX (**2**), but dcSEA (**8**) showed about hundred times less potent activity, in marked contrast to the relationship between STX (**1**) and dcSTX (**2**).[26] Interestingly, the inhibitory activity of 11-benziidenSTX (**25**) was in a similar level with dcSTX (**2**), and interacting mode of **25** with Na$_V$Ch is quite intrigued.

Acknowledgements

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Keywords: 11-saxitoxinethanoic acid, Mukaiyama-aldol condensation, total synthesis, sodium channel inhibitor

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[14] Stereochemistry of olefin in **16a** was determined by NOESY (see supporting information), and according to **16a**, the stereochemistries for **16b-f** were determined.

[15] Metal catalysts (Pd/C, Pd(OH)$_2$/C, PtO$_2$, RhCl(PPh$_3$)$_3$, [Ir(cod)py(PCy$_3$)]PF$_6$ and Raney Ni) were tried first under hydrogenation conditions. In the case of Pd/C and Pd(OH)$_2$/C, the desired product was not obtained and Boc-deprotected products were generated. In the case of the next three catalysts, the reaction did not proceed at all, and starting material **15** was recovered quantitatively. Raney Ni in MeOH under hydrogenation conditions gave desired **17** in 70% yield, but reproducibility was poor in large-scale reaction. In the case of

single electron reduction using activated Mg in dry methanol,[16] the desired product **17** was obtained in 30% yield.

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[17] The ^{1}H NMR spectrum indicated the presence of only one diastereoisomer, but the stereochemistry at C11 in **17** was difficult to determine.

[18] Standard conditions (DDQ and CAN) did not give **18** and caused deprotection of the Boc groups in **17**.

[19] For the synthesis of silyl enol ether **19**, see supporting information.

[20] In the case of Bu_4NF, the substrate **21** decomposed immediately. When HF·Py was tried, the reaction proceeded extremely slowly.

[21] Intermediates **20**, **21**, **22** and **23** were quite unstable under regular silica gel column purification conditions. After extensive investigation, we found that rapid purification on neutral silica gel gave acceptable results. Since C11 in **22** and **23** epimerized easily, the products were obtained as diastereomeric mixtures. Data for the major diastereomers are presented in supporting information. (For the data collection process, **22** and **23** were purified by preparative thin layer chromatography. During this process, the minor diastereomer decomposed, and we collected only the major diastereomer.).

[22] 11-BenzylidenSTX (**25**) exists as a keto-form at C12 (from ^{13}C NMR in D_2O), which is different from the other member of STX derivatives.

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[24] In the case of 11-benzylidenSTX (**25**), the IC_{50} values of dsSTX (**2**) and TTX, used as controls were, 18±2.1 nM (n = 3) and 5.0±2.8 nM (n = 4), respectively.

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[26] The Na_VCh inhibitory activity of dcSTX (**2**) has been reported to be 2~10 fold less potent than that of STX.[27]

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Entry for the Table of Contents (Please choose one layout)

Layout 1:

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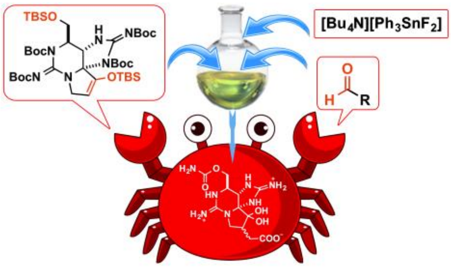
A direct construction the C-C bond at the C11 position of saxitoxin skeleton by using Mukaiyama condensation reaction was utilized for an efficient synthesis of 11-saxitoxinethanoic acid.



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

Page No. – Page No.

Total synthesis of 11-saxitoxinethanoic acid and evaluation of its inhibitory activity on voltage-gated sodium channels

Layout 2:

COMMUNICATION

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Page No. – Page No.

Title

Text for Table of Contents

Supporting Information

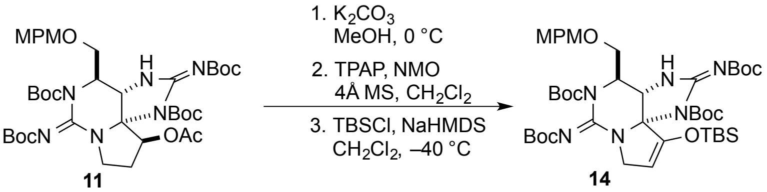
Table of contents

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:



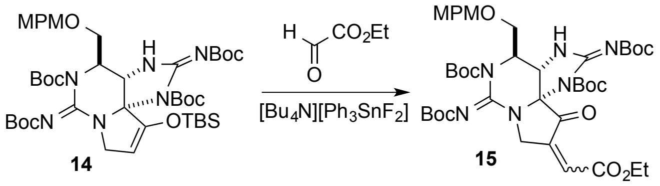
To a solution of protected STXol **11** (100 mg, 0.125 mmol) in methanol (2 mL) was added K_2CO_3 (35 mg, 0.25 mmol) at 0 °C. After stirring for 15 min, the reaction was diluted with EtOAc (5 mL) and H_2O (5 mL), and extracted with EtOAc (5 mL) three times. The organic layer was dried over $MgSO_4$, 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 $CHCl_3$); ^1H 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:

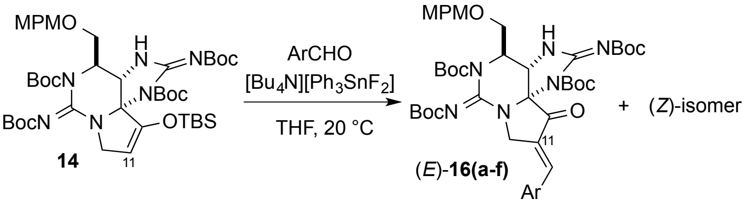


To a solution of silyl enol ether **14** (87 mg, 0.10 mmol) in THF (4 mL) was added ethyl glyoxylate (80 μL) at 0 °C. After stirring for 10 min, [Bu$_4$][Ph$_3$SnF$_2$] (67 mg, 0.11 mmol) was added and the reaction was stirred for another 2 hrs at the same temperature. Then, the reaction was quenched with sat. NH$_4$Cl 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.

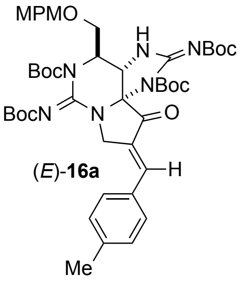
Synthesis of Mukaiyama aldol condensation adduct 16a-f

General procedure for the Mukaiyama aldol condensation:



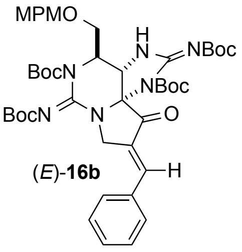
To a solution of silyl enol ether **14** (1 equiv) in THF was added aldehyde (5 equiv) at 0 °C. After stirring for several minutes, [Bu$_4$][Ph$_3$SnF$_2$] (1.05 equiv) was added and the reaction was stirred at the same temperature. Upon completion of the reaction (2-48 h), the reaction was quenched with sat. NH$_4$Cl 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:**



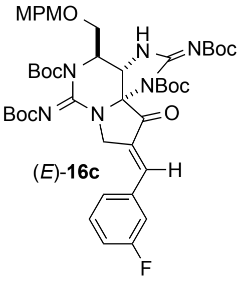
(*E*)-**16a**

(*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.



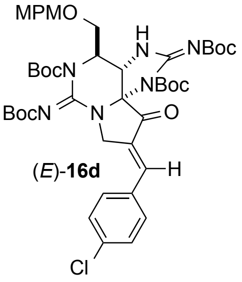
(*E*)-**16b**

(*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**

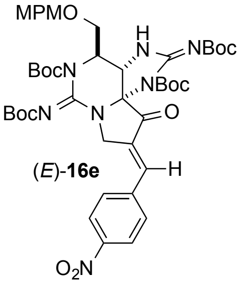
(*E*)-**16c**: $[\alpha]^{25}_{D}$= +17.9 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.37 (dd, *J* = 7.9, 14.1 Hz, 1H), 7.30 (s, 1H), 7.16-7.07 (m, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 2H), 6.45 (d, *J* = 8.3 Hz, 2H), 4.91 (s, 1H), 4.69 (s, 1H), 4.61 (d, *J* = 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.



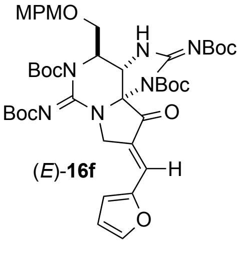
(*E*)-**16d**

(*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.

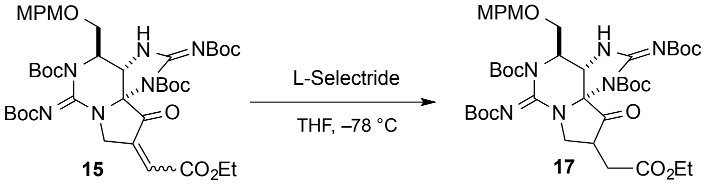


(*E*)-**16e**: $[\alpha]^{25}_{D}$ = +32.7 (*c* 0.8 in CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.54 (s, 1H), 8.20 (d, *J* = 8.6 Hz, 2H), 7.35-7.28 (m, 3H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.31 (d, *J* = 8.6 Hz, 2H), 4.92 (s, 1H), 4.69 (s, 1H), 4.66-4.57 (m, 1H), 4.30-4.20 (m, 1H), 4.14 (d, *J* = 11.0 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**: $[\alpha]^{25}_{D}$ = +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:



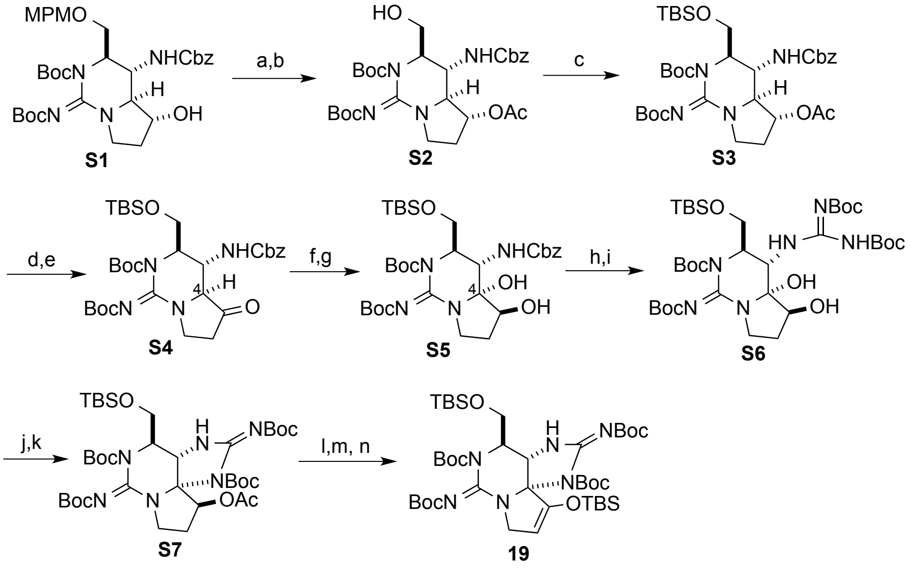
To a solution of **15** (20 mg, 0.024 mmol) in THF (1 mL) was added L-selectride (71 μL, 0.071 mmol) at −78 °C. After stirring for 5 min, the reaction was quenched with sat. NH_4Cl aq (1 mL), and the solution was extracted with EtOAc (2 mL) three times. The combined organic layers was dried over $MgSO_4$, 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]

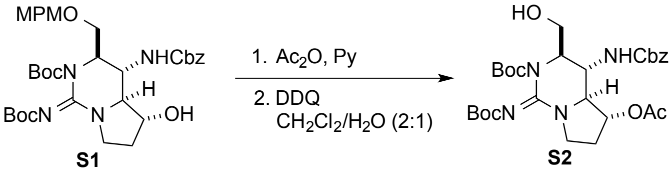
The route was commenced with the known compound **S1** (Scheme S1), acylation of the hydroxyl group with acetic anhydride followed by removal of the MPM group with DDQ afforded **S2** and further protection with TBS gave **S3**. Hydrolysis of the acetate with potassium carbonate followed by Swern oxidation 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

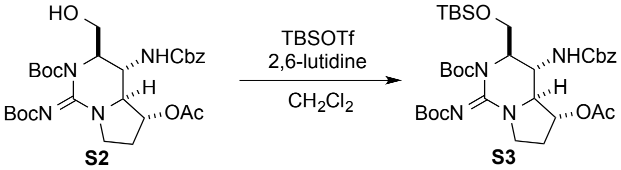


To a solution of alcohol S**1** (7.6 g, 11.38 mmol) in pyridine (10 mL) was added acetic anhydride (5 mL) at room temperature. After stirring for 3 hrs, the reaction mixture was concentrated *in vacuo* to give ester.

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 $CHCl_3$); ^1H 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.

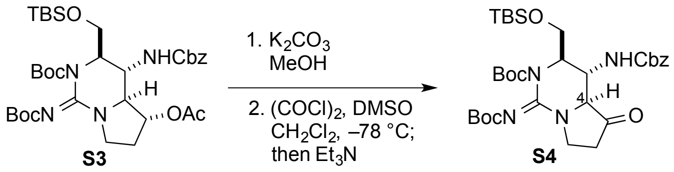
Synthesis of S3



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 $CHCl_3$); ^1H 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.

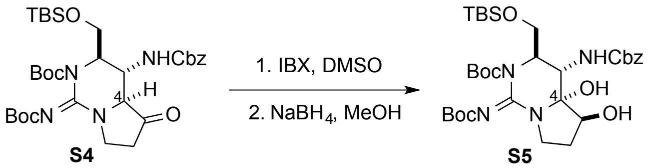
Synthesis of S4



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

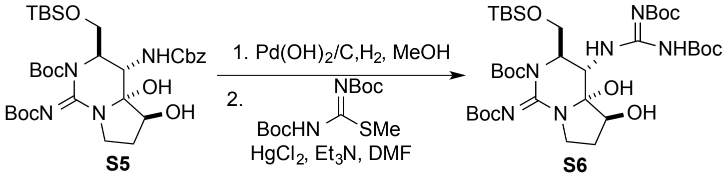


To a solution of ketone **S4** in DMSO (65 mL) and H_2O (0.24 mL) was added IBX (2.43 g, 8.63 mmol) at room temperature. Then the reaction mixture was warmed to 50 °C and stirred for 1 h. After that, the reaction was quenched with 10% $Na_2S_2O_3$ aq (30 mL) and saturated $NaHCO_3$ aq (30 mL). Then, 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 $CHCl_3$); ^1H 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

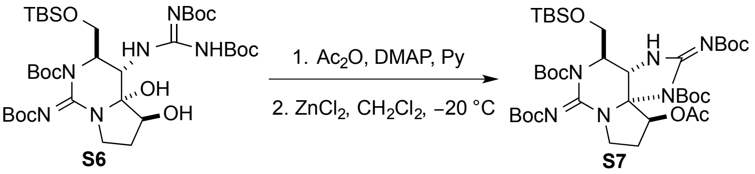


To a solution of diol **S5** (3.56 g, 5.36 mmol) in methanol (45 mL) was added 20% Pd(OH)$_2$ (0.71 g). The suspension was vigorously stirred under H$_2$ atmosphere (balloon) at room temperature for 3 hrs and then was filtered through a pad of Celite. The filtrates were concentrated *in vacuo* to give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

To a solution of the amine, Et$_3$N (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

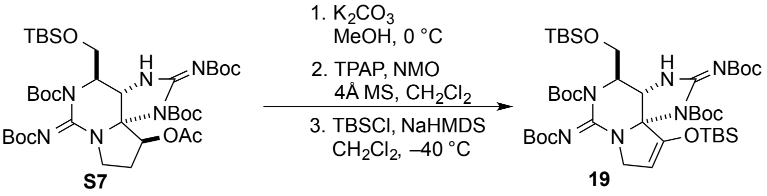


To a solution of bis-guanidine **S6** (3.89 g, 5.03 mmol) in pyridine (16 mL) was added catalytic amount of DMAP (62 mg, 0.05 mmol) and acetic anhydride (8 mL) at room temperature. After stirring for 1 h, the reaction mixture was concentrated *in vacuo* to give diester.

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



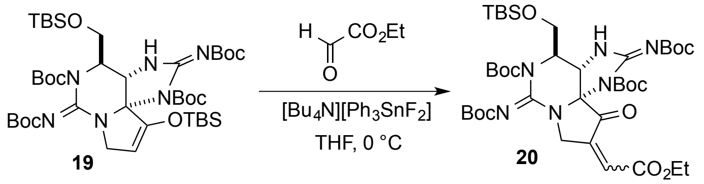
To a solution of protected STXol **S7** (0.95 g, 1.19 mmol) in methanol (12 mL) was added K_2CO_3 (0.33 g, 2.38 mmol) at 0 °C. After stirring for 15 min, the reaction was diluted with EtOAc (10 mL)and H_2O (10 mL), and extracted with EtOAc (15 mL) three times. The organic layer was dried over $MgSO_4$, 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 $CHCl_3$); ^1H 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.

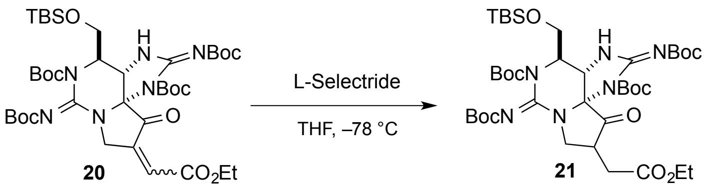
Synthesis of 20



To a solution of silyl enpl ether **19** (0.23 g, 0.27 mmol) in THF (10 mL) was added ethyl glyoxylate (210 *μ*L) 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.

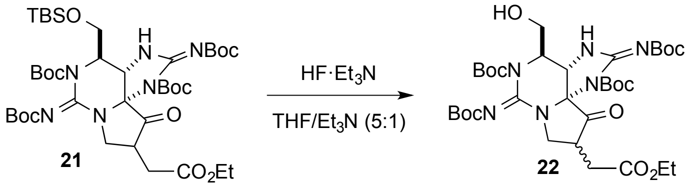
Synthesis of 21



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 $CHCl_3$); ^1H 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.

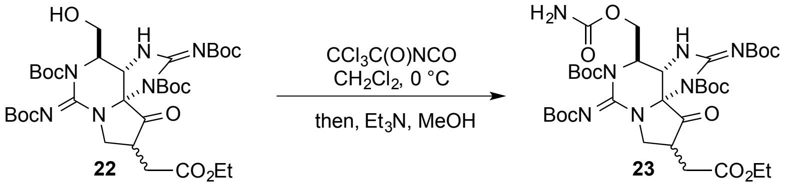
Synthesis of 22



To a solution of **21** (145 mg, 0.17 mmol) in a mixture solvent (THF = 4 mL, Et_3N = 0.8 mL) was added $HF{\cdot}Et_3N$ (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 $CHCl_3$); ^1H 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

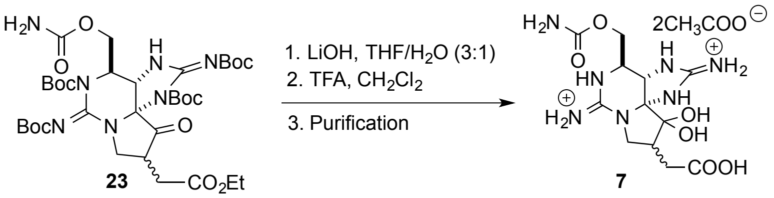


To a solution of **22** (109 mg, 0.15 mmol) in CH_2Cl_2 (6 mL) was added $CCl_3C(O)NCO$ (90 μL, 0.75 mmol). After stirring for 15 min, Et_3N (0.48 mL) and MeOH (2 mL) were added, and the reaction temperature was increased to room temperature. After stirring for another 5 hrs, the resulting mixture was 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**)

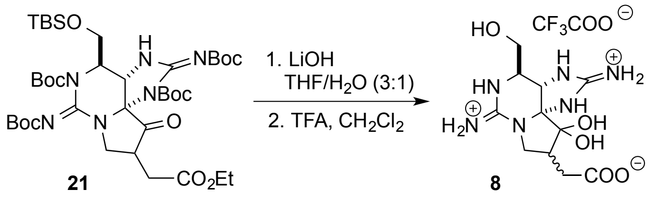


To a solution of **23** (78 mg, 0.10 mmol) in a mixture solvent (THF = 2 mL, H_2O = 0.6 mL) was added LiOH·H_2O (21 mg, 0.51 mmol) at 0 °C. After stirring for 1.5 h, the reaction was quenched with 1.2 *N* HCl aq until the pH reached 1, and the solution was extracted with EtOAc (3 mL) three times. The 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

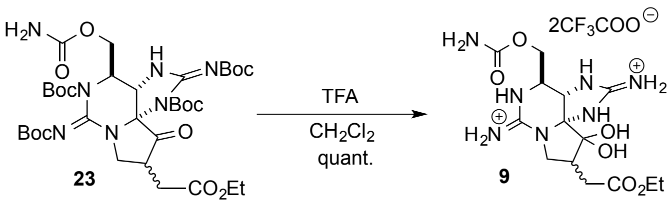


To a solution of **21** (22 mg, 0.0256mmol) in a mixture solvent (THF = 0.6 mL, H_2O = 0.2 mL) was added $LiOH \cdot H_2O$ (6 mg, 0.128 mmol) at 0 °C. After stirring for 2 h, the reaction was quenched with 1.2 *N* HCl aq until the pH reached 1, and the solution was extracted with EtOAc (2 mL) three times. 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.

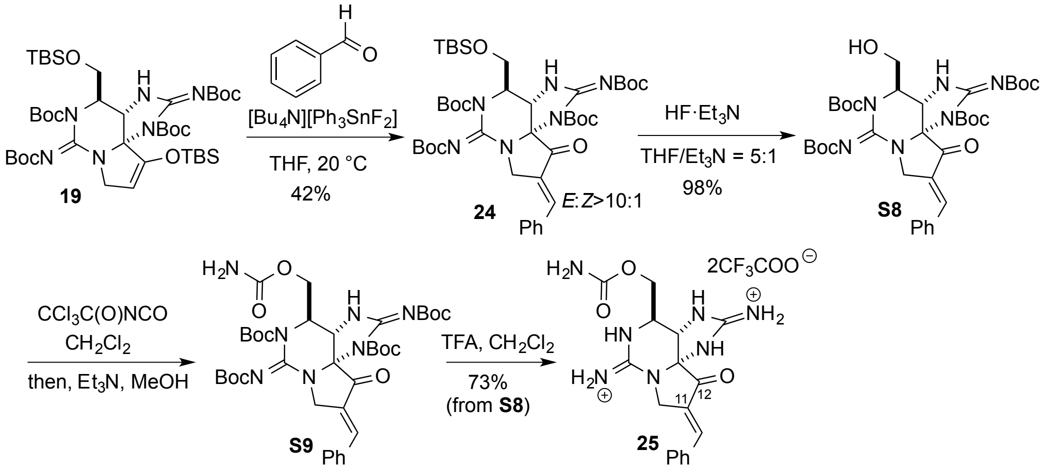
Synthesis of 9



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.).

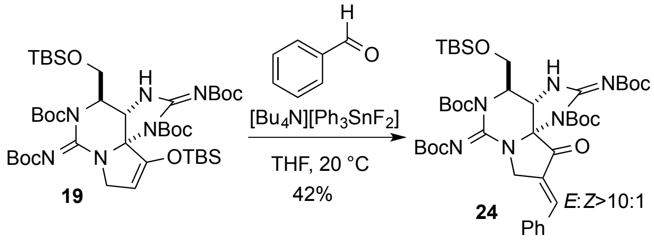
Spectral data for **9**: $[\alpha]^{25}_{D}$ = +49.5 (*c* 0.6 in MeOH); ^{1}H NMR (300 MHz, D_2O, after 12 h in D_2O) δ 4.75 (d, *J* = 1.1Hz, 1H), 4.25 (dd, *J* = 9.6, 11.7 Hz, 1H), 4.17 (dd, *J* = 7.2, 14.4 Hz, 2H), 4.05-3.96 (m, 2H), 3.80 (dd, *J* = 5.2, 10.3 Hz, 1H), 3.25 (d, *J* = 10.3 Hz, 1H), 2.83 (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**

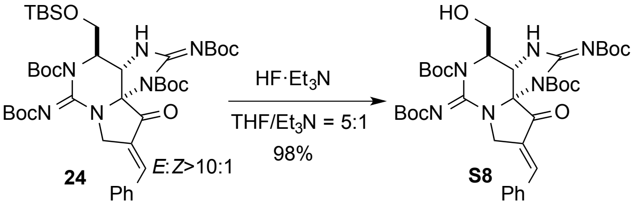
Synthesis of 24



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 $CHCl_3$); ^1H 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.

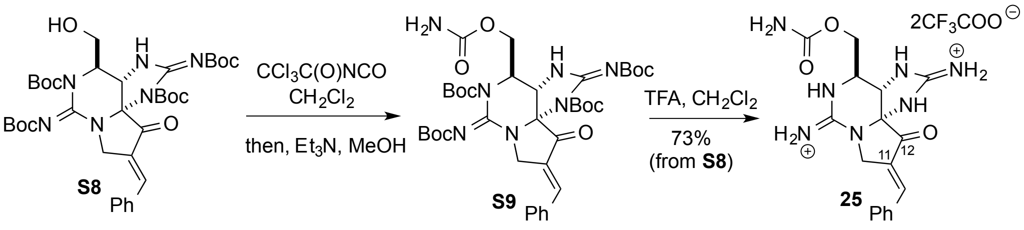
Synthesis of S8



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 $CHCl_3$); ^1H 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.

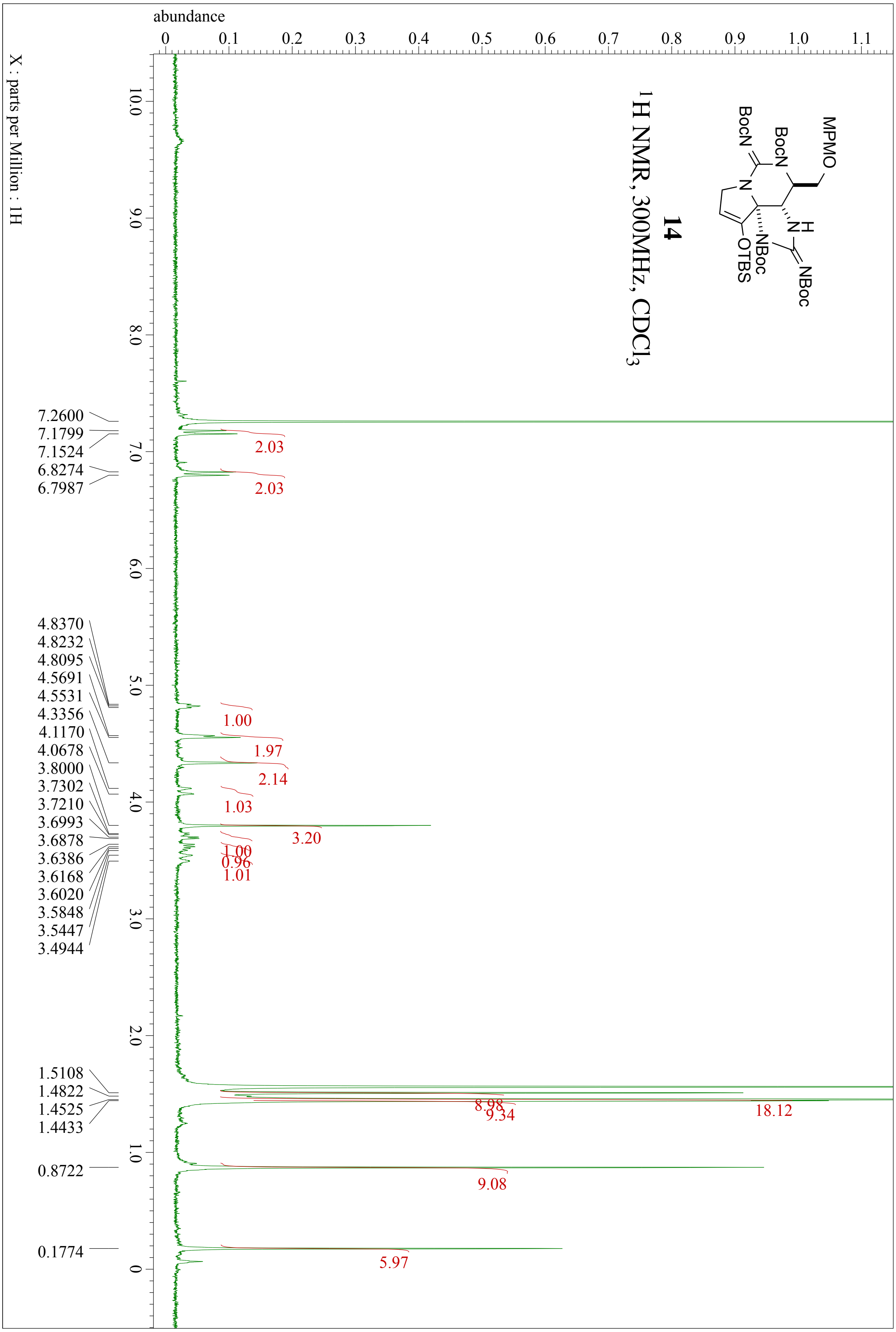
To a solution of **S9** (5.4 mg) in CH_2Cl_2 (0.5 mL) was added TFA (0.25 mL) at room temperature. After stirring for 1 h, the reaction was concentrated *in vacuo*. The residue was dissolved in milli-Q (1 mL), washed with CH_2Cl_2 (5 mL) and filtered through Millex filter unit (Millipore, 0.45 μm). The 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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1.1
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6.0
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2.0
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0
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18.12
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14
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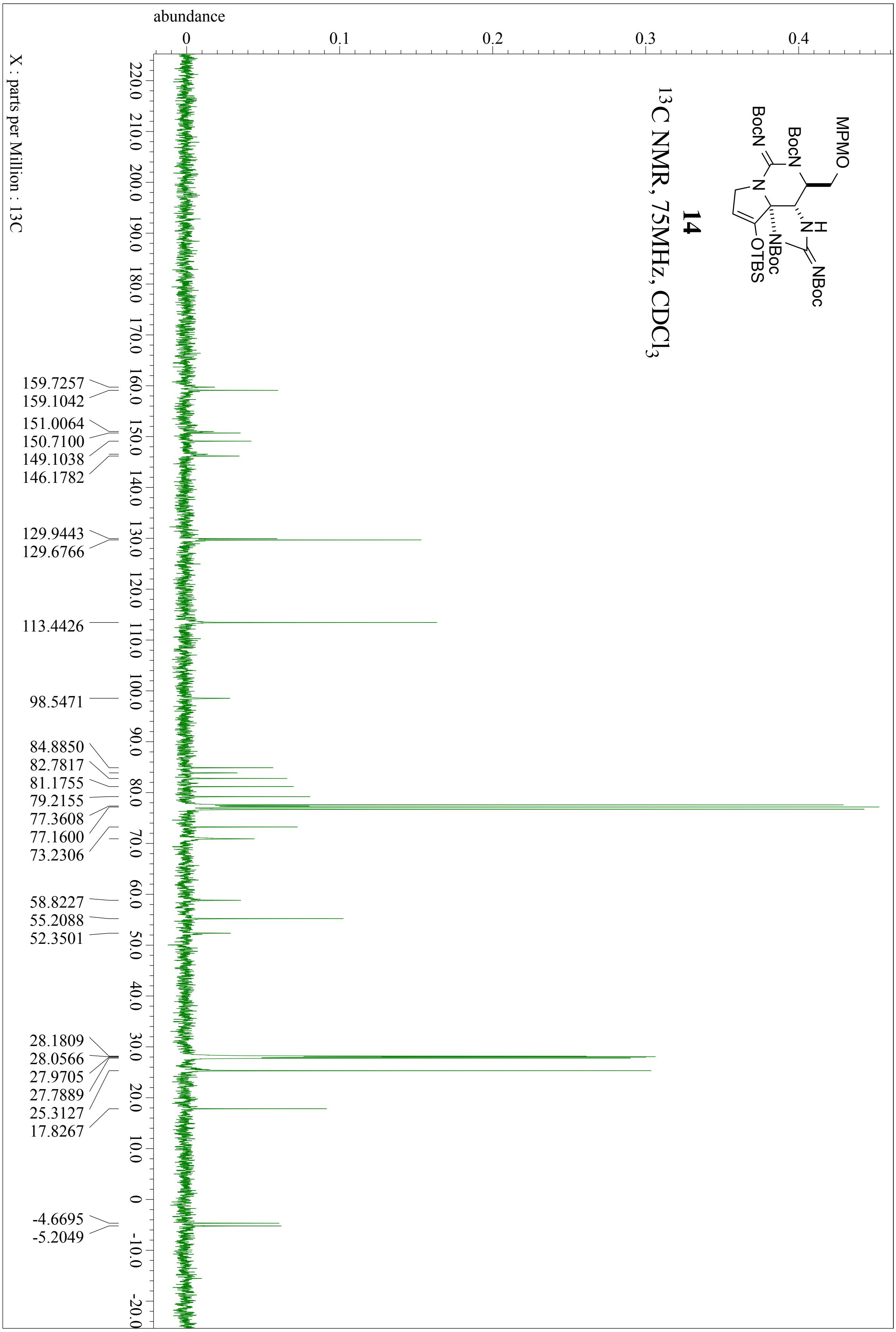
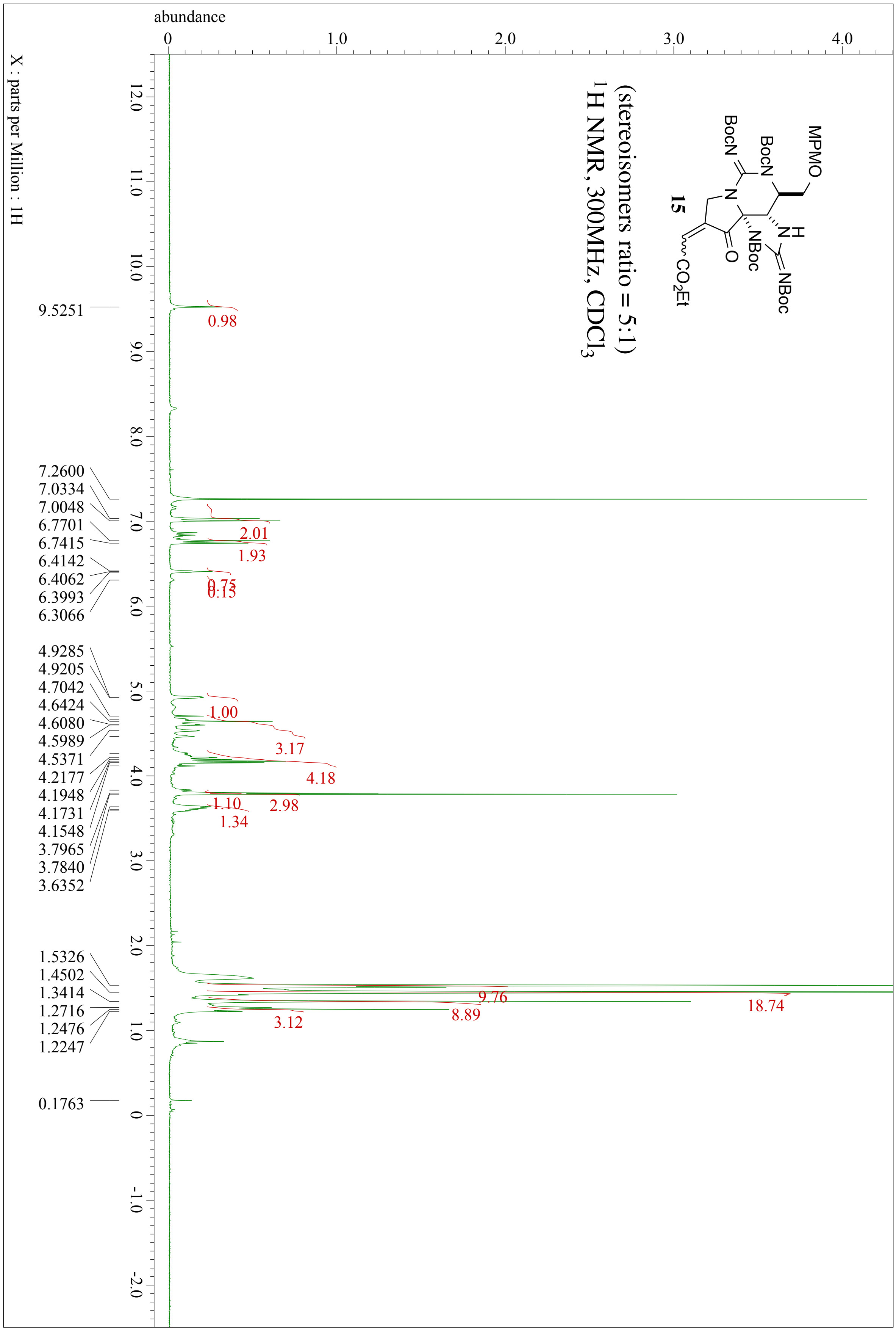


14

^{13}C NMR, 75MHz, $CDCl_3$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7.0
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4.0
3.0
2.0
1.0
0
-1.0
-2.0
MPMO
BocN
BocN
N
H
N
NBoc
NBoc
O
15
CO$_2$Et
(stereoisomers ratio = 5:1)
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6.4062
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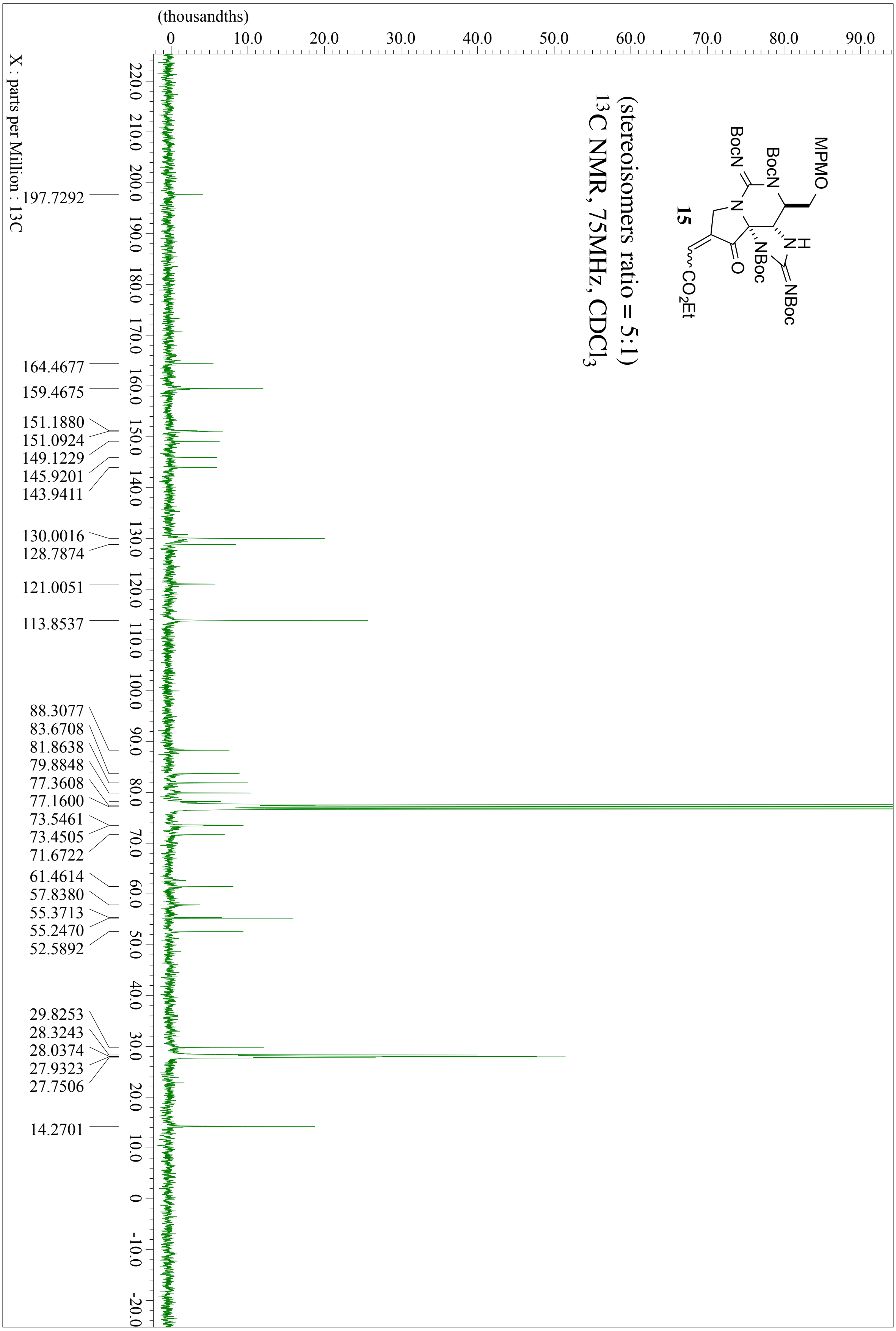
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NBoc
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CO2Et
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90.0
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210.0
200.0
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120.0
110.0
100.0
90.0
80.0
70.0
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30.0
20.0
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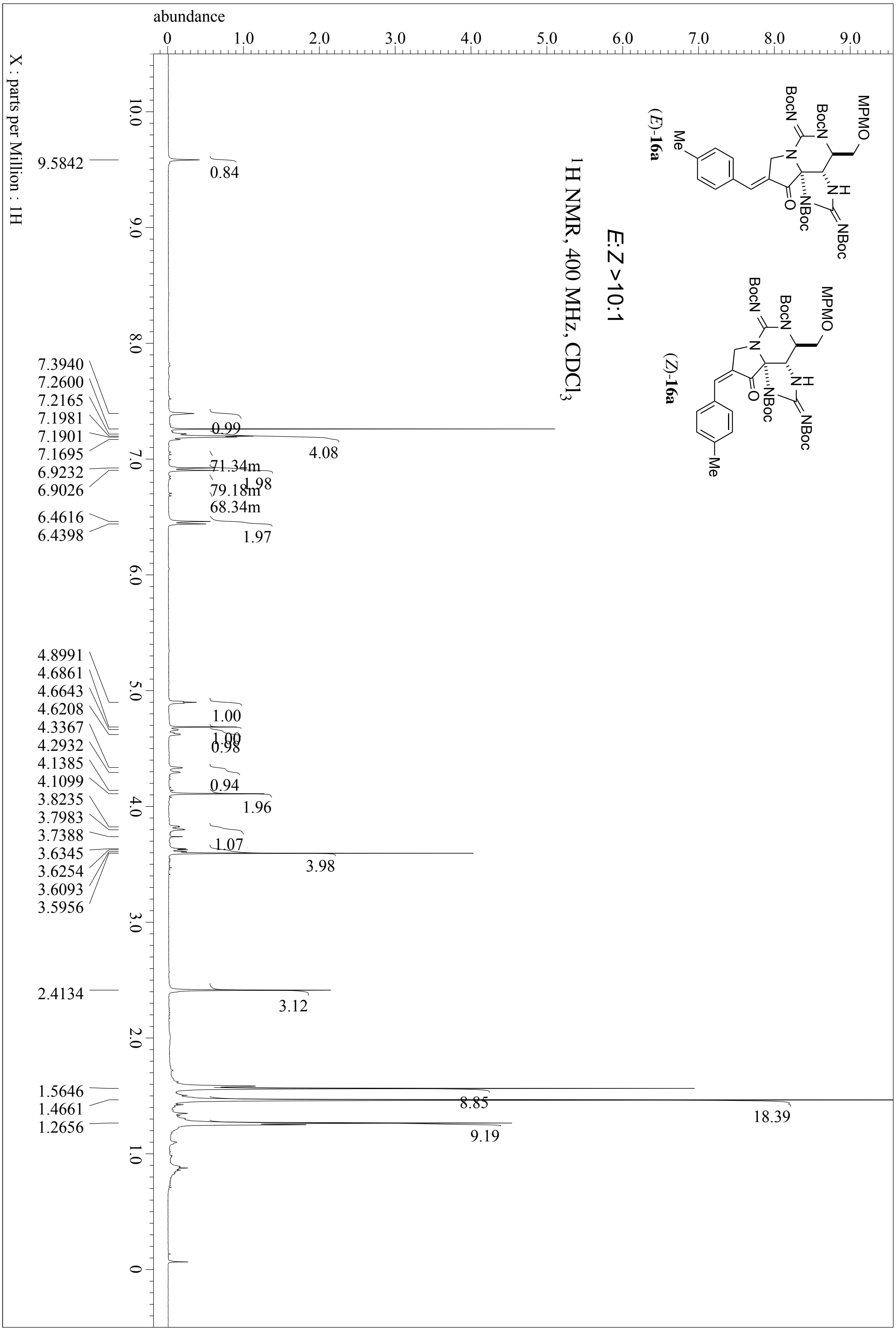
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68.34m
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3.98
3.12
8.85
18.39
9.19
E:Z >10:1
^{1}H NMR, 400 MHz, CDCl$_3$
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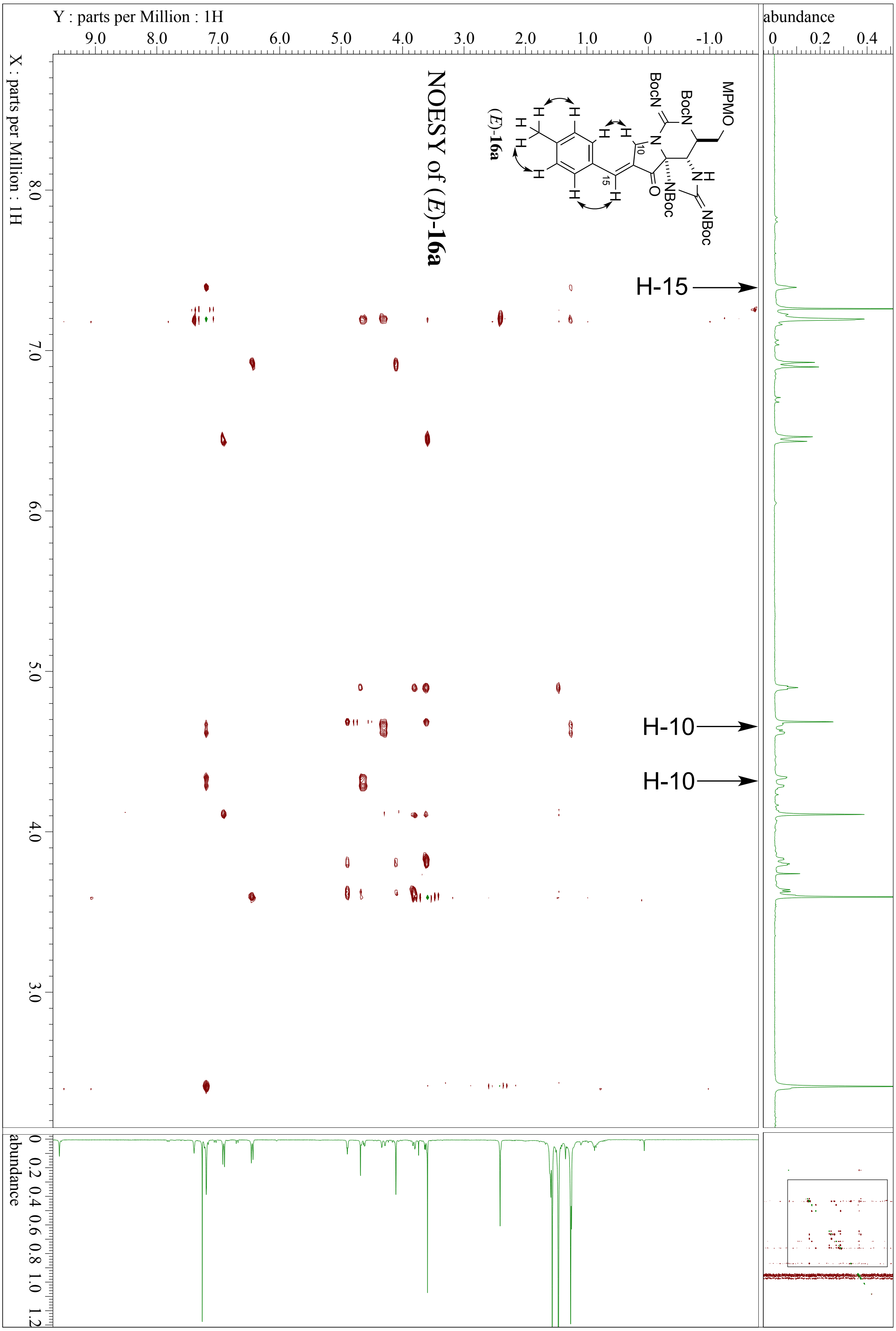
(Z)-16a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O
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H-10
H-10
Y : parts per Million : 1H
X : parts per Million : 1H
abundance
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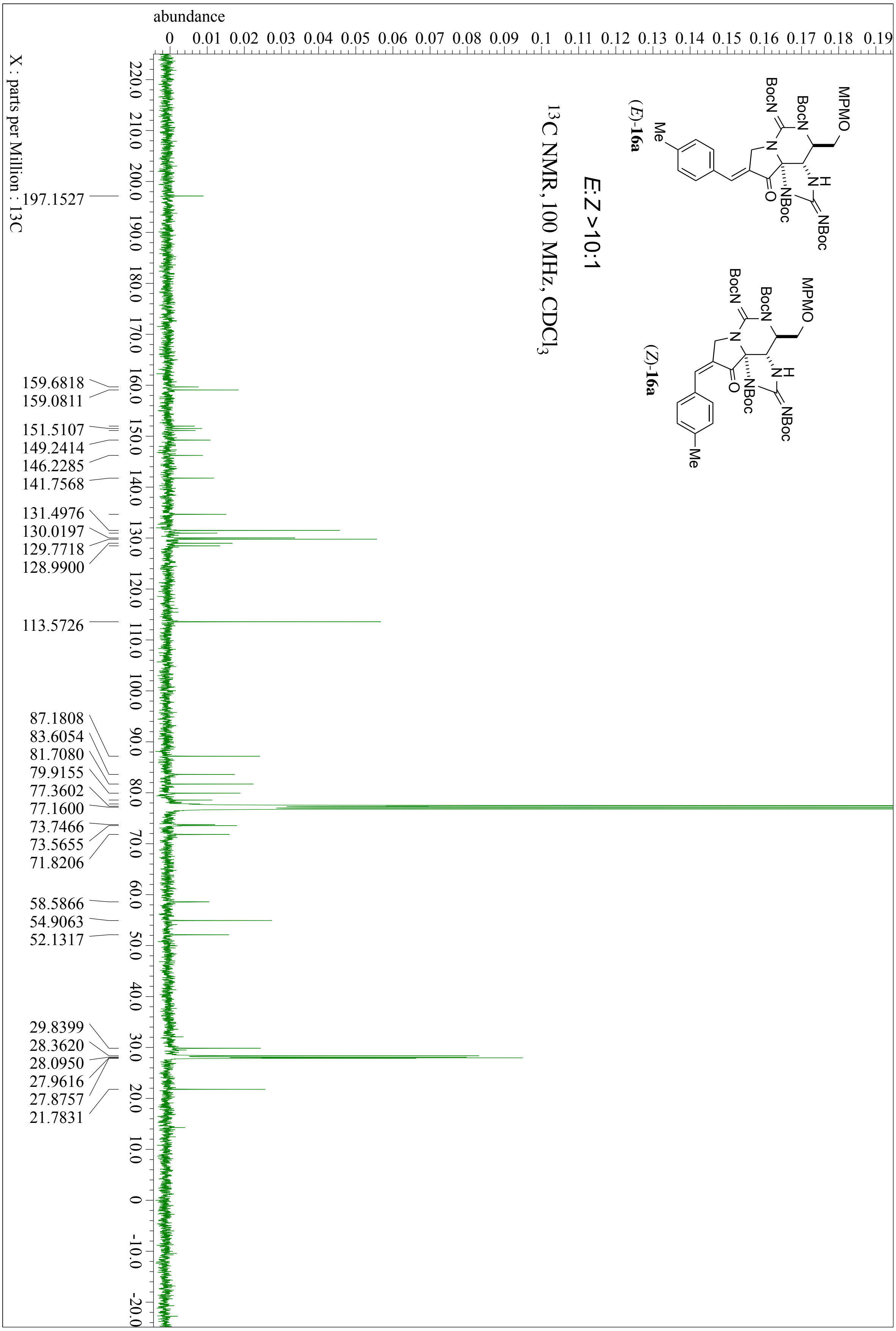
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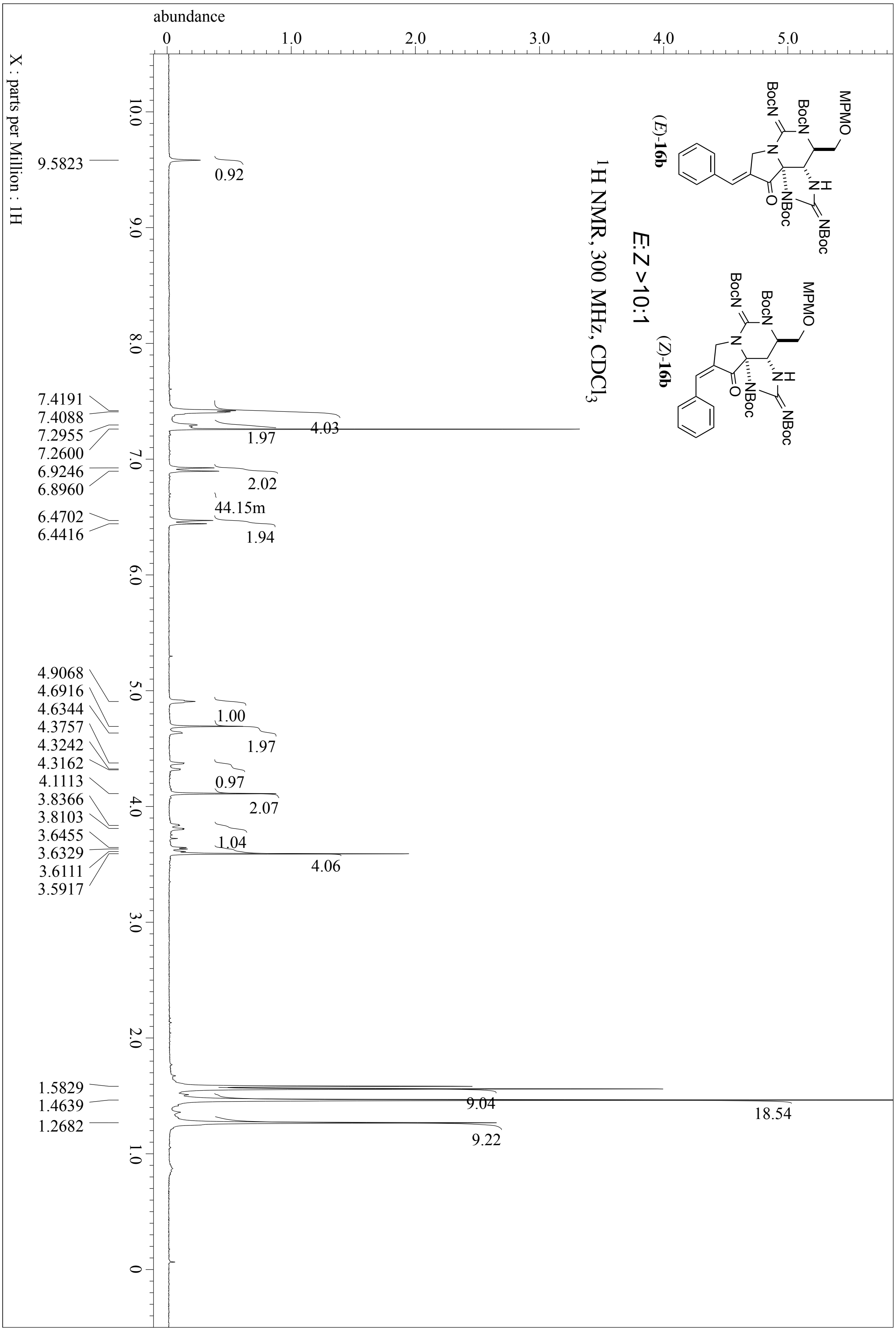
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X : parts per Million : 1H
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NBoc
NBoc
O
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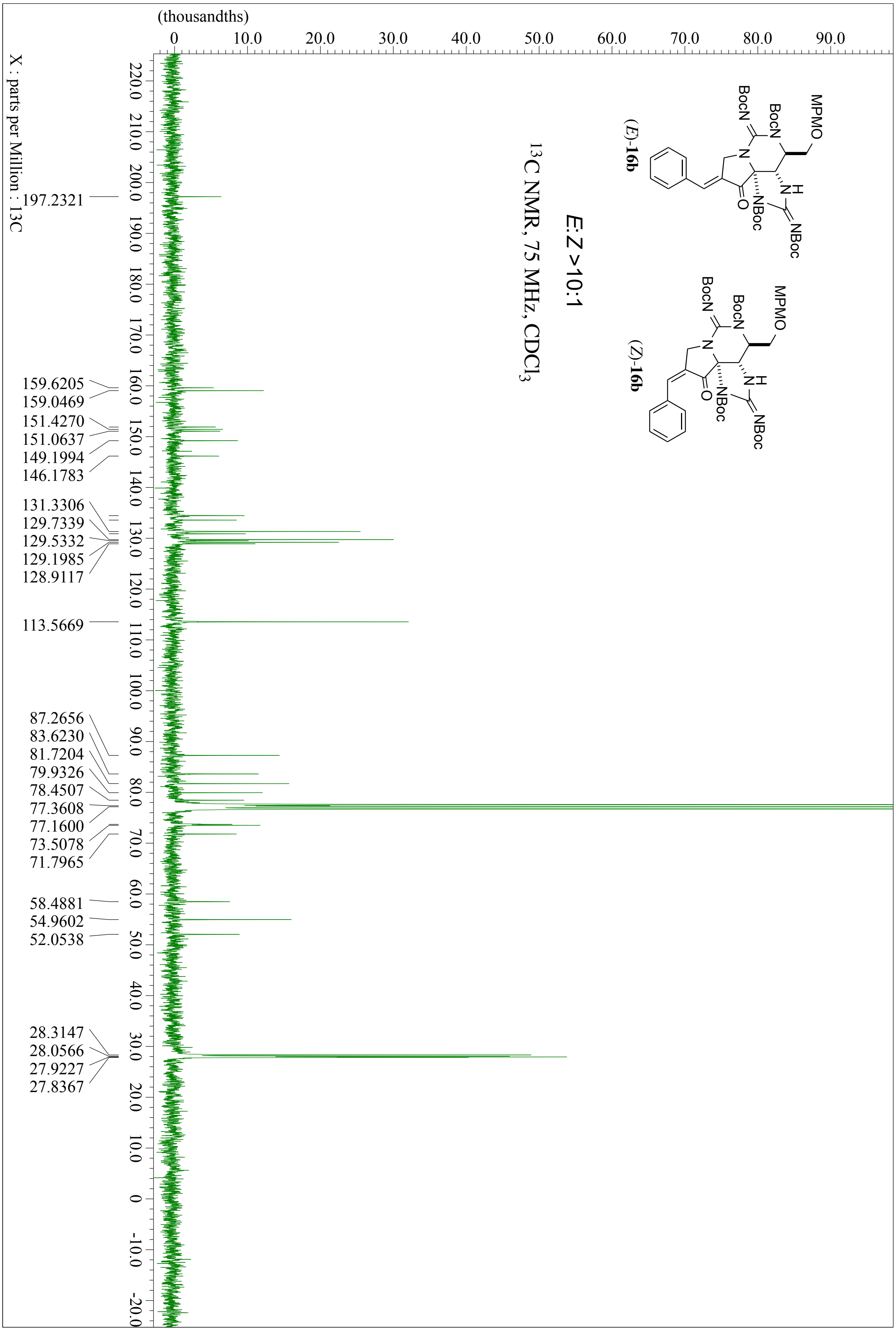
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(thousandths)
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20.0
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40.0
50.0
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80.0
90.0
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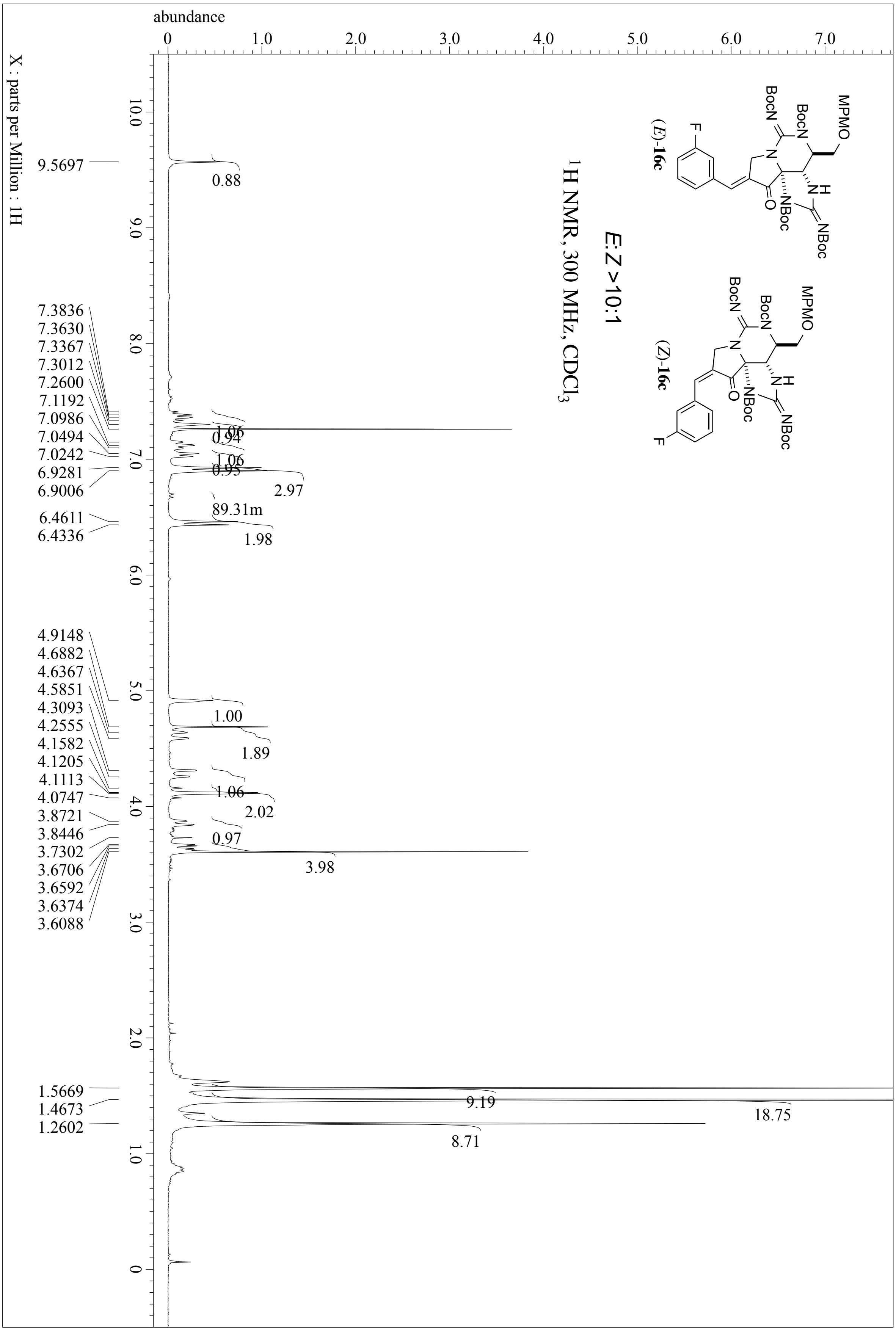

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(*Z*)-**16c**

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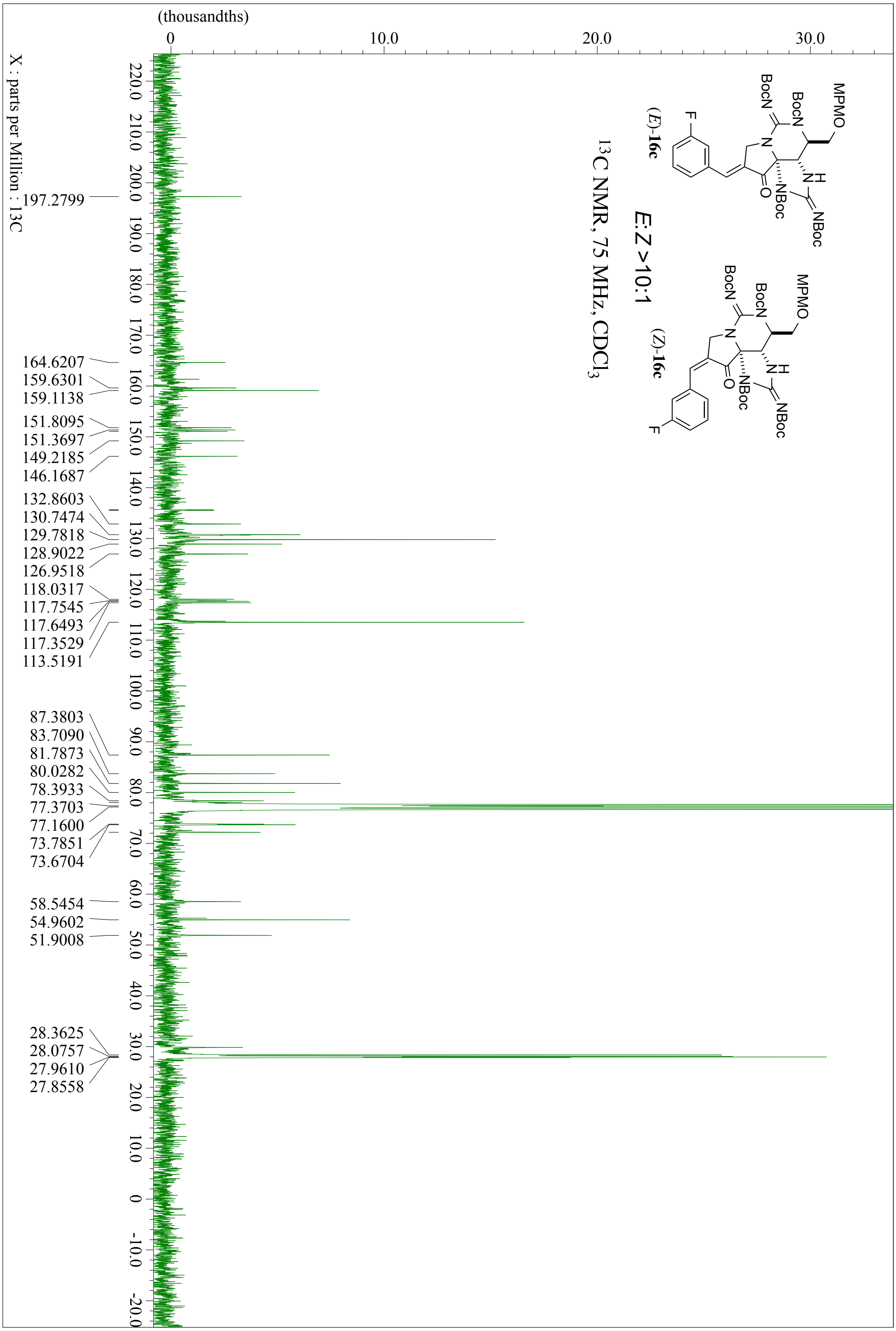
^{1}H NMR, 300 MHz, CDCl$_3$


(thousandths)
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20.0
30.0
X : parts per Million : 13C
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210.0
200.0
190.0
180.0
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140.0
130.0
120.0
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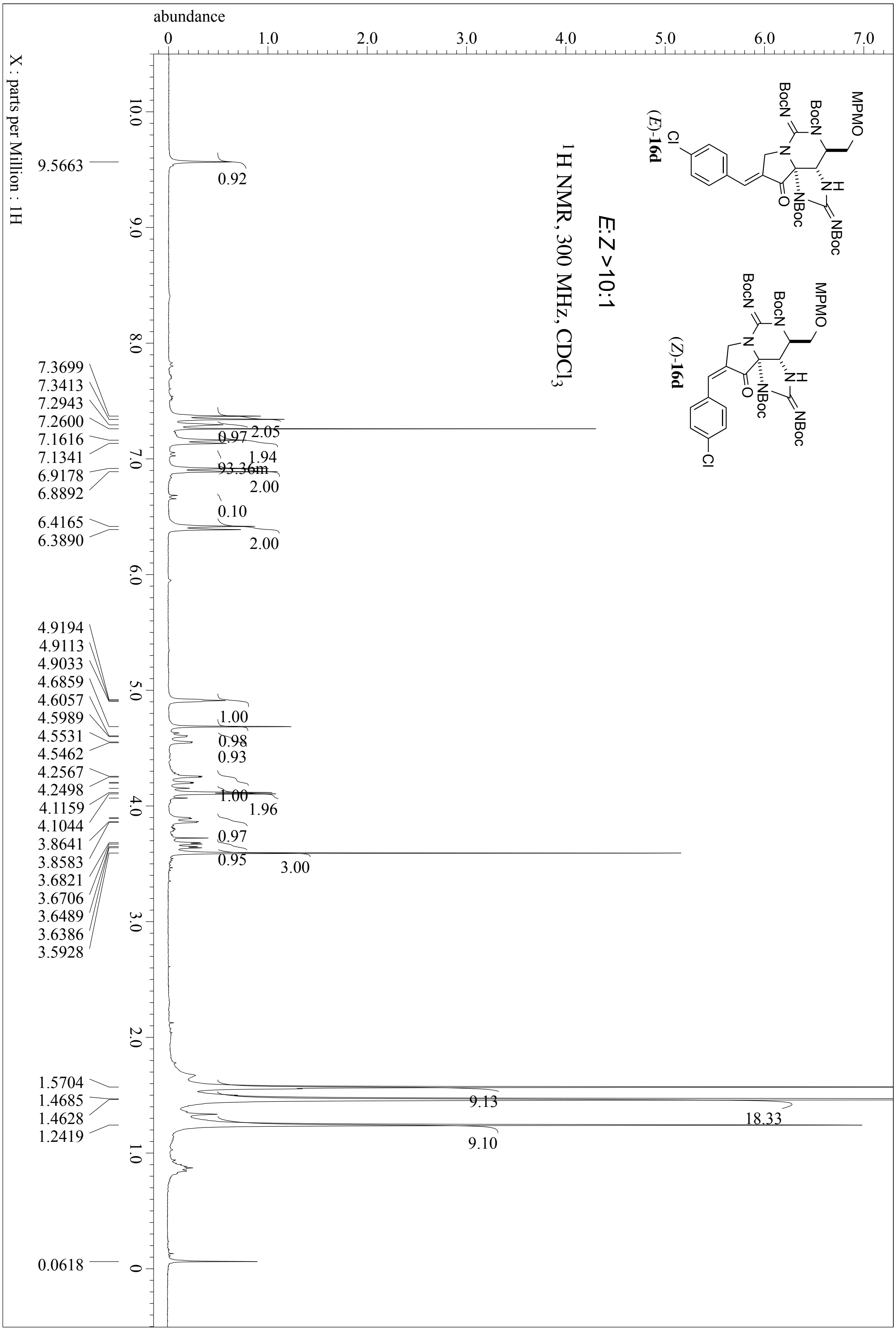
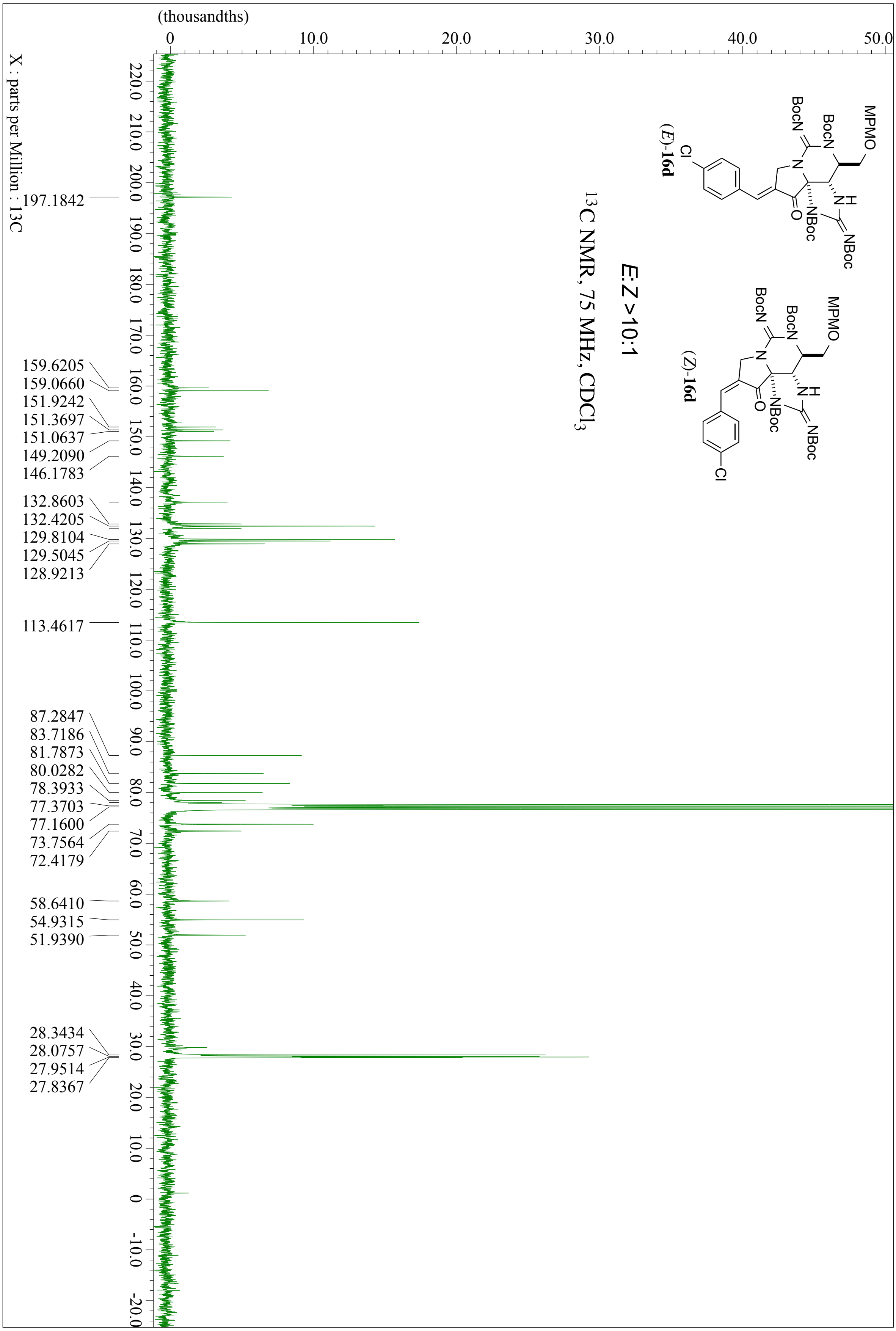
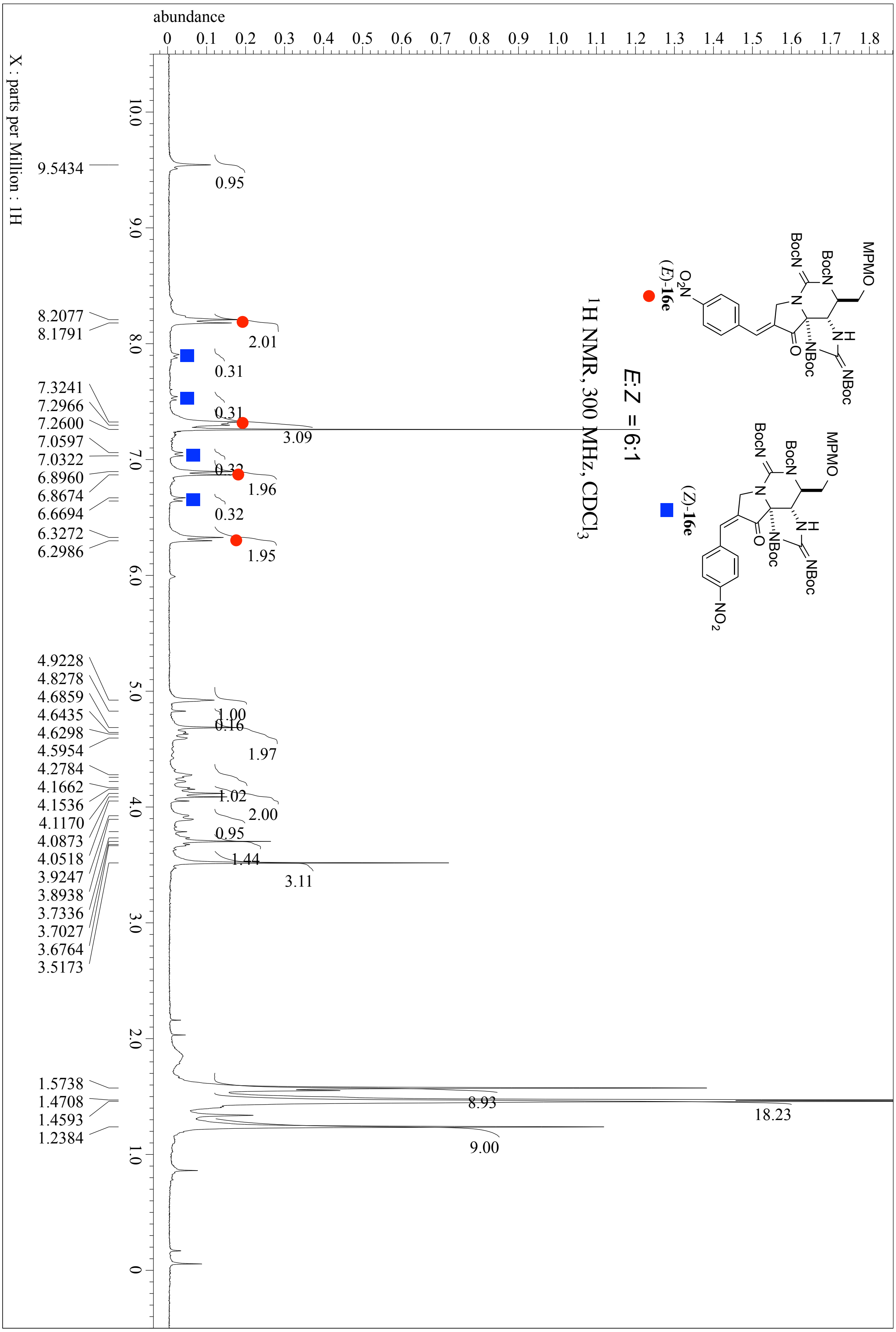
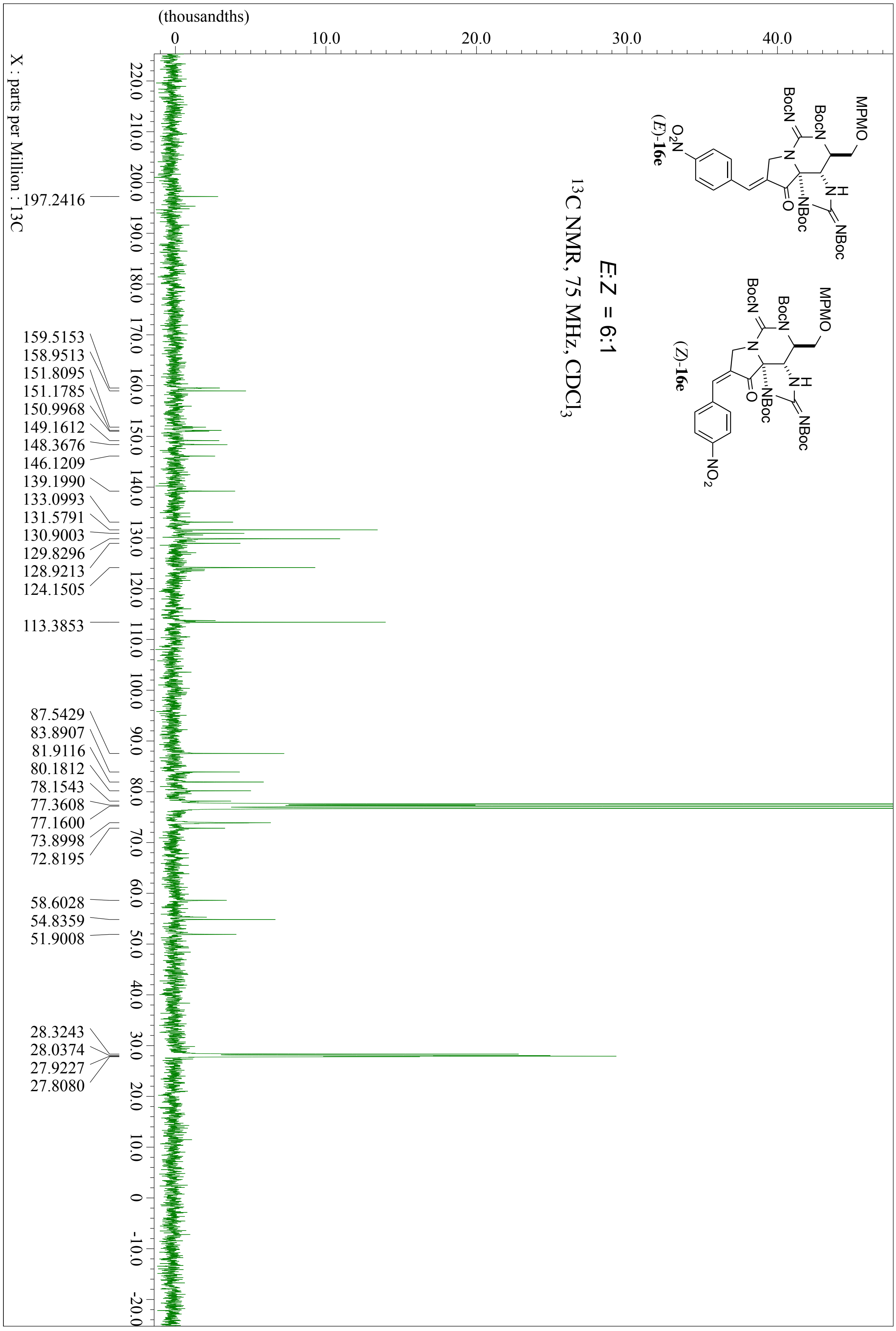
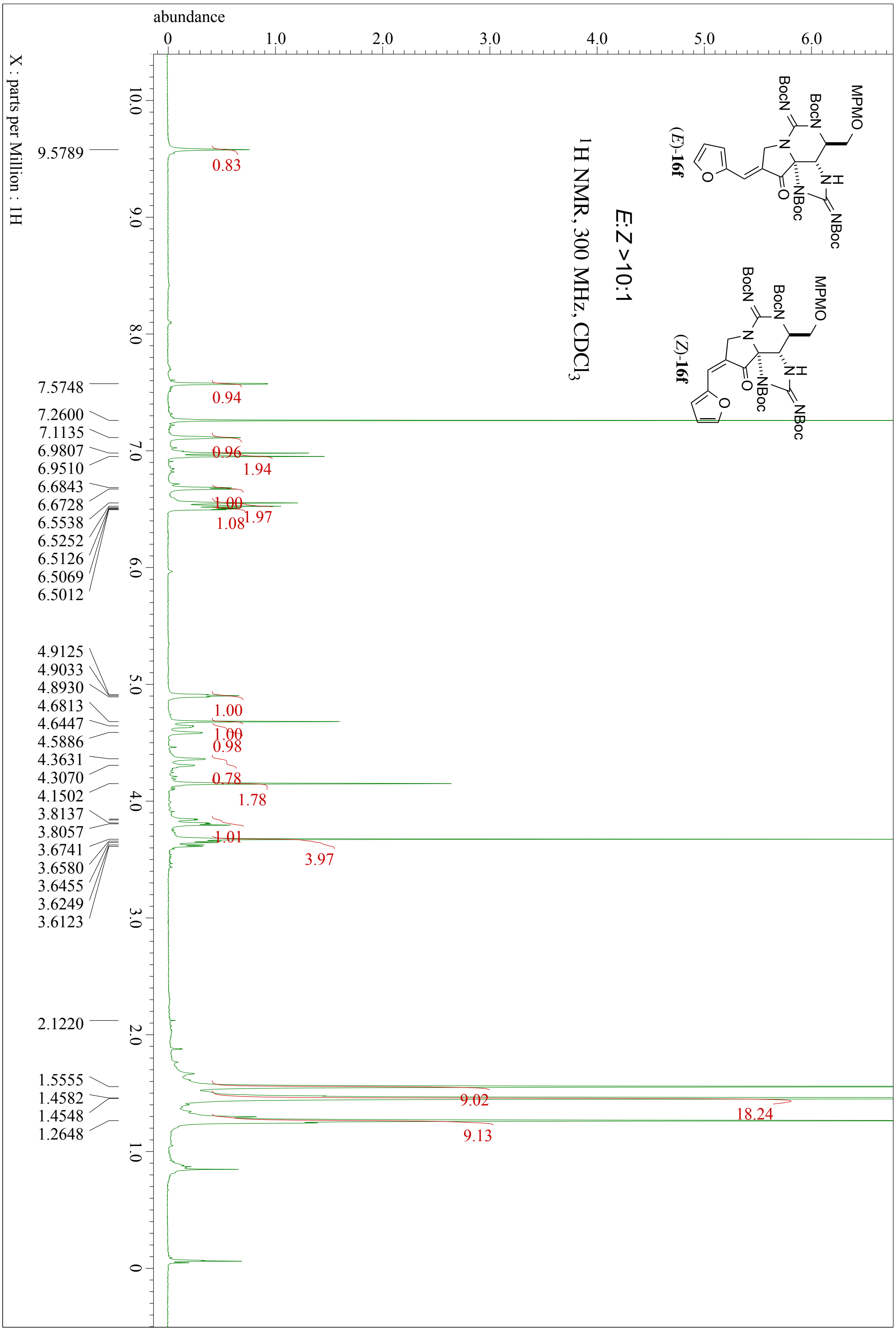
151.3697
149.2185
146.1687
132.8603
130.7474
129.7818
128.9022
126.9518
118.0317
117.7545
117.6493
117.3529
113.5191
87.3803
83.7090
81.7873
80.0282
78.3933
77.3703
77.1600
73.7851
73.6704
58.5454
54.9602
51.9008
28.3625
28.0757
27.9610
27.8558
MPMO
BocN
BocN
N
H
N
NBoc
NBoc
O
F
(E)-16c
(Z)-16c
E:Z >10:1
13C NMR, 75 MHz, CDCl3

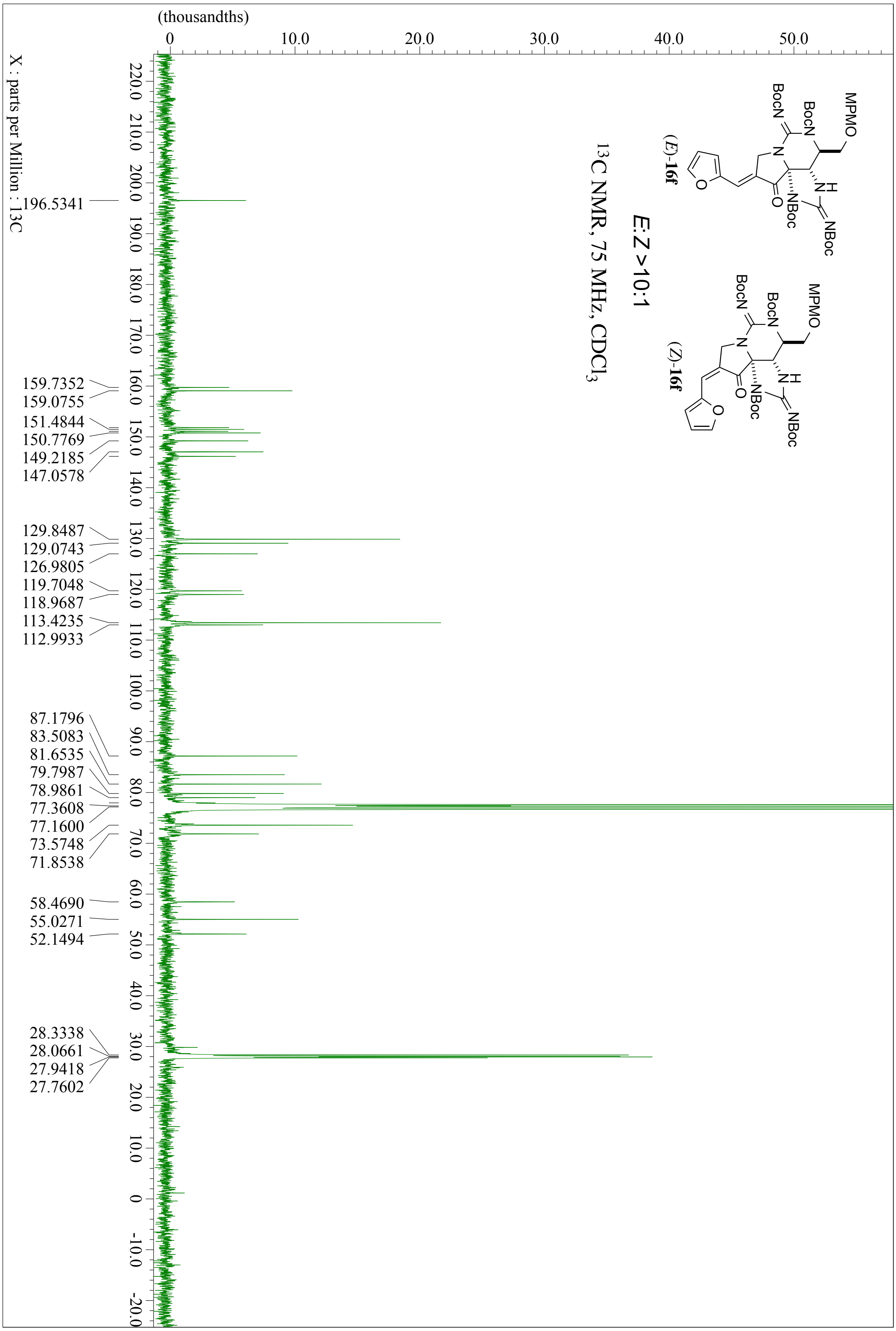

E:Z >10:1
^{1}H NMR, 300 MHz, CDCl$_3$
(E)-16d
(Z)-16d
MPMO
BocN
BocN
N
H
NBoc
NBoc
O
Cl
abundance
X : parts per Million : 1H
9.5663
7.3699
7.3413
7.2943
7.2600
7.1616
7.1341
6.9178
6.8892
6.4165
6.3890
4.9194
4.9113
4.9033
4.6859
4.6057
4.5989
4.5531
4.5462
4.2567
4.2498
4.1159
4.1044
3.8641
3.8583
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

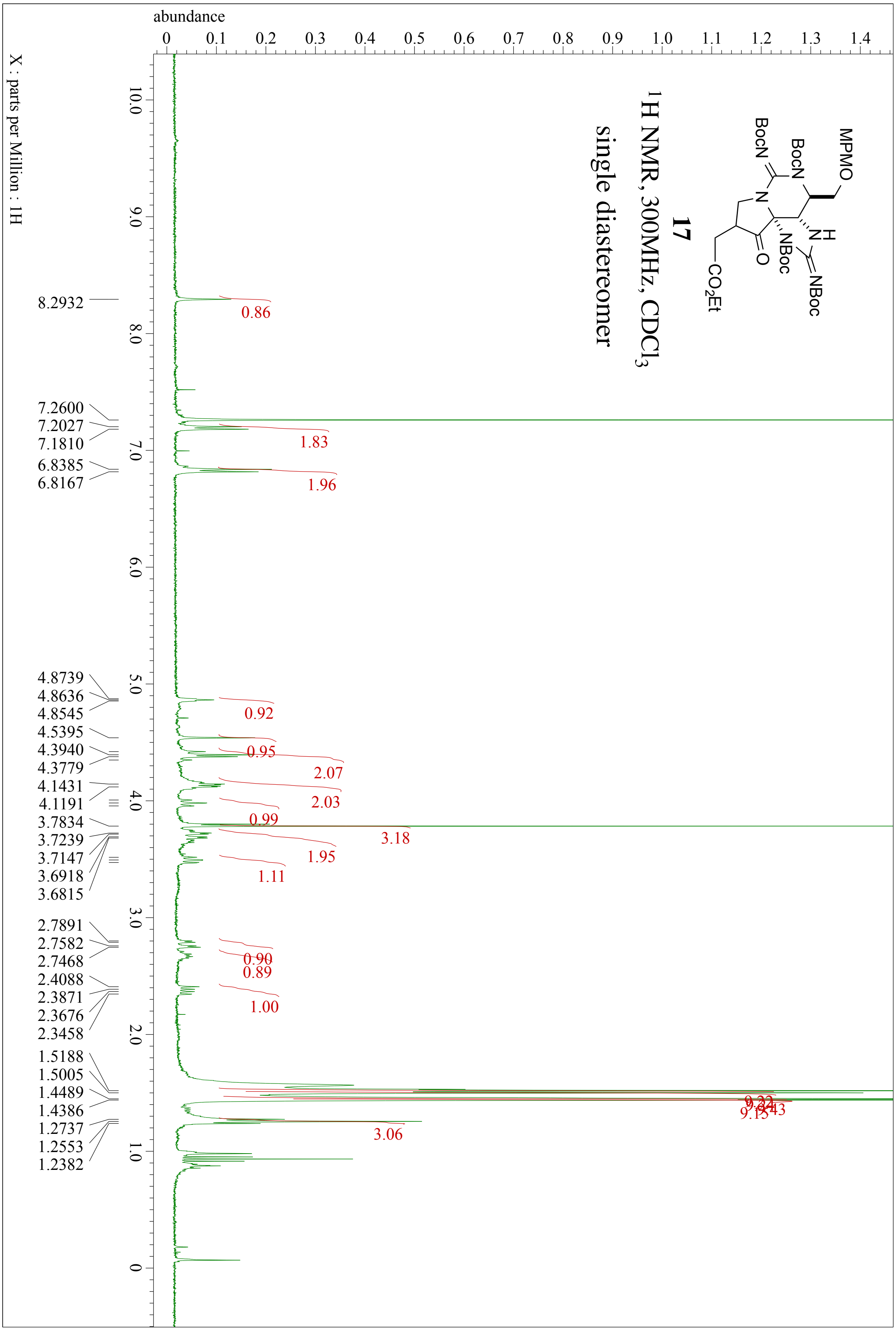

(E)-16d
(Z)-16d
MPMO
BocN
BocN
N
H
N
NBoc
NBoc
O
Cl
E:Z >10:1
^{13}C NMR, 75 MHz, CDCl$_3$
(thousandths)
0
10.0
20.0
30.0
40.0
50.0
X : parts per Million : 13C
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
-10.0
-20.0
197.1842
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

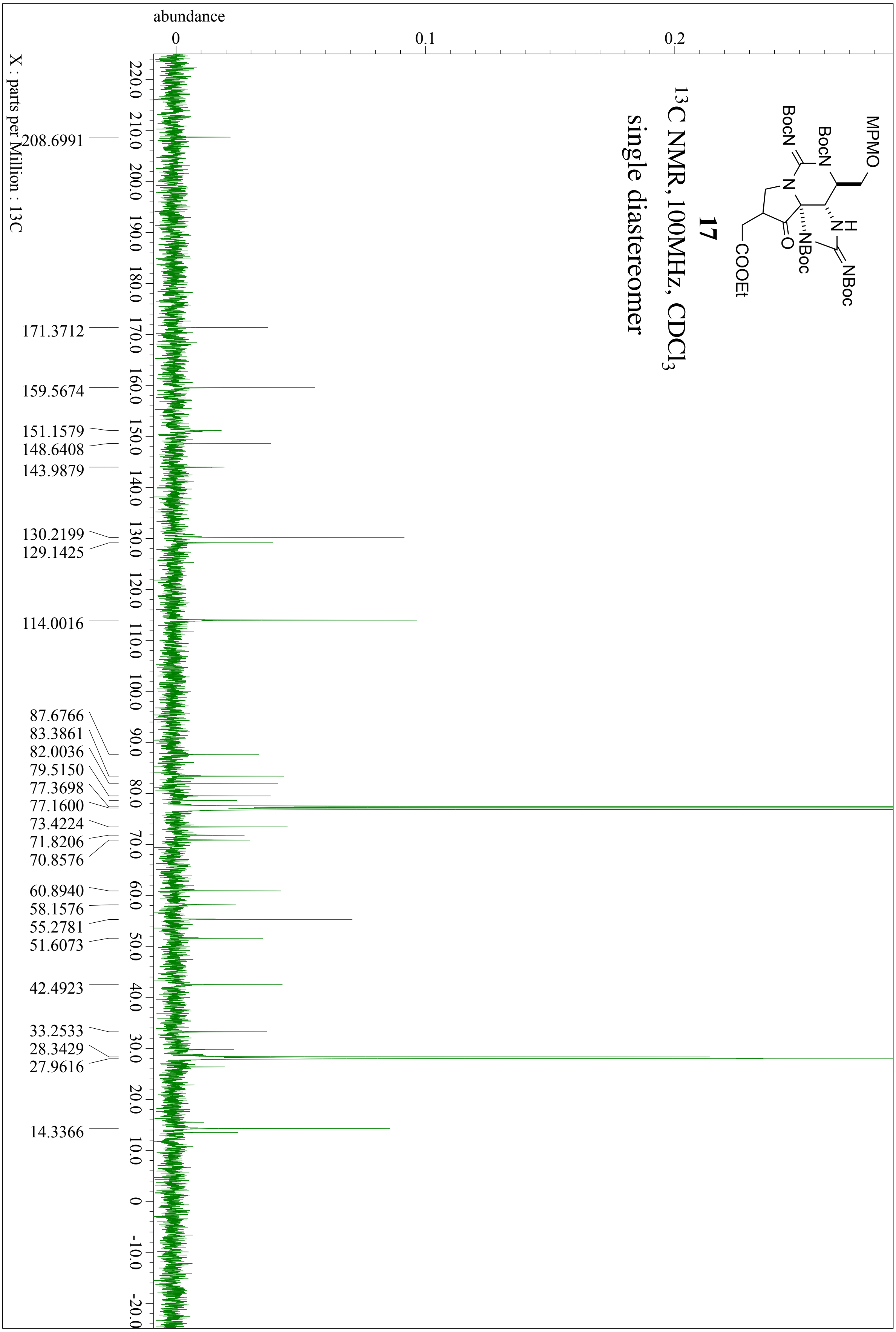

abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
X : parts per Million : 1H
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
9.5434
8.2077
8.1791
7.3241
7.2966
7.2600
7.0597
7.0322
6.8960
6.8674
6.6694
6.3272
6.2986
4.9228
4.8278
4.6859
4.6435
4.6298
4.5954
4.2784
4.1662
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
MPMO
BocN
BocN
N
H
N
NBoc
NBoc
O
O_2N
(*E*)-**16e**
●
MPMO
BocN
BocN
N
H
N
NBoc
NBoc
O
NO_2
(*Z*)-**16e**
■
E:*Z* = 6:1
^{1}H NMR, 300 MHz, $CDCl_3$


(thousandths)
0
10.0
20.0
30.0
40.0
MPMO
BocN
BocN
N
H
N
NBoc
NBoc
O
O_2N
(E)-16e
MPMO
BocN
BocN
N
H
N
NBoc
NBoc
O
(Z)-16e
NO_2
E:Z = 6:1
^{13}C NMR, 75 MHz, $CDCl_3$
X : parts per Million : 13C
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
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)-16f
(Z)-16f
MPMO
BocN
BocN
N
H
NBoc
NBoc
O
E:Z >10:1
^{1}H NMR, 300 MHz, CDCl$_3$
abundance
0
1.0
2.0
3.0
4.0
5.0
6.0
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
9.5789
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
1.08
1.97
1.00
1.00
0.98
0.78
1.78
1.01
3.97
9.02
18.24
9.13


(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
MPMO
BocN
BocN
N
H
N
NBoc
NBoc
O
O
(E)-16f
(Z)-16f
E:Z >10:1
13C NMR, 75 MHz, CDCl3

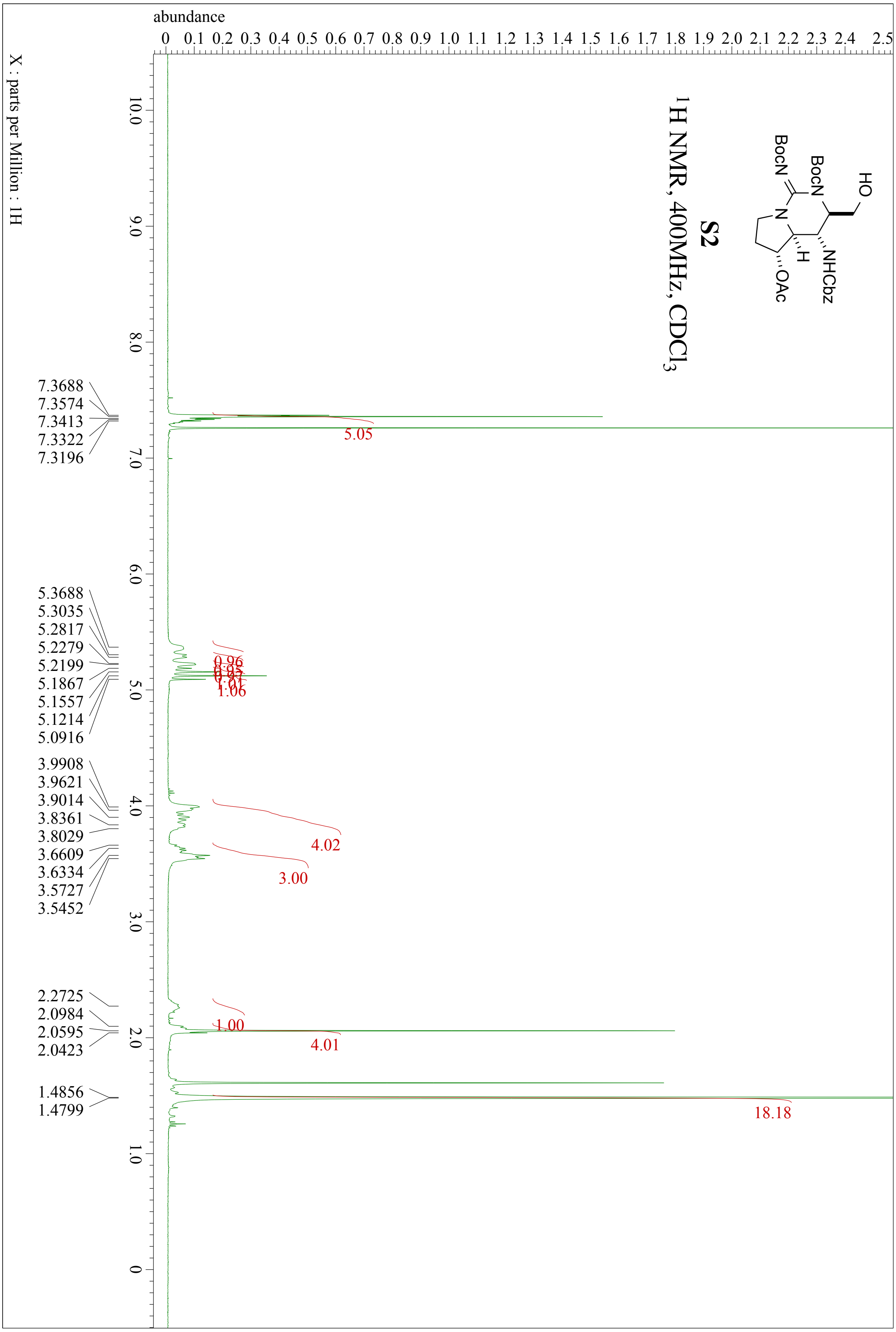

abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
X : parts per Million : 1H
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
MPMO
BocN
BocN
N
H
N
NBoc
NBoc
O
CO2Et
17
1H NMR, 300MHz, CDCl3
single diastereomer
8.2932
7.2600
7.2027
7.1810
6.8385
6.8167
4.8739
4.8636
4.8545
4.5395
4.3940
4.3779
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
9.22
9.43
9.15
3.06

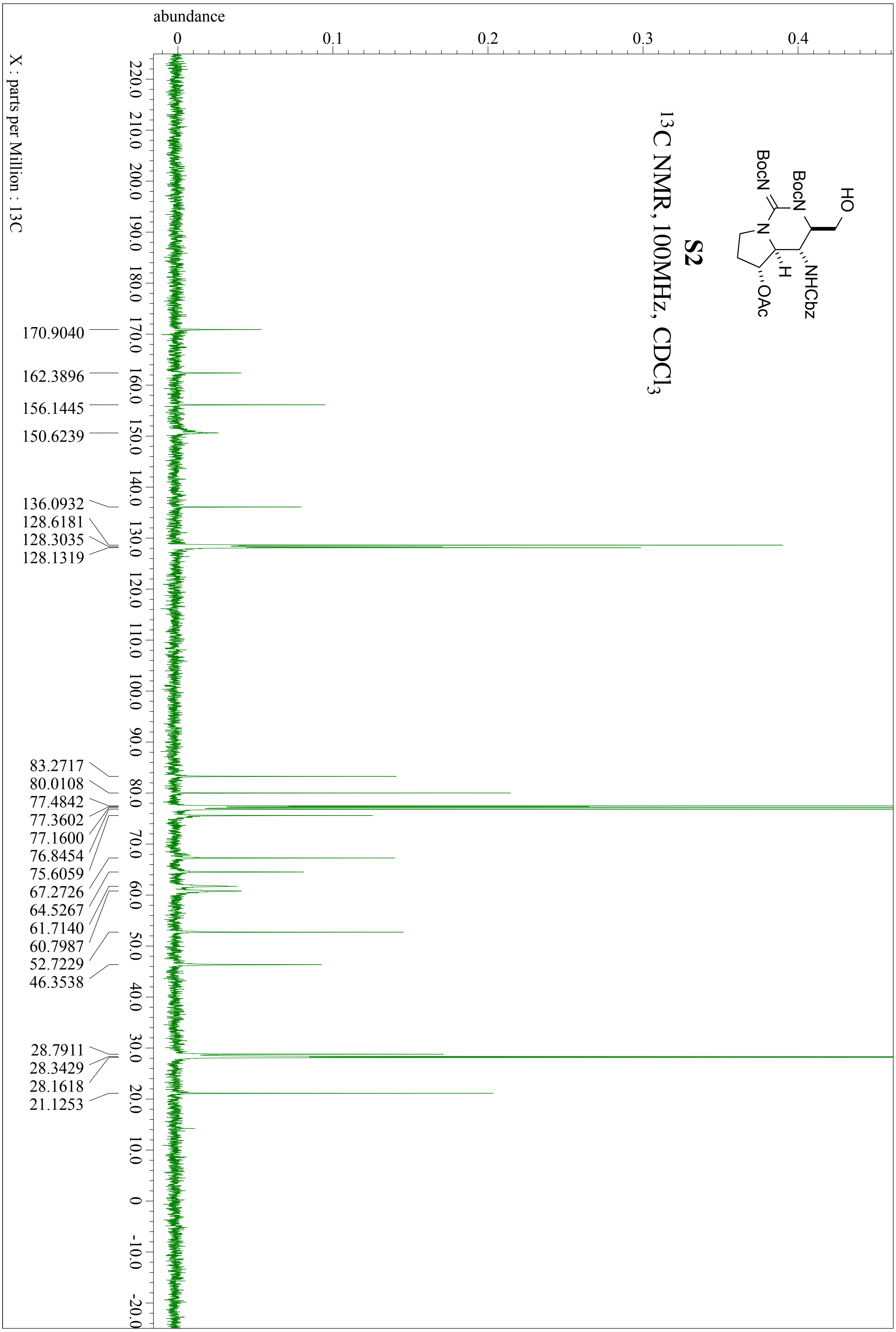


17

^{13}C NMR, 100MHz, $CDCl_3$

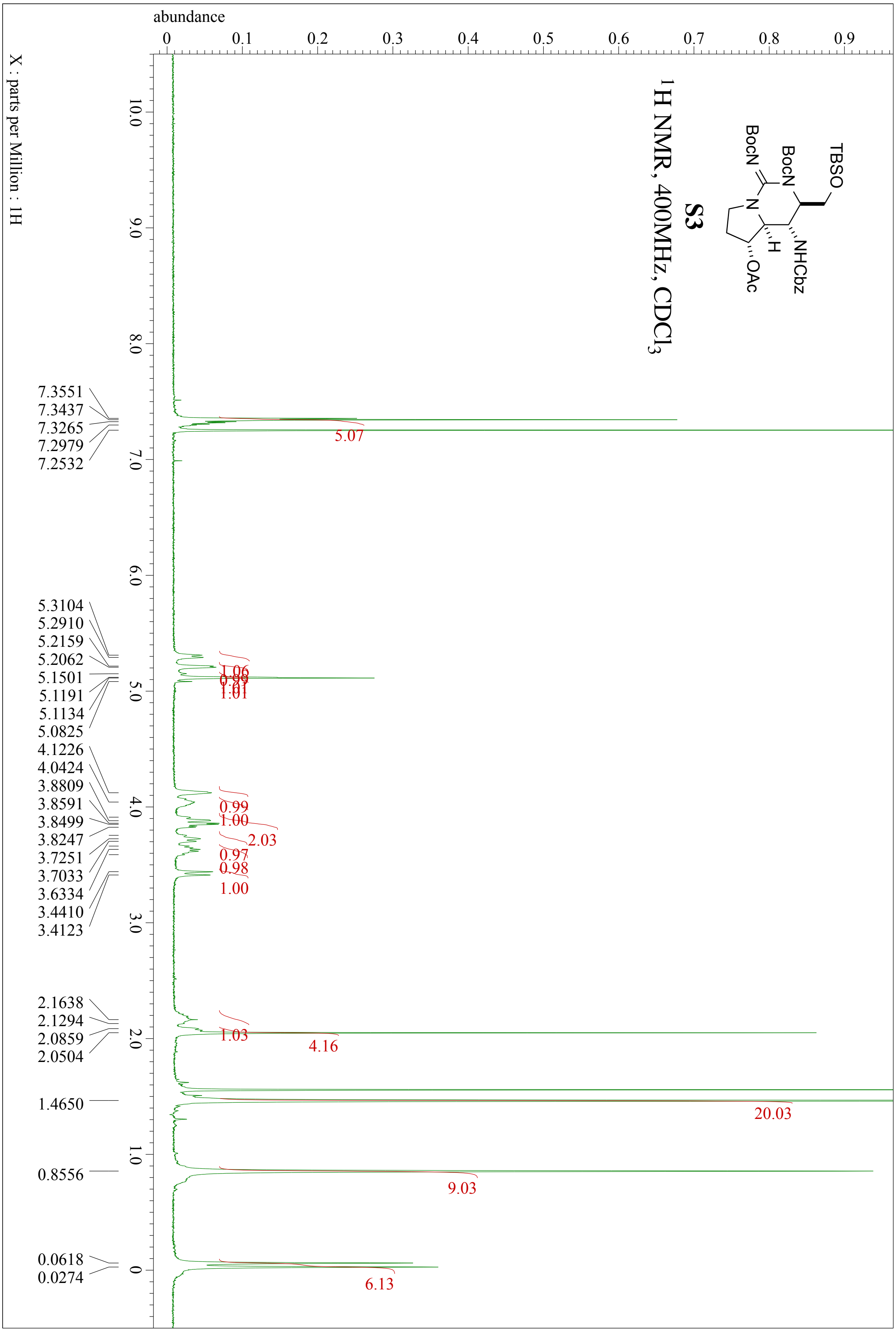
single diastereomer

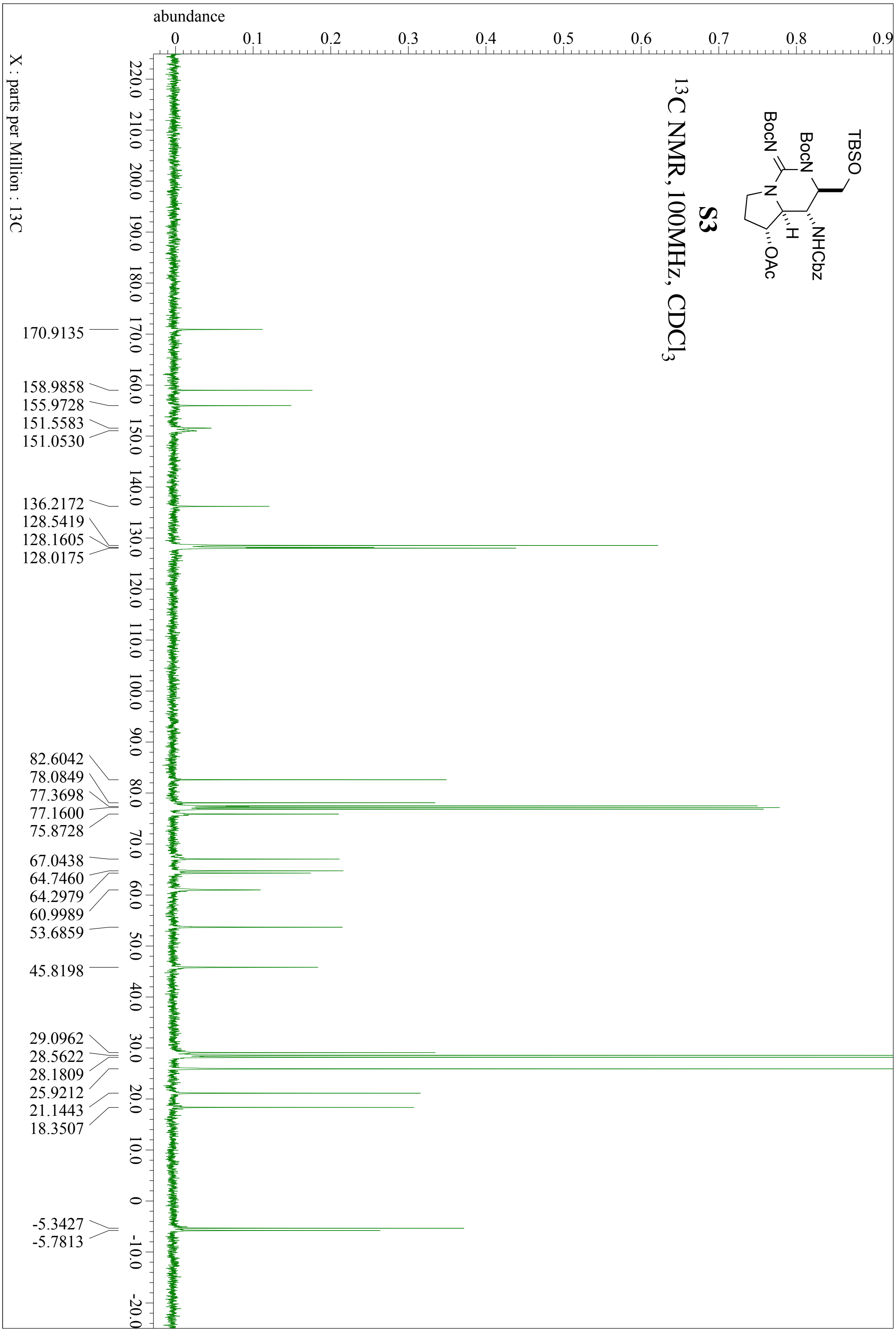

S2
¹H NMR, 400MHz, CDCl₃
HO
BocN
NHCbz
BocN
N
H
OAc
abundance
0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8 1.9 2.0 2.1 2.2 2.3 2.4 2.5
X : parts per Million : 1H
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0
7.3688
7.3574
7.3413
7.3322
7.3196
5.3688
5.3035
5.2817
5.2279
5.2199
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
0.96
0.95
0.97
1.01
1.06
4.02
3.00
1.00
4.01
18.18

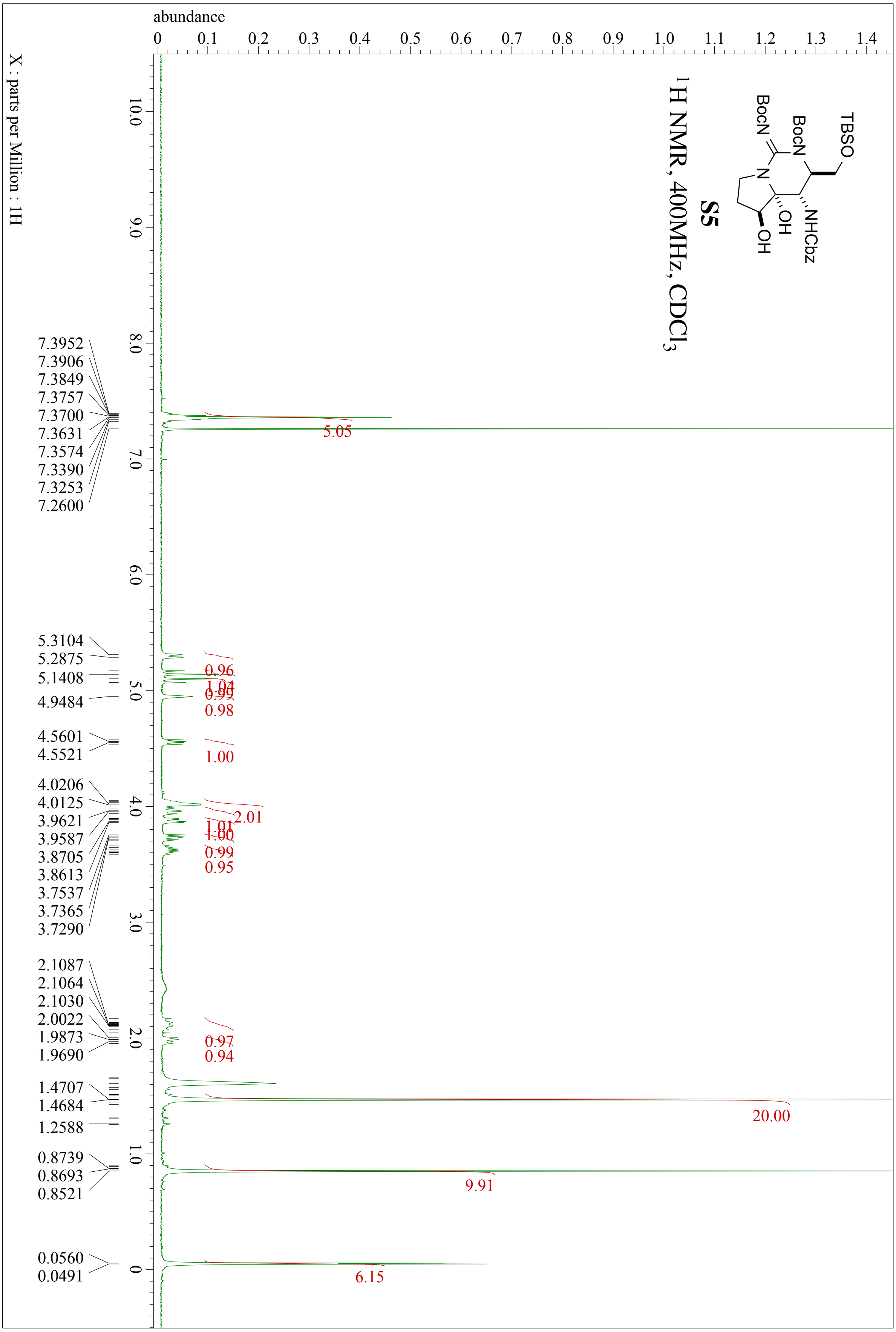


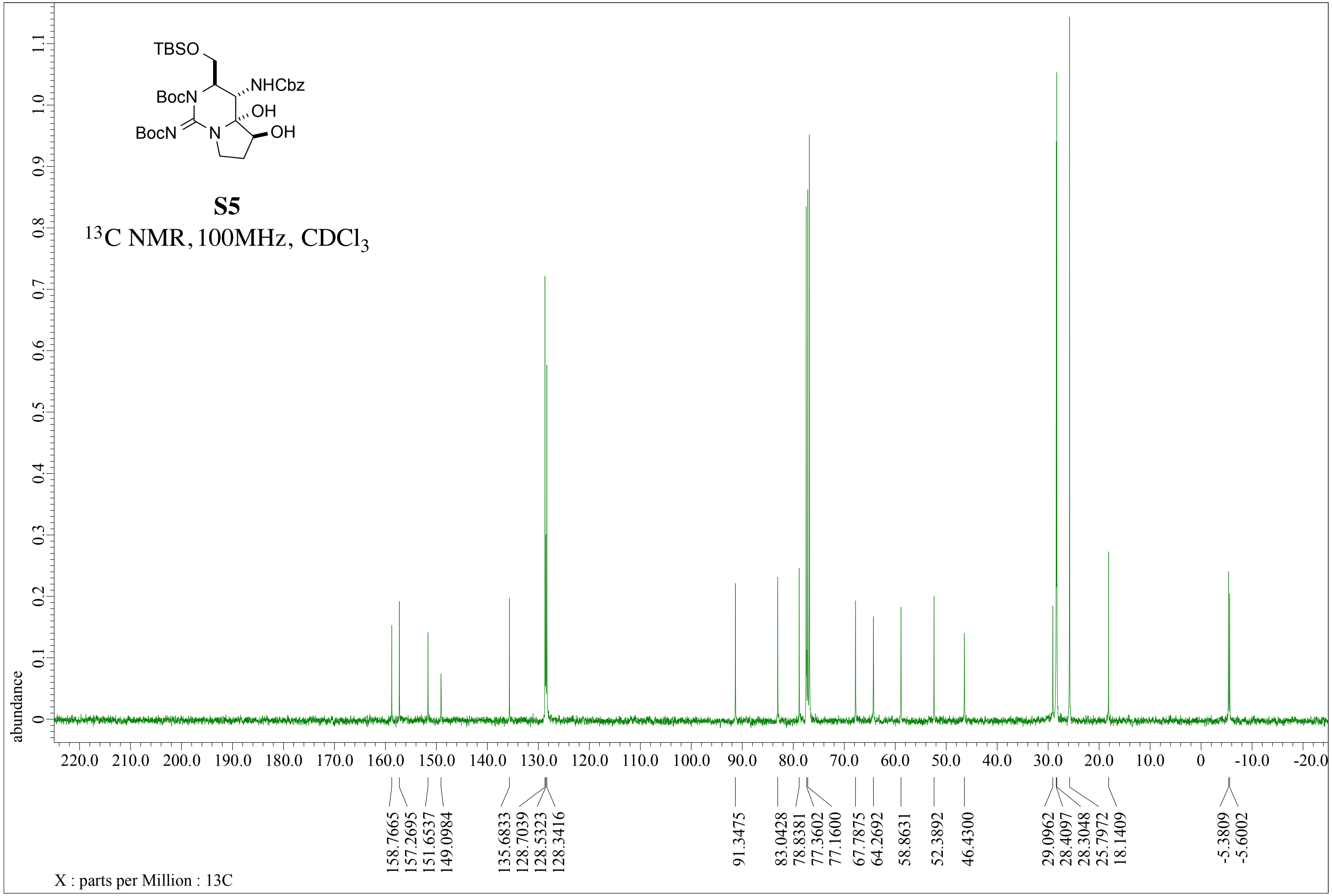
S2

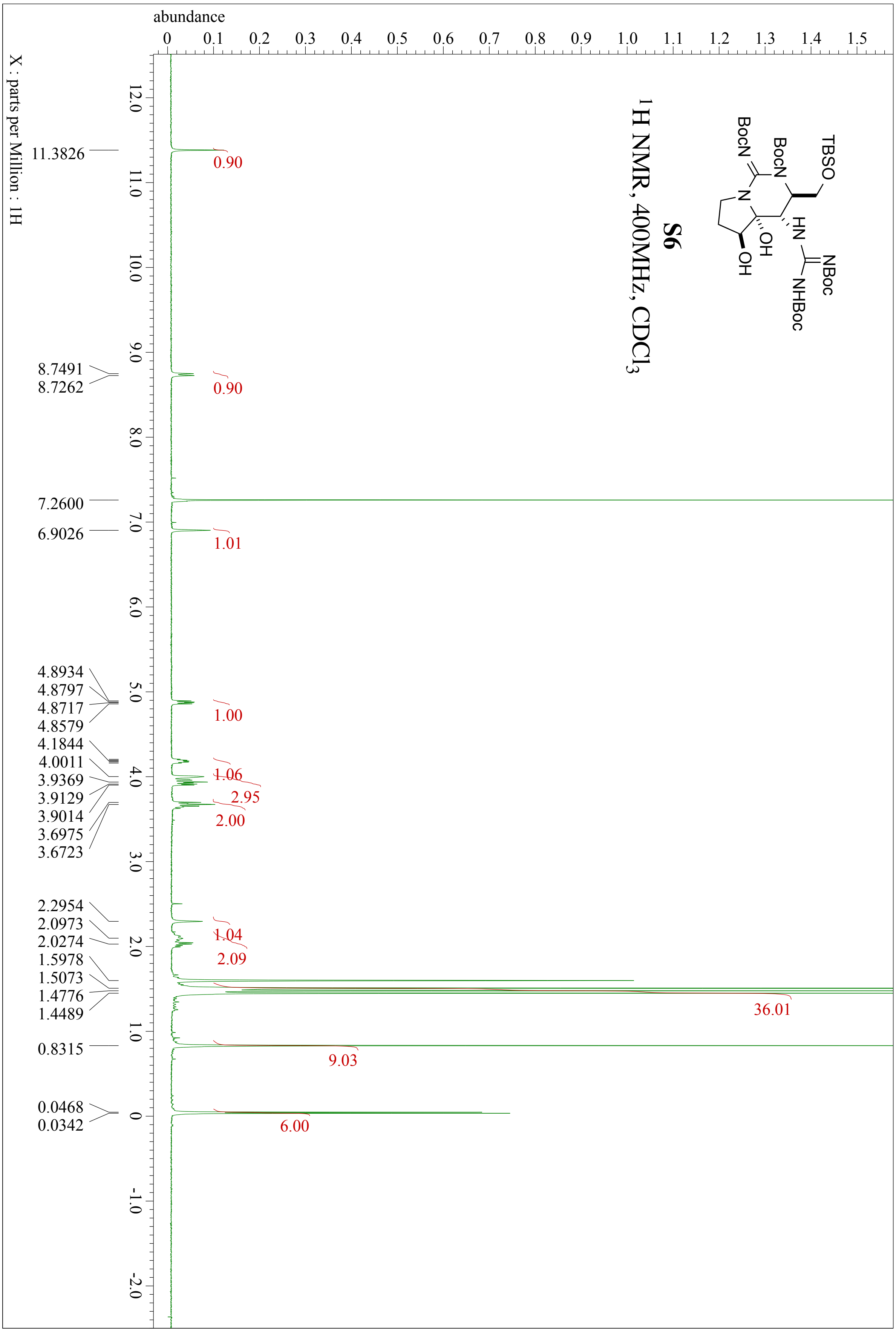
^{13}C NMR, 100MHz, CDCl$_3$


abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
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
TBSO
BocN
BocN
N
NHCbz
H
OAc
S3
^{1}H NMR, 400MHz, CDCl$_3$
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
0.99
1.01
0.99
1.00
2.03
0.97
0.98
1.00
1.03
4.16
20.03
9.03
6.13


TBSO
BocN
NHCbz
BocN
N
H
OAc
S3
^{13}C NMR, 100MHz, $CDCl_3$
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

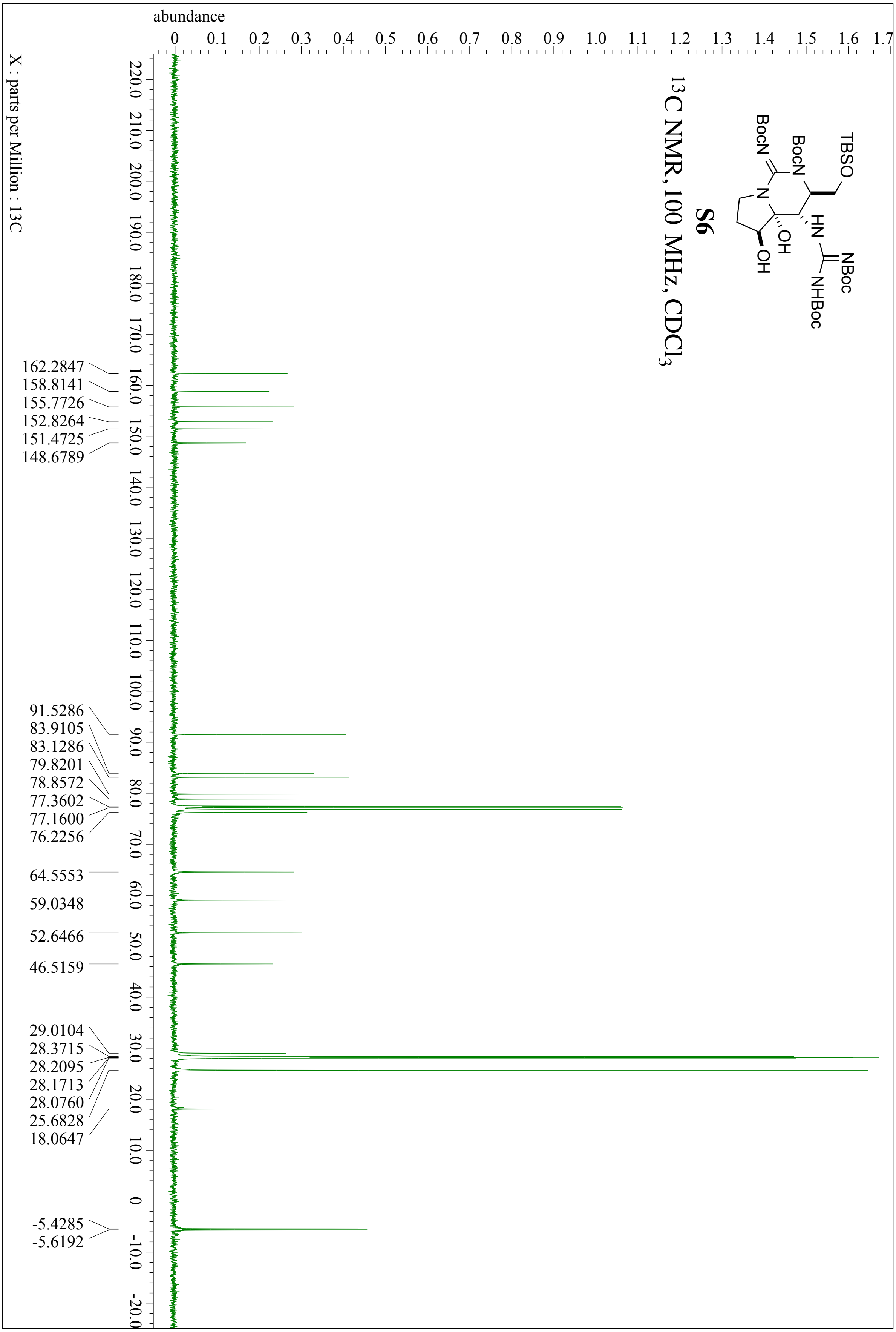

TBSO
BocN
BocN
N
NHCbz
OH
OH
S5
^{1}H NMR, 400MHz, CDCl$_3$
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
X : parts per Million : 1H
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.3952
7.3906
7.3849
7.3757
7.3700
7.3631
7.3574
7.3390
7.3253
7.2600
5.3104
5.2875
5.1408
4.9484
4.5601
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
0.99
0.98
1.00
2.01
1.01
1.00
0.99
0.95
0.97
0.94
20.00
9.91
6.15


TBSO
BocN
NHCbz
OH
BocN
N
OH
S5
13C NMR, 100MHz, CDCl3
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
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
X : parts per Million : 13C



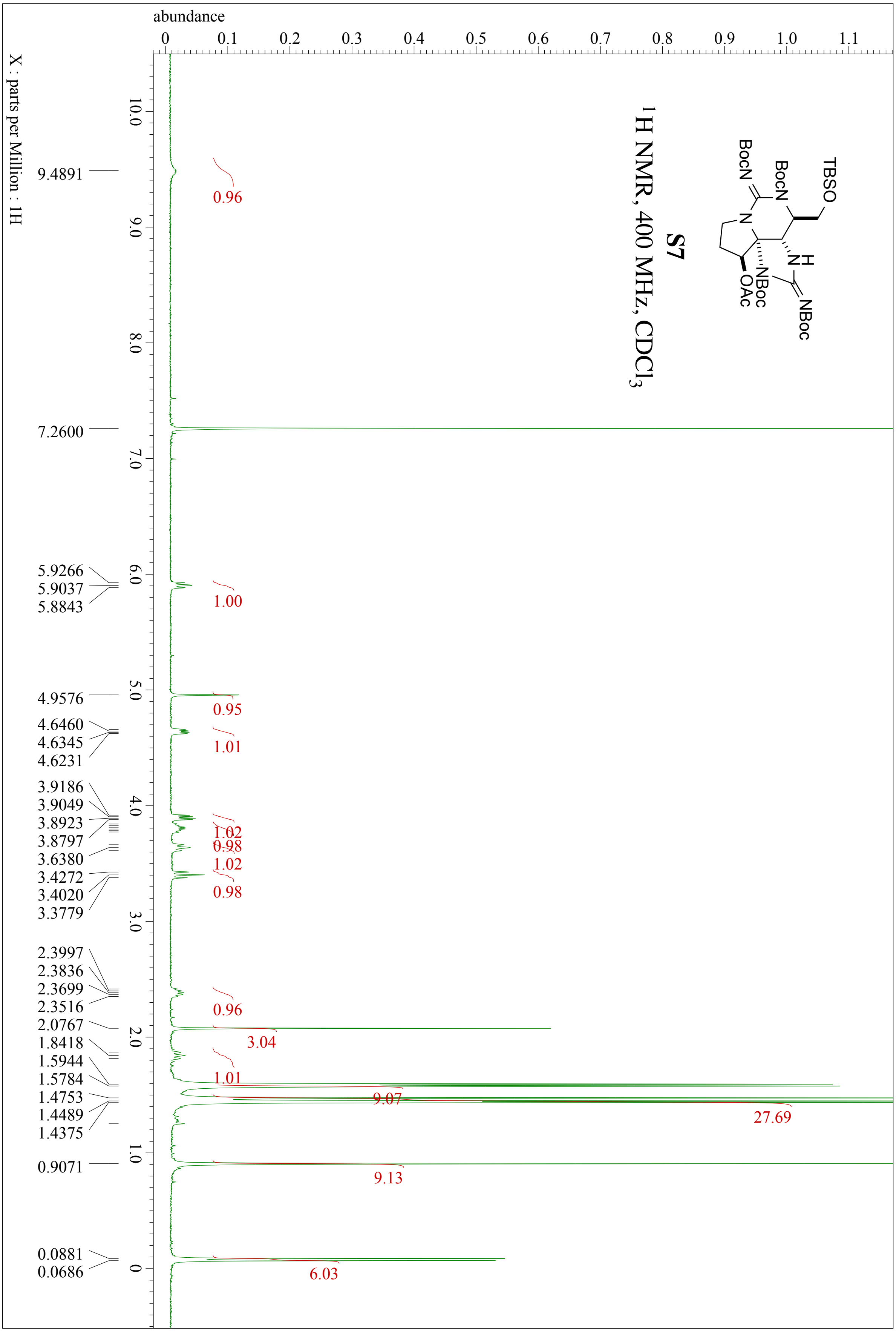
S6

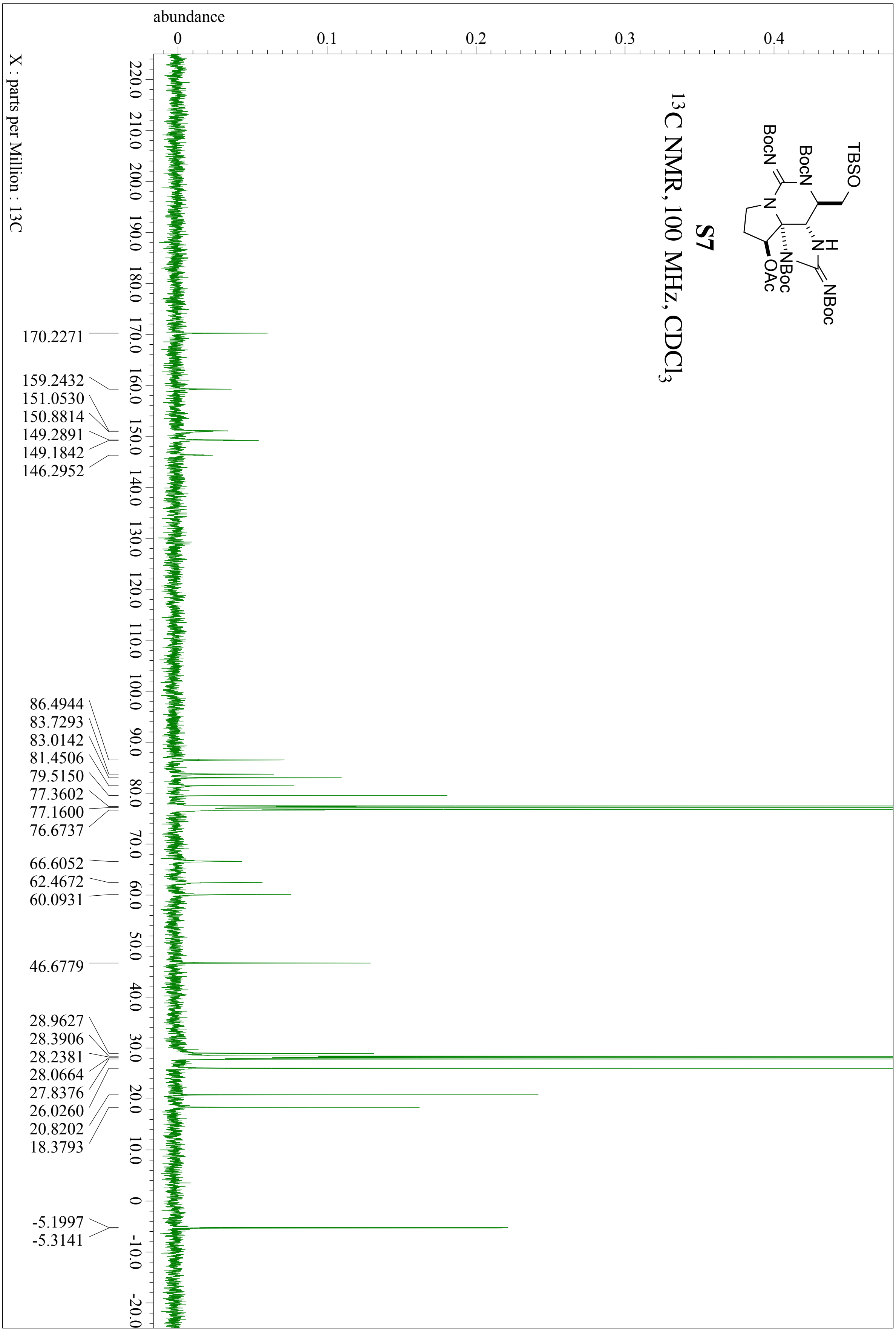
^{1}H NMR, 400MHz, CDCl$_3$

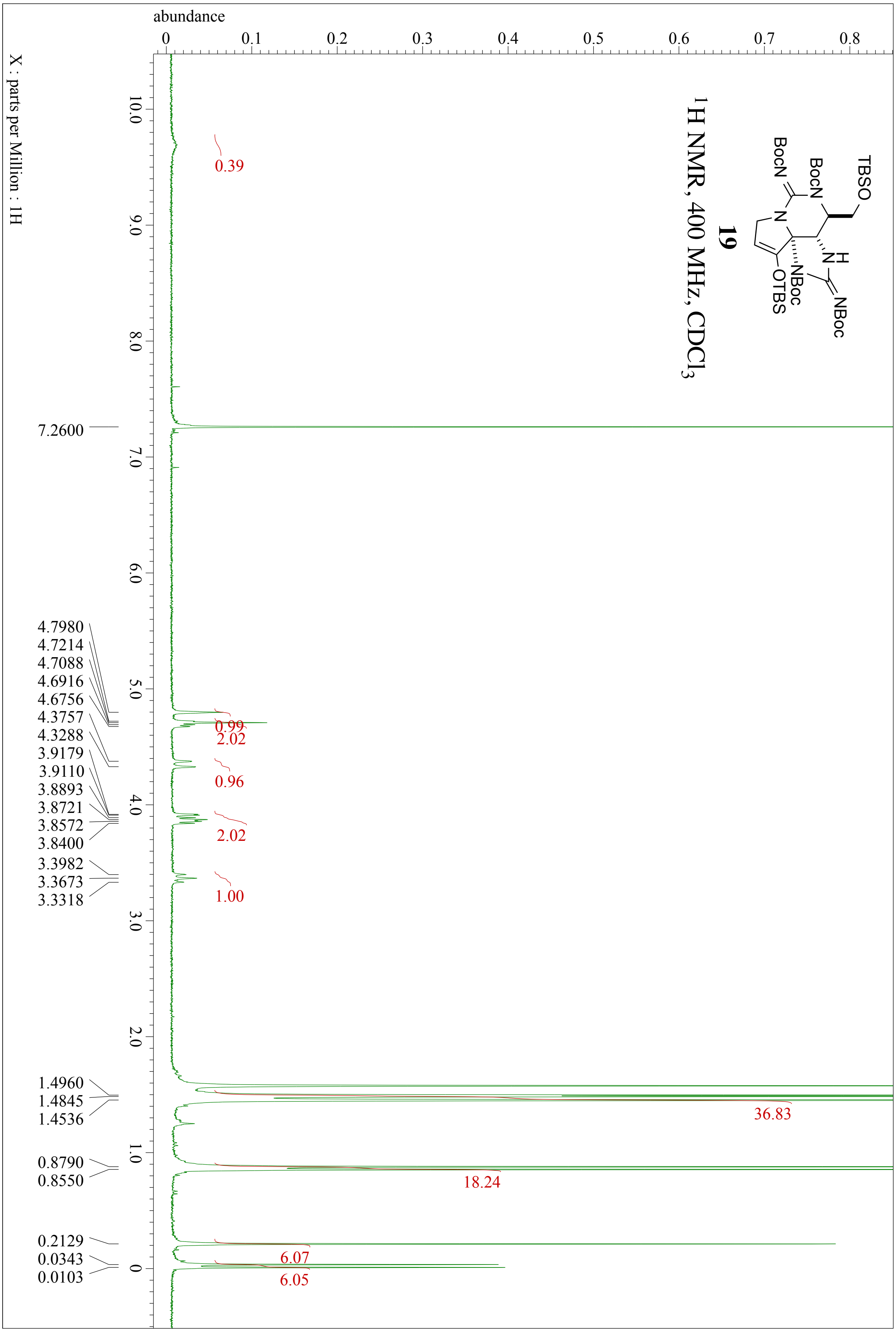


S6

^{13}C NMR, 100 MHz, $CDCl_3$

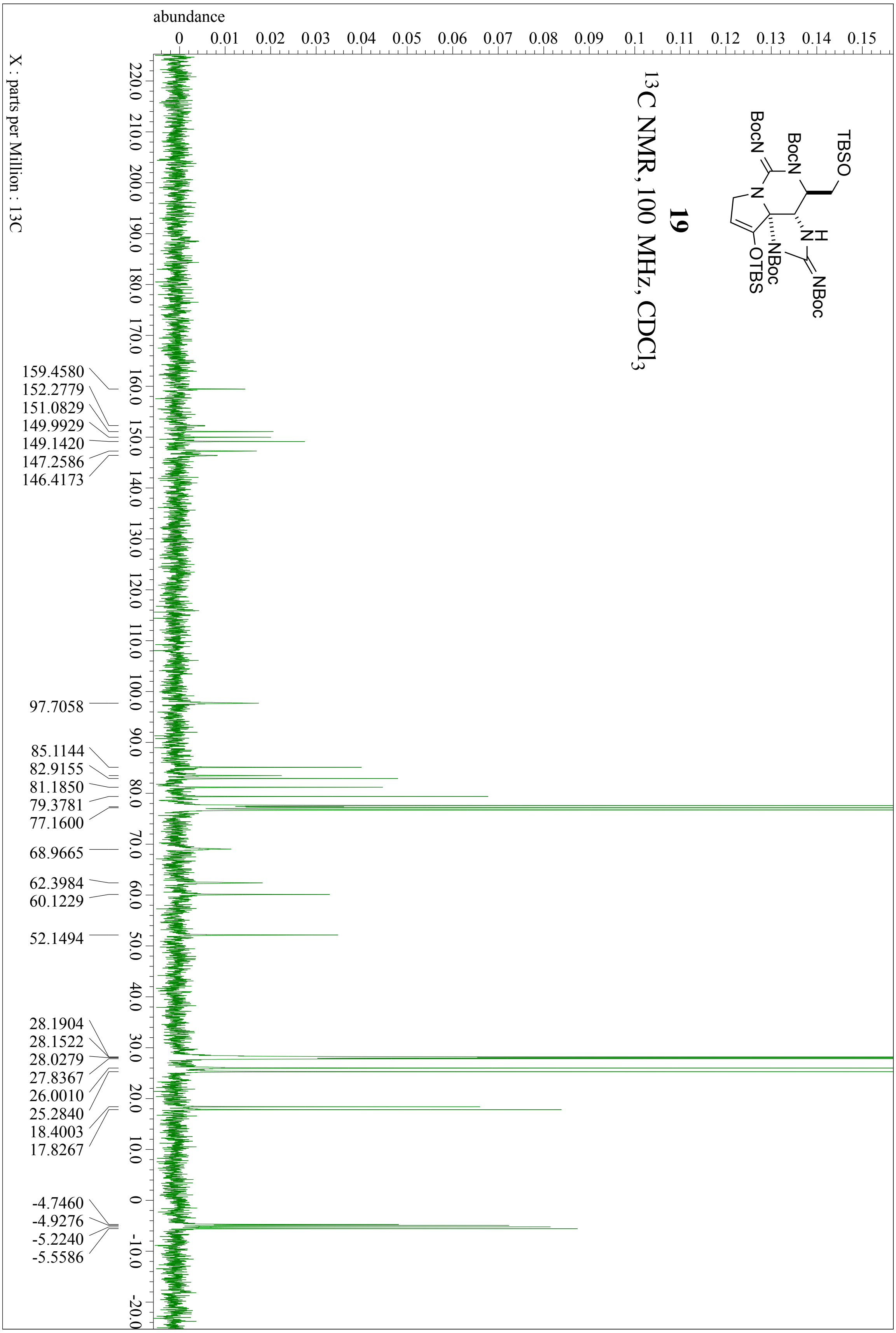

S7
¹H NMR, 400 MHz, CDCl₃
TBSO
BocN
BocN
N
H
N
NBoc
NBoc
OAc
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
X : parts per Million : 1H
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
9.4891
7.2600
5.9266
5.9037
5.8843
4.9576
4.6460
4.6345
4.6231
3.9186
3.9049
3.8923
3.8797
3.6380
3.4272
3.4020
3.3779
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$_3$
TBSO
BocN
BocN
N
H
N
NBoc
NBoc
OAc
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
170.2271
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

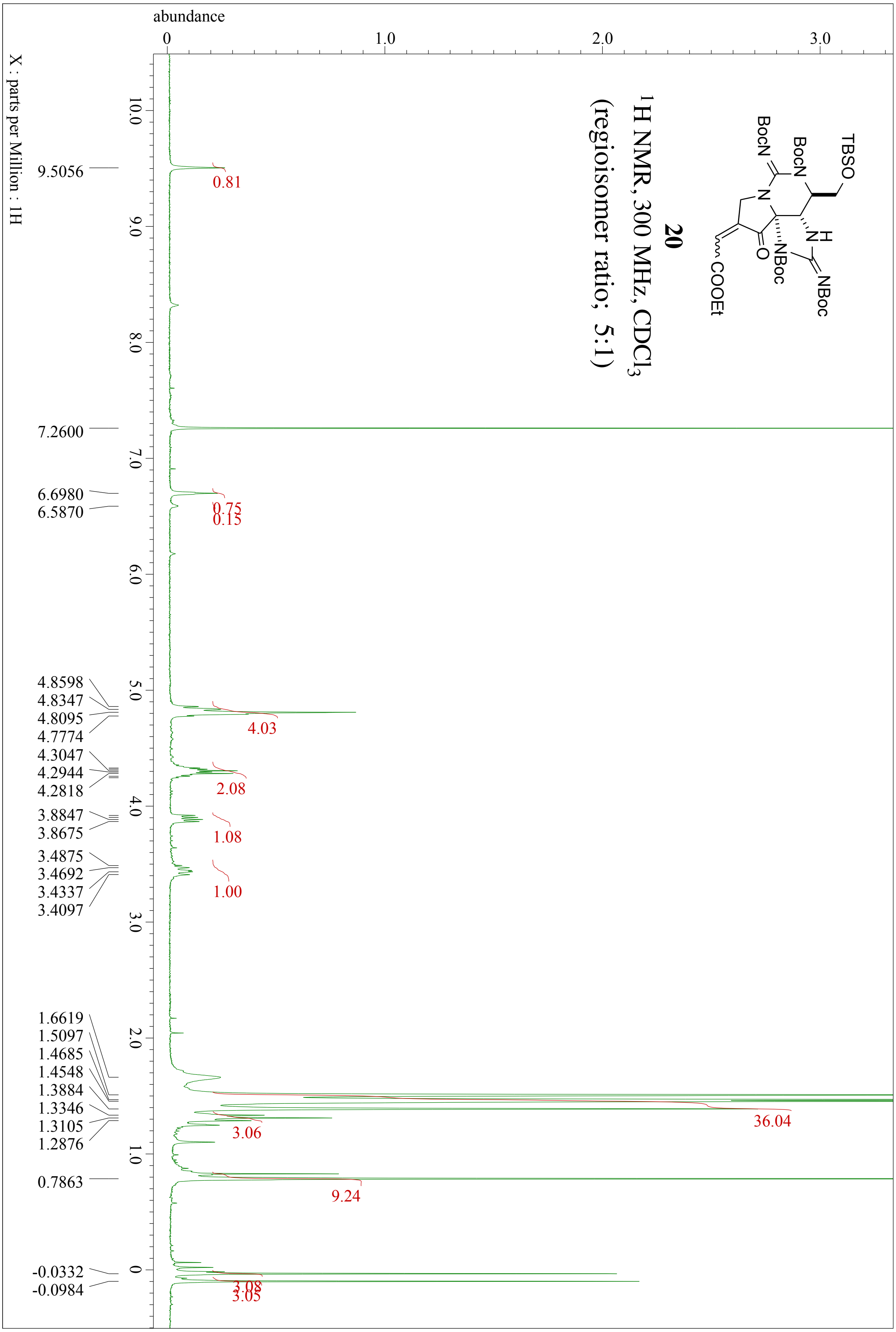


19

^{1}H NMR, 400 MHz, $CDCl_3$


19

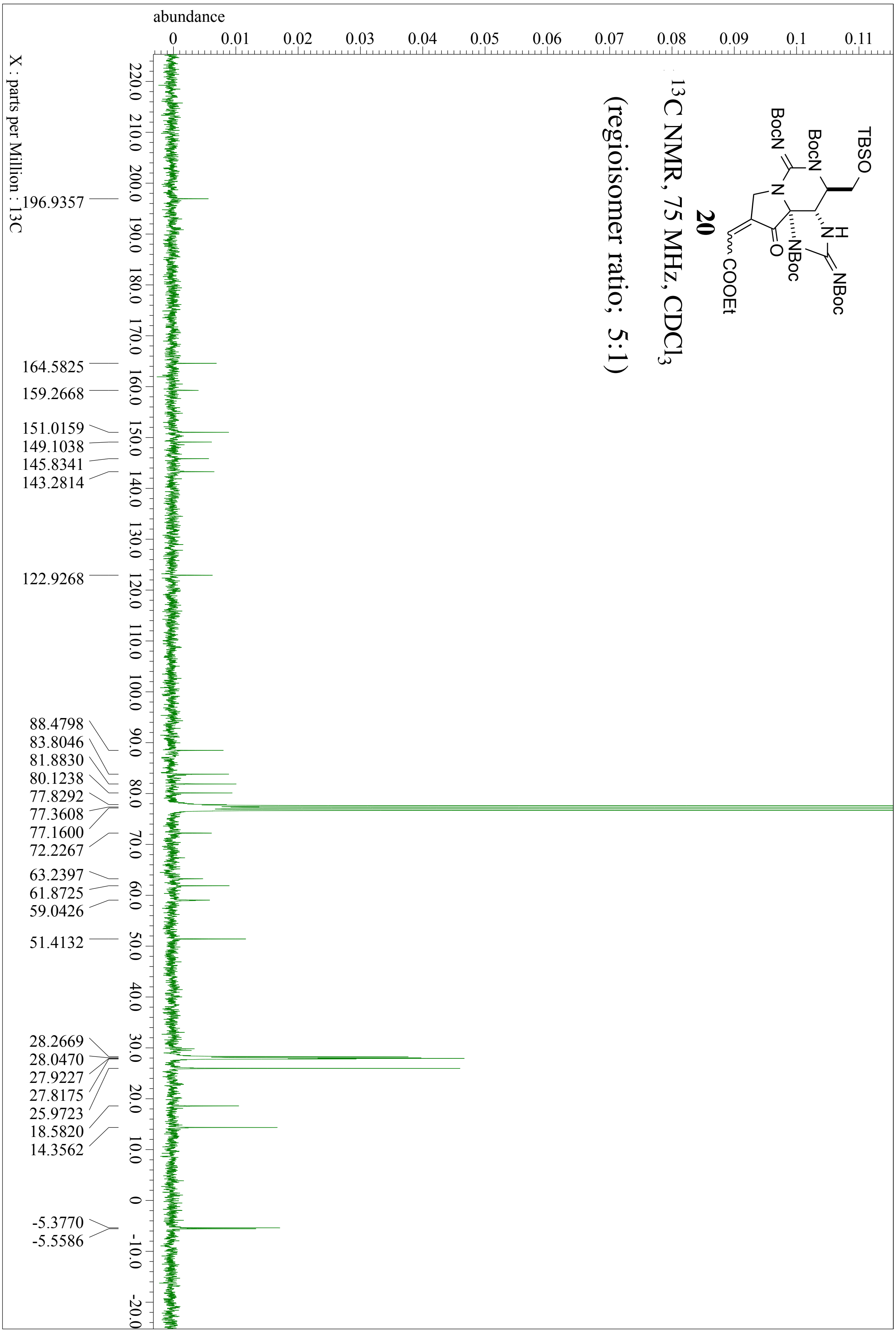
^{13}C NMR, 100 MHz, CDCl$_3$



20

^{1}H NMR, 300 MHz, $CDCl_3$

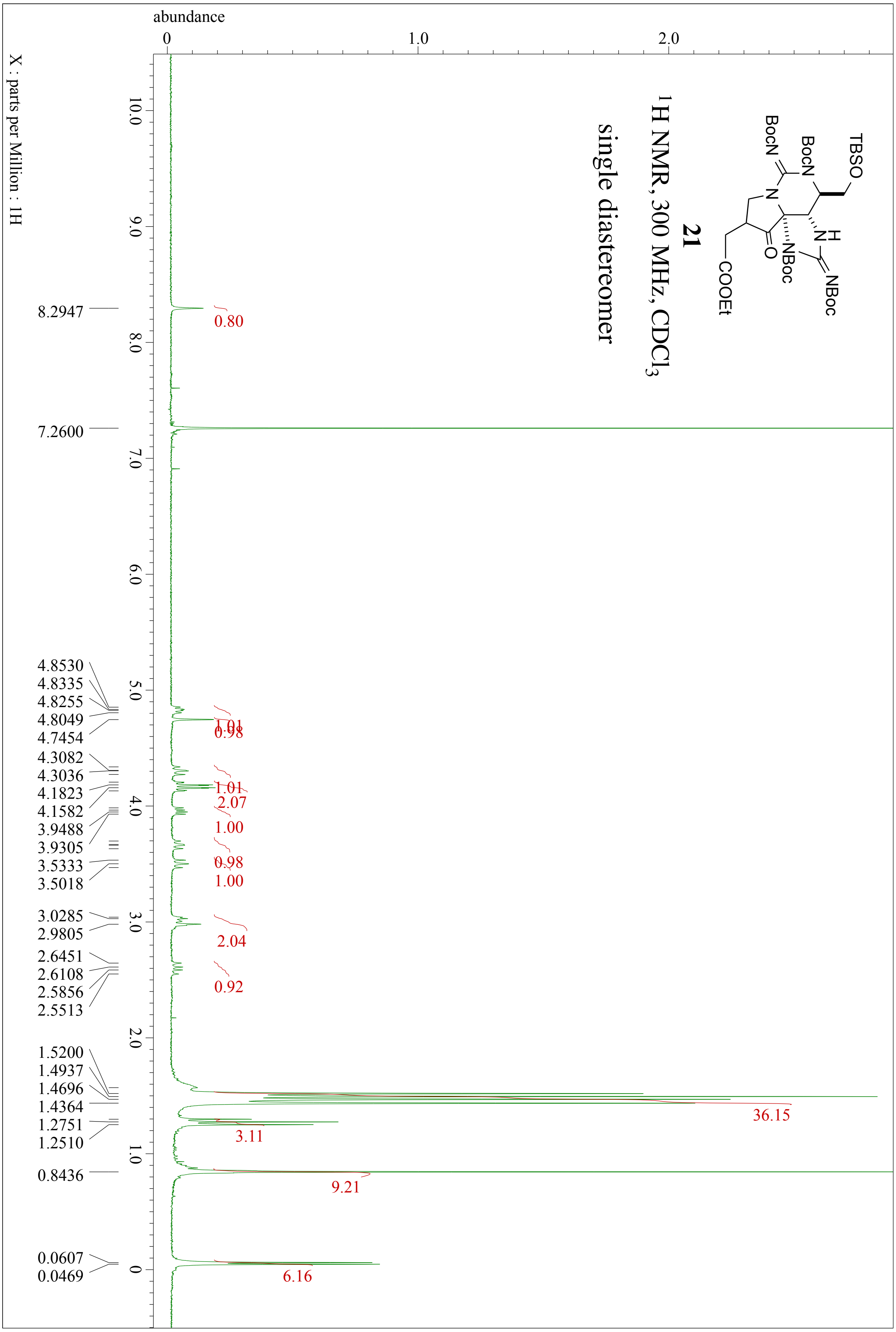
(regioisomer ratio; 5:1)



20

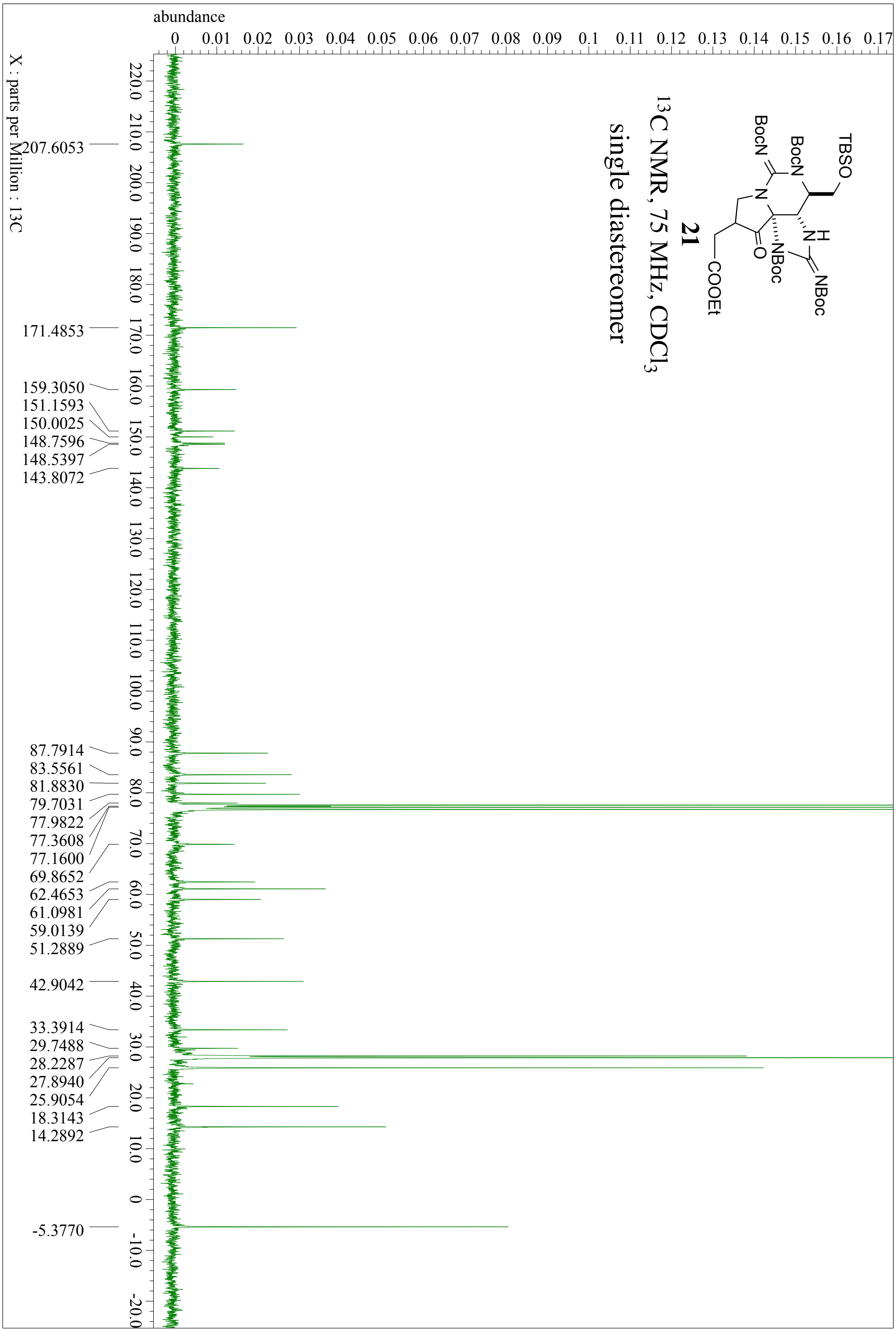
^{13}C NMR, 75 MHz, $CDCl_3$

(regioisomer ratio; 5:1)



21

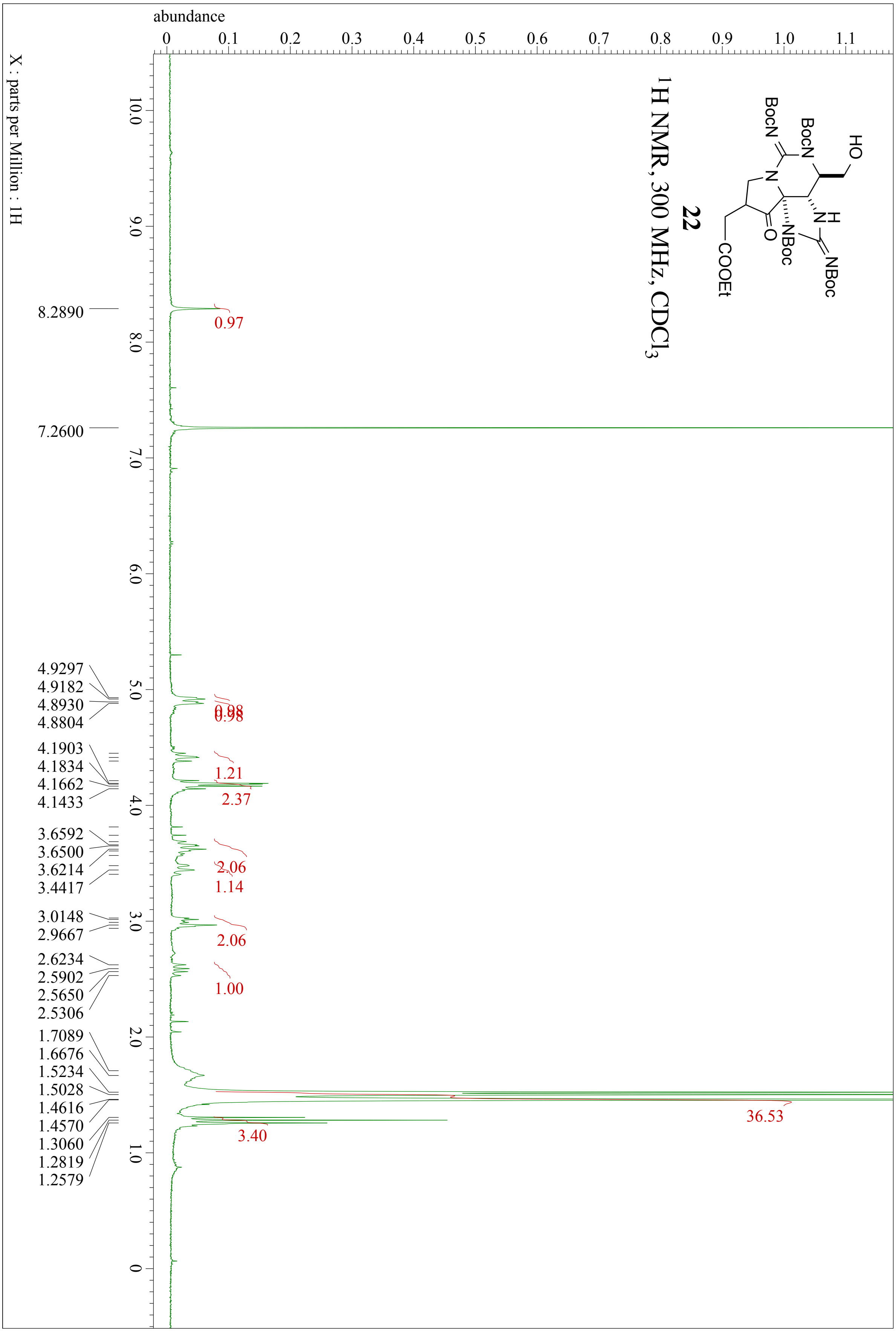
^{1}H NMR, 300 MHz, $CDCl_3$
single diastereomer



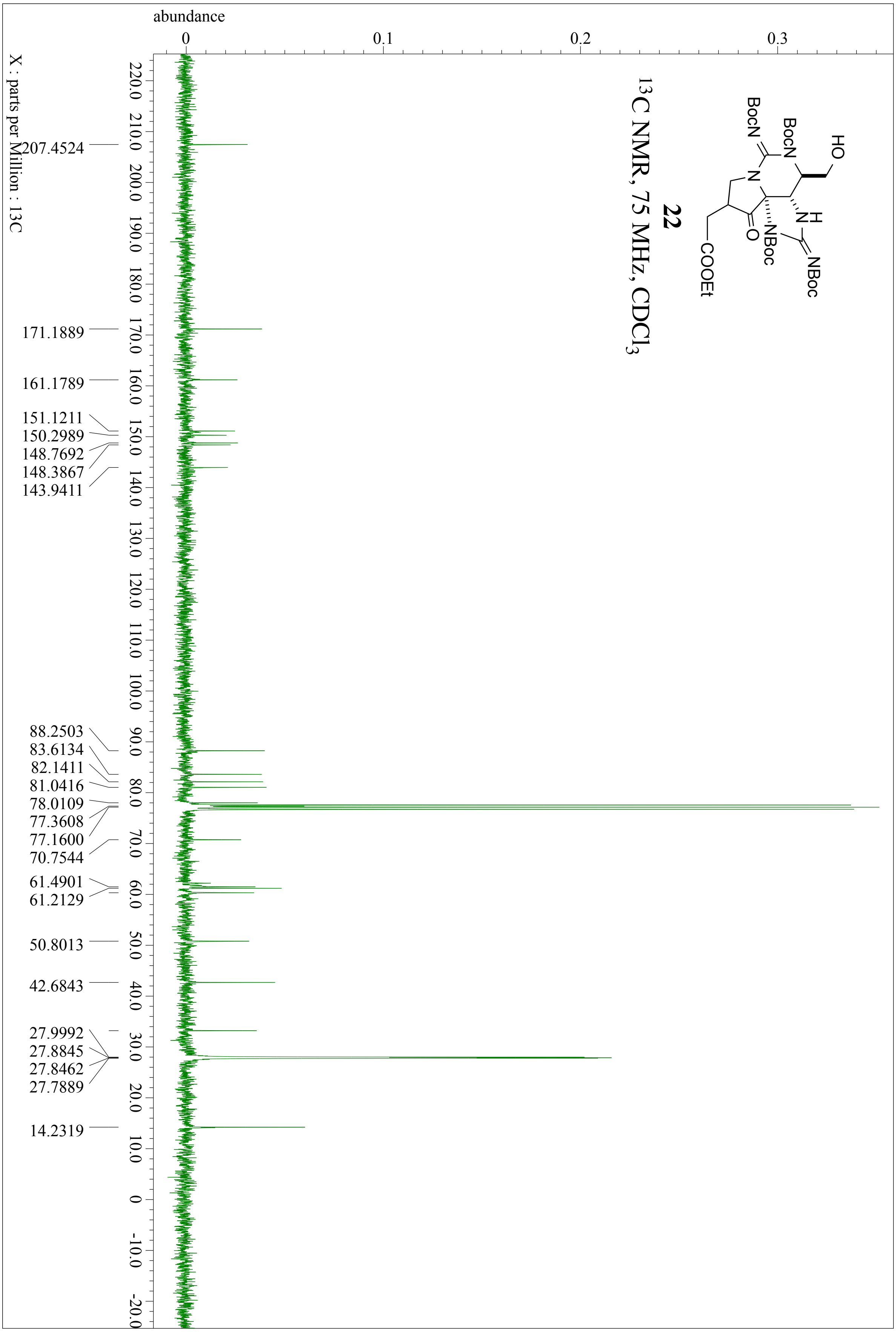
21

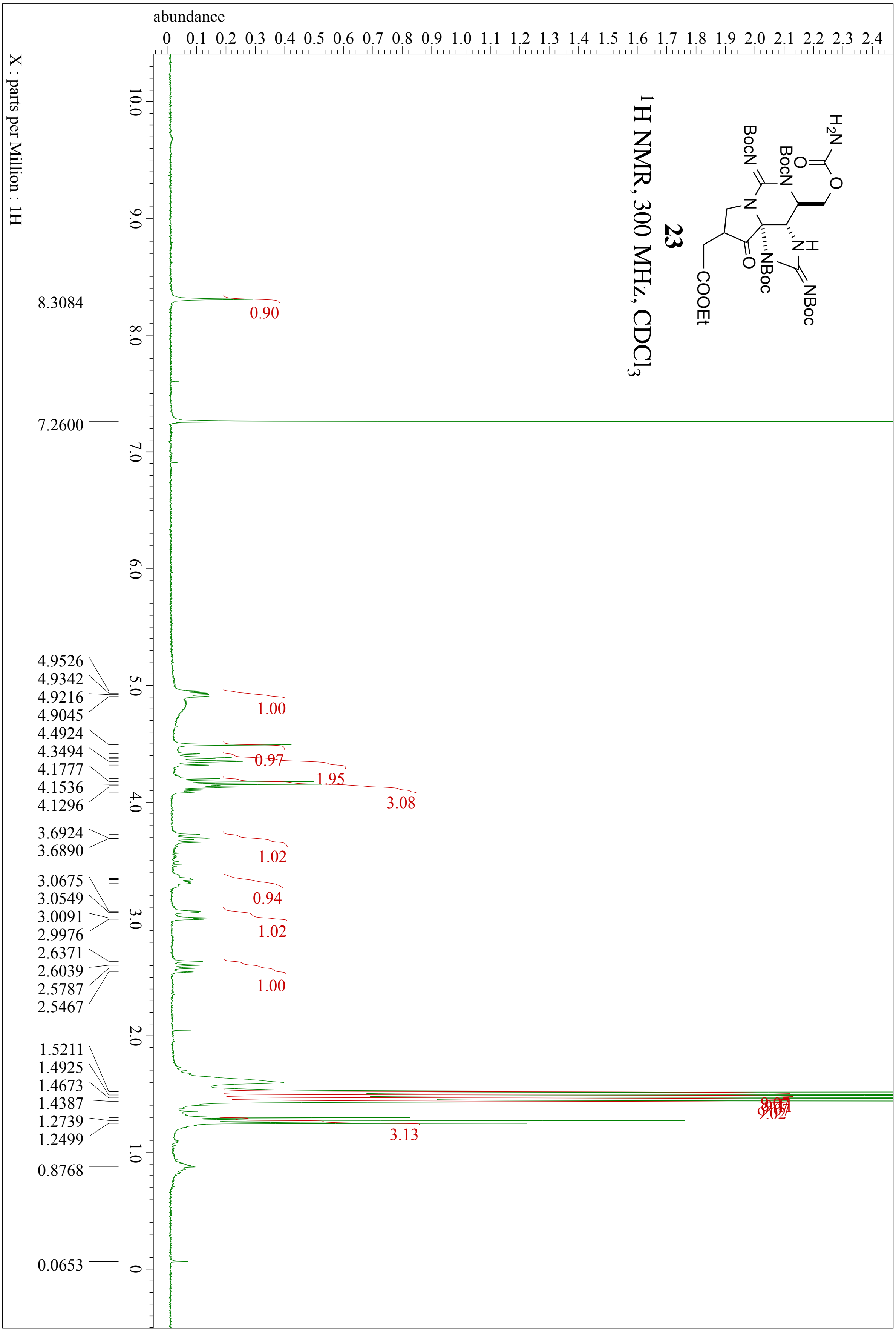
^{13}C NMR, 75 MHz, $CDCl_3$

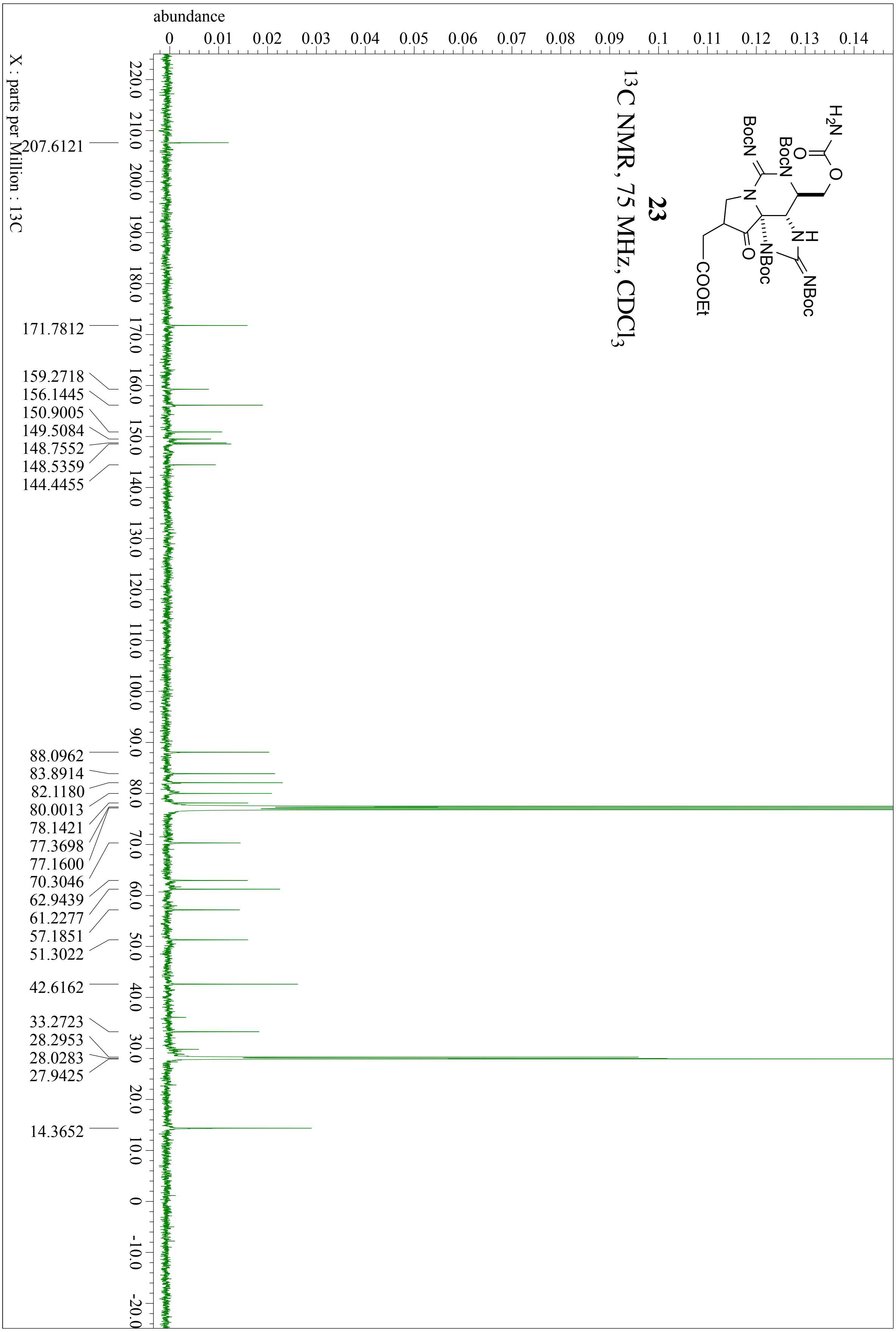
single diastereomer



abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
HO
BocN
BocN
N
H
N
NBoc
NBoc
O
COOEt
22
^{1}H NMR, 300 MHz, CDCl$_3$
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
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
0.98
1.21
2.37
2.06
1.14
2.06
1.00
36.53
3.40

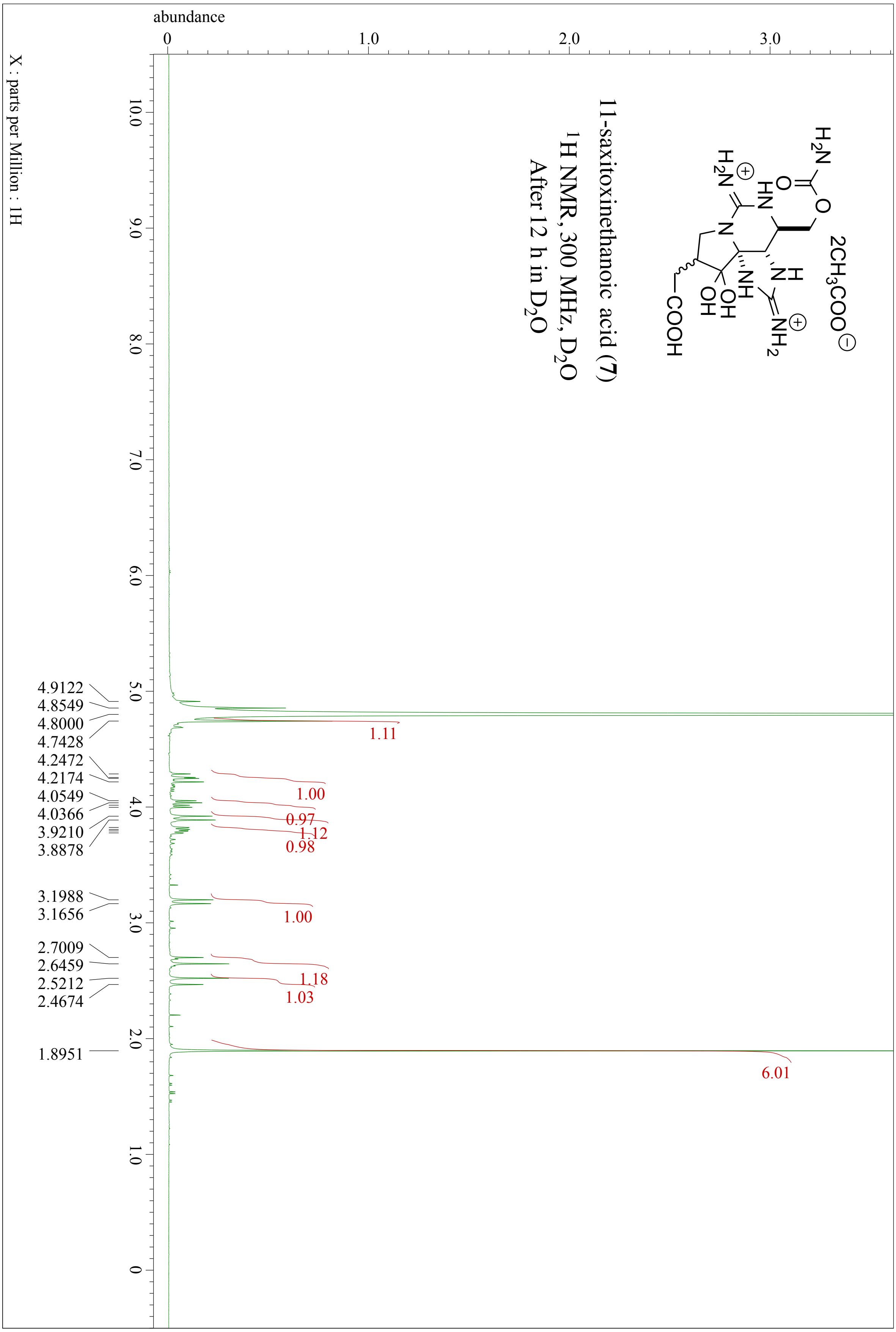

HO
BocN
NBoc
H
N
BocN
N
NBoc
O
COOEt
22
^{13}C NMR, 75 MHz, CDCl$_3$
abundance
0
0.1
0.2
0.3
X : parts per Million : 13C
207.4524
171.1889
161.1789
151.1211
150.2989
148.7692
148.3867
143.9411
88.2503
83.6134
82.1411
81.0416
78.0109
77.3608
77.1600
70.7544
61.4901
61.2129
50.8013
42.6843
27.9992
27.8845
27.8462
27.7889
14.2319
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


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
1.8
1.9
2.0
2.1
2.2
2.3
2.4
H_2N
O
O
BocN
BocN
N
H
N
NBoc
NBoc
O
COOEt
23
^1H NMR, 300 MHz, $CDCl_3$
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
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
9.07
9.02
3.13



23

^{13}C NMR, 75 MHz, CDCl$_3$

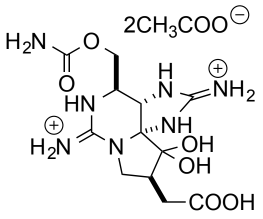


11-saxitoxinethanoic acid (**7**)

^{1}H NMR, 300 MHz, D_2O

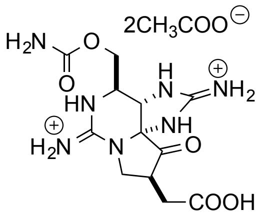
After 12 h in D_2O

Precise assignment of 7



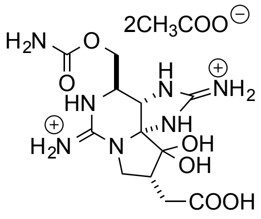
(β)-SEA

●



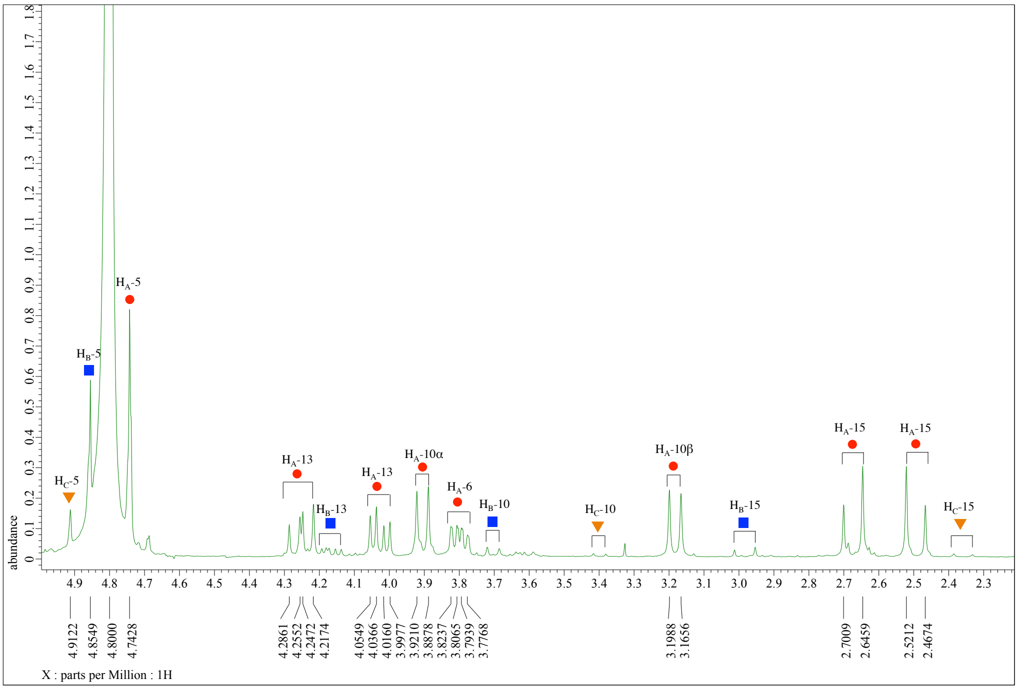
SEA (keto form)

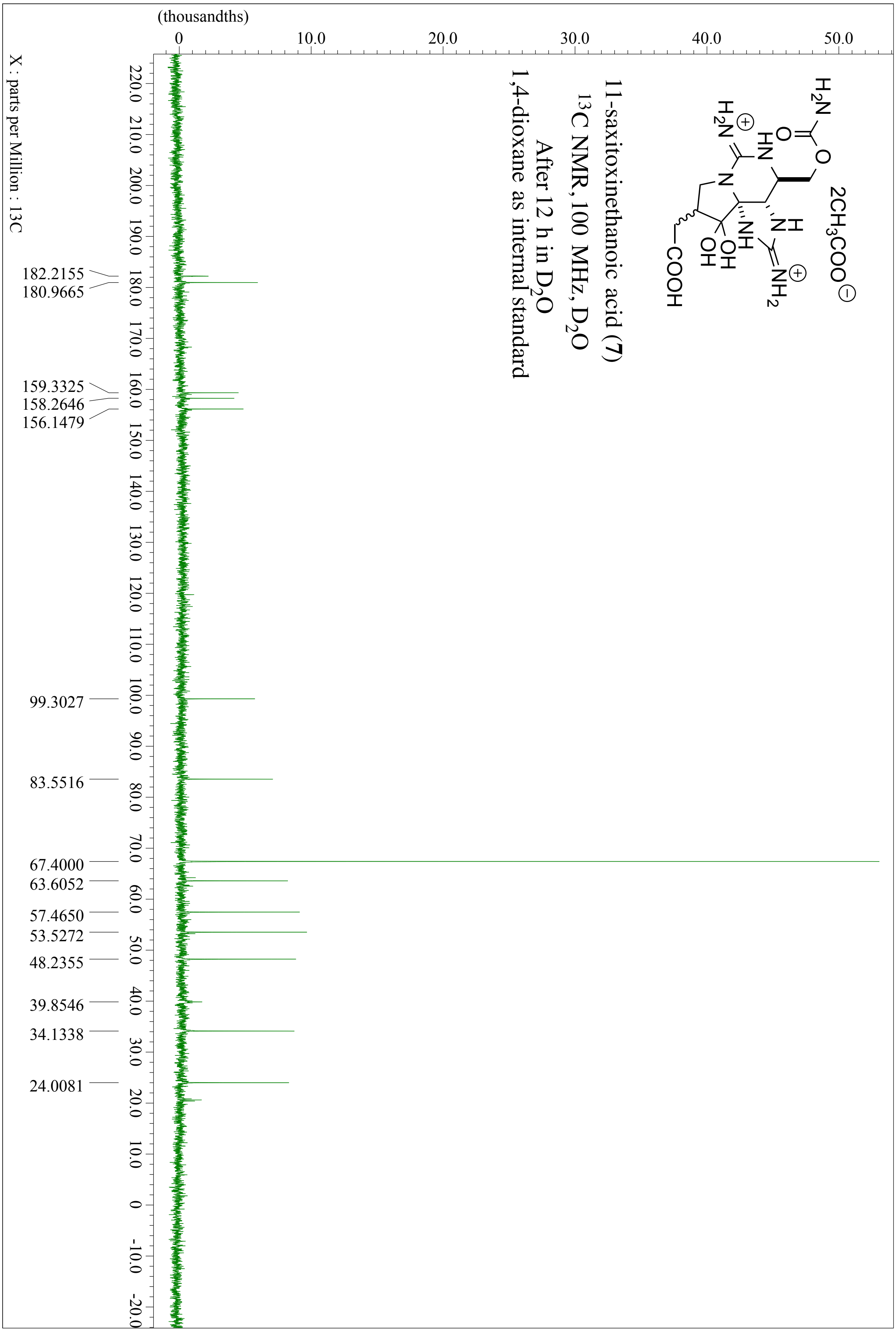
■



(α)-SEA

▼





11-saxitoxinethanoic acid (**7**)

^{13}C NMR, 100 MHz, D_2O

After 12 h in D_2O

1,4-dioxane as internal standard

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)

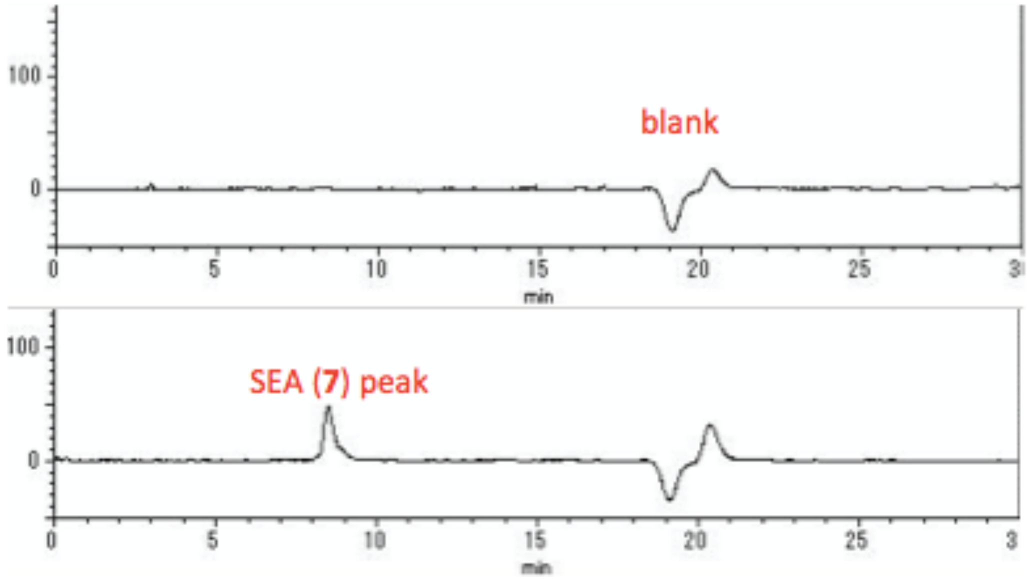
^{13}C NMR data for synthetic and natural SEA (7)

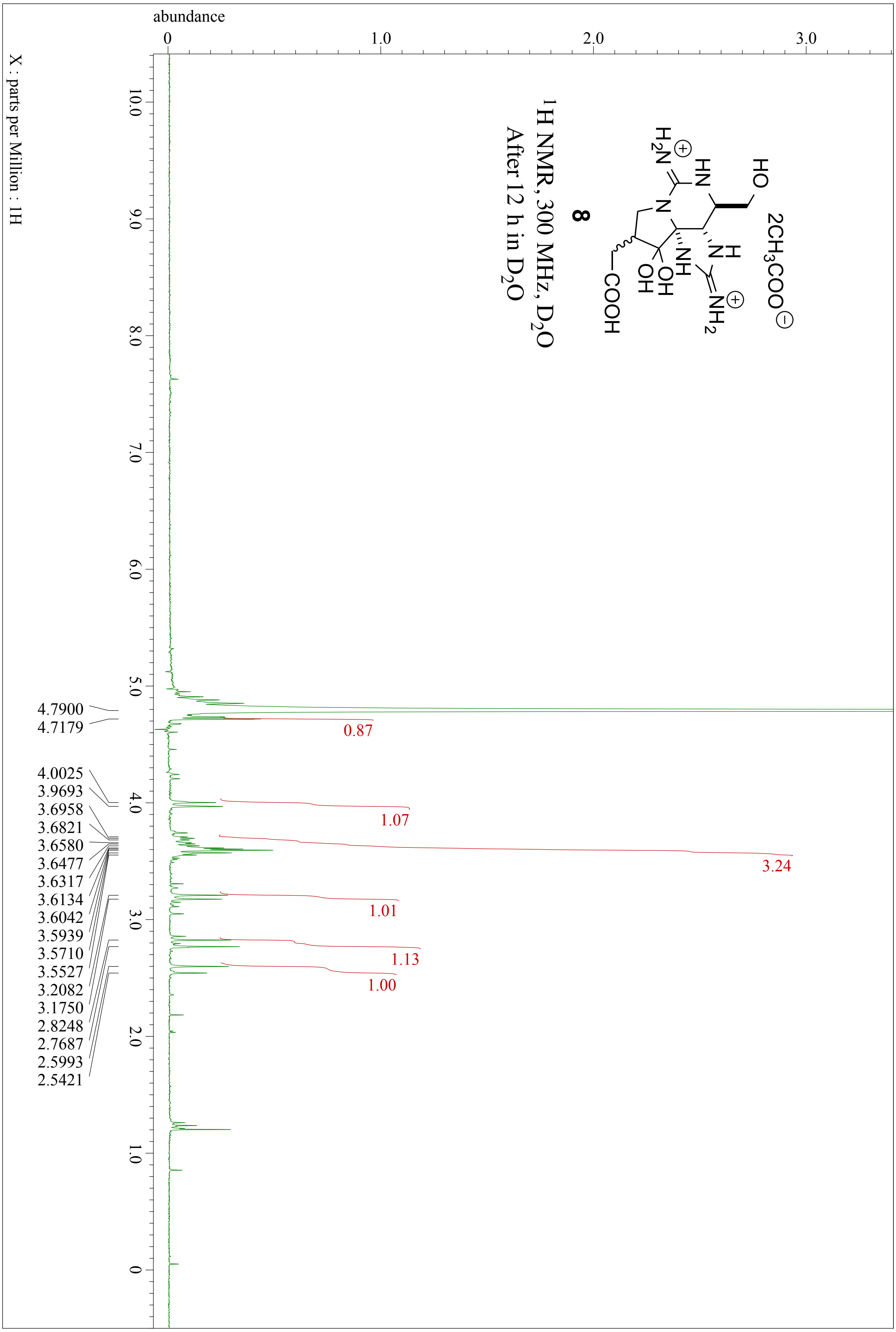
	Synthetic	Natural
Position	^{13}C NMR	^{13}C NMR
C-2	156.1	156.2
C-4	83.6	83.5
C-5	57.5	57.5
C-6	53.5	53.5
C-8	158.3	158.3
C-10	48.2	48.2
C-11	39.9	39.9
C-12	99.3	99.3
C-13	63.6	63.6
C-14	159.3	159.3
C-15	34.1	33.9
C-16*	182.2	180.6

* 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).

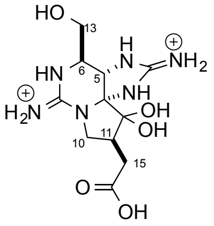




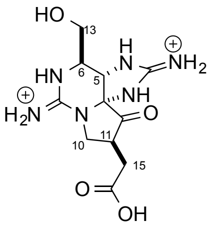
8

^{1}H NMR, 300 MHz, D$_2$O
After 12 h in D$_2$O

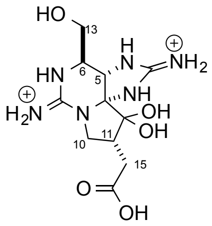
Precise assignment of 8



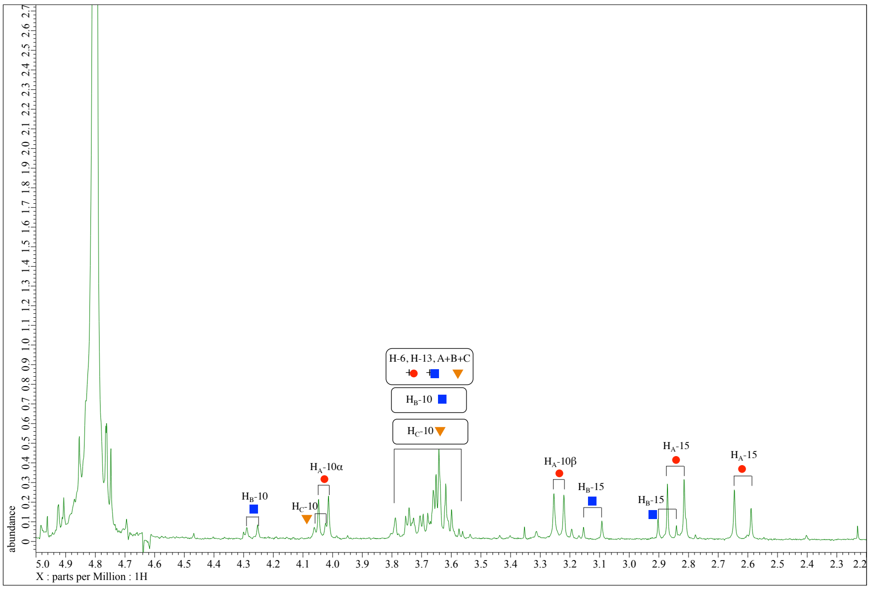
A ●

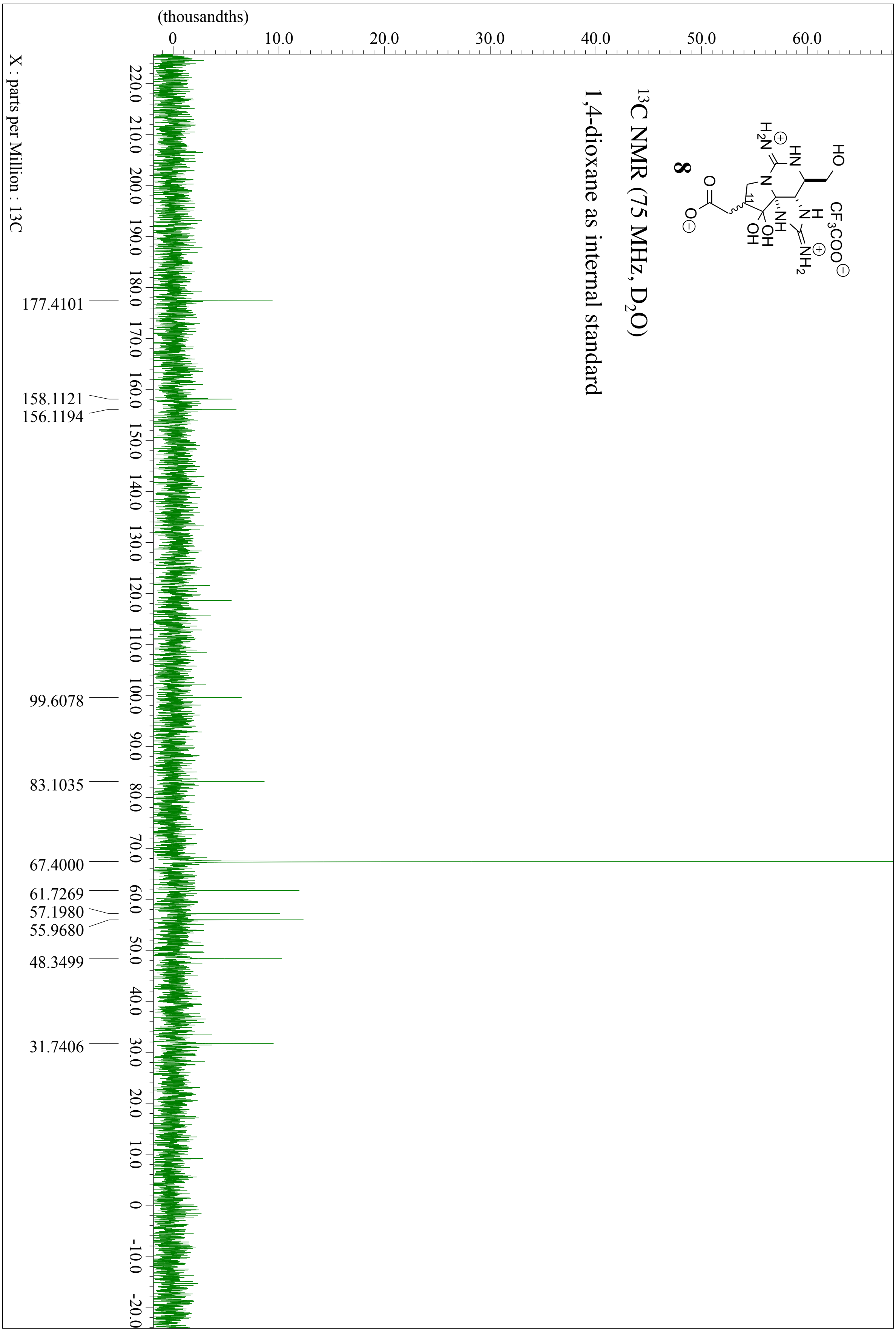


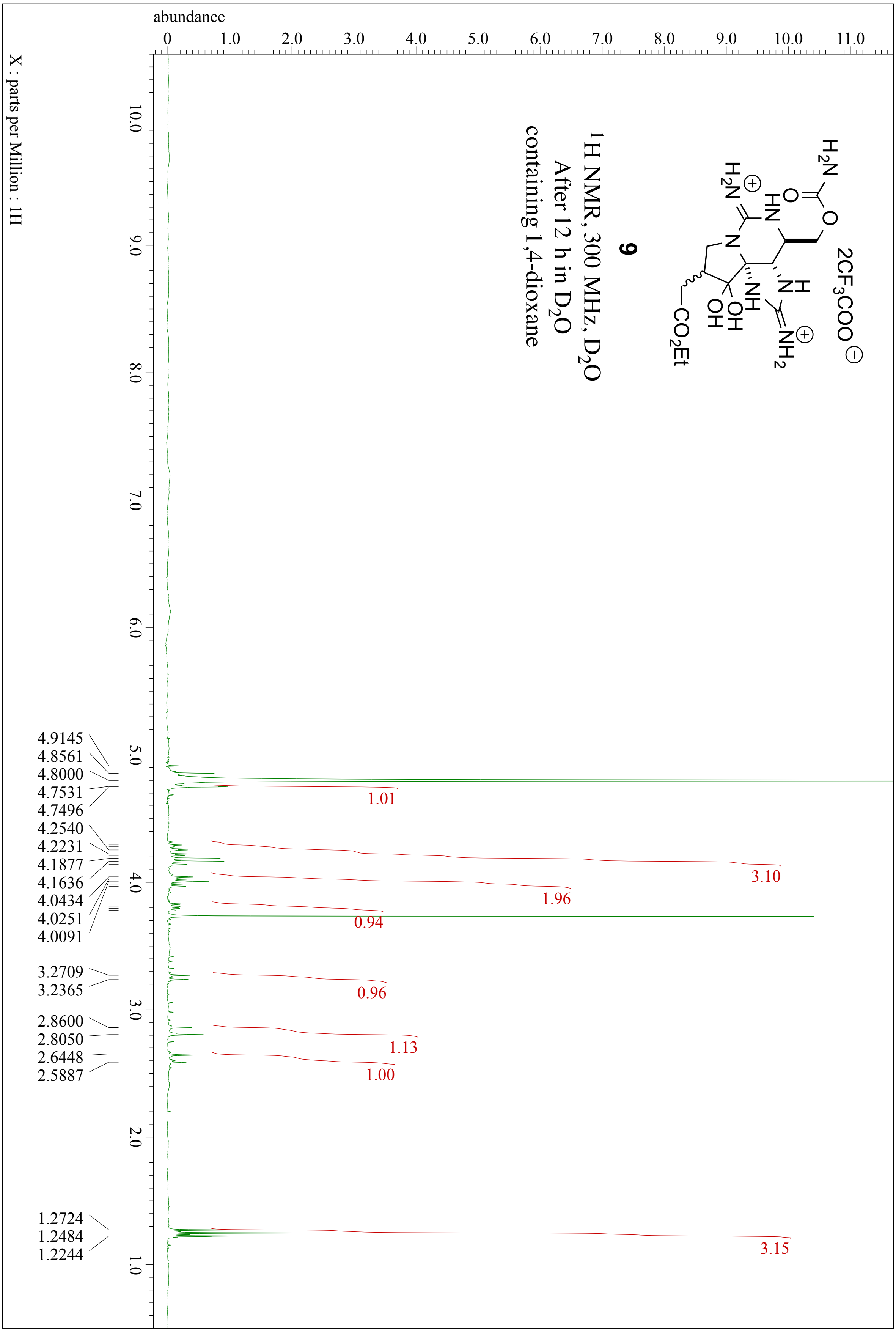
B ■



C ▼



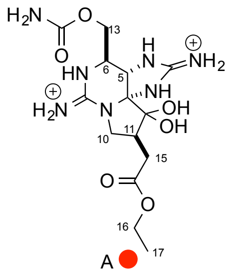

8
^{13}C NMR (75 MHz, D$_2$O)
1,4-dioxane as internal standard
HO
CF$_3$COO$^{\ominus}$
H
N
NH$_2$
HN
H$_2$N
NH
OH
OH
O
O$^{\ominus}$
11
(thousandths)
0
10.0
20.0
30.0
40.0
50.0
60.0
X : parts per Million : 13C
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
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

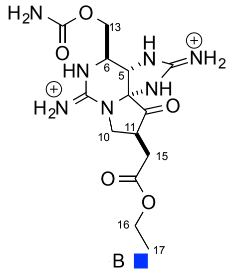


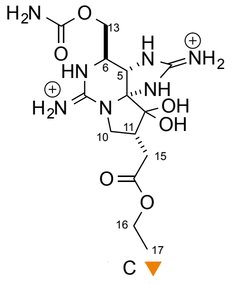
9

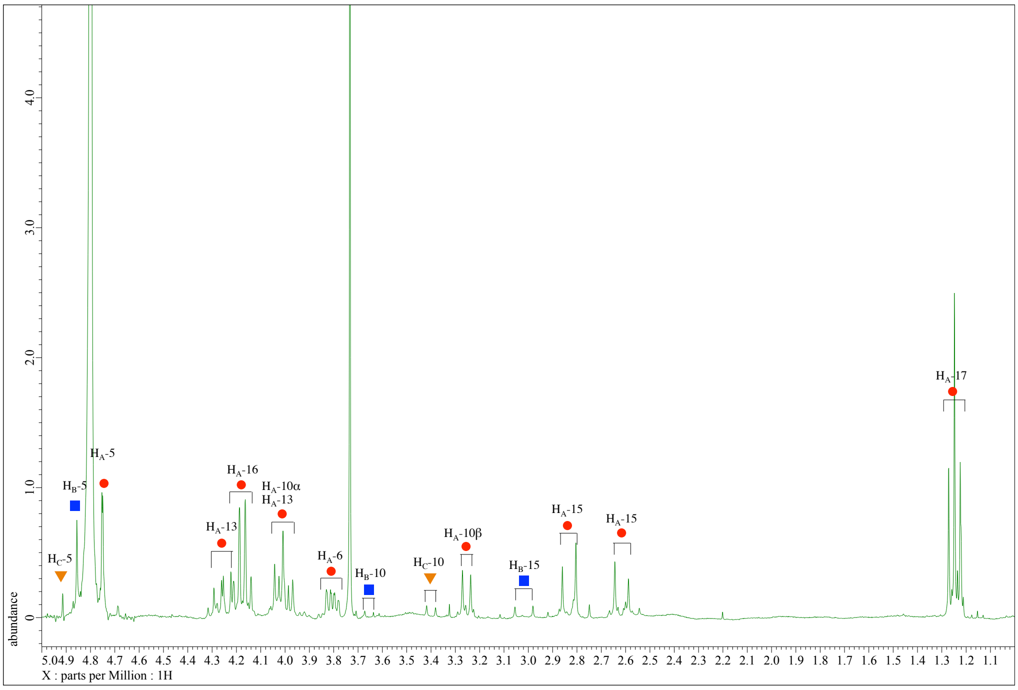
^{1}H NMR, 300 MHz, D_2O
After 12 h in D_2O
containing 1,4-dioxane

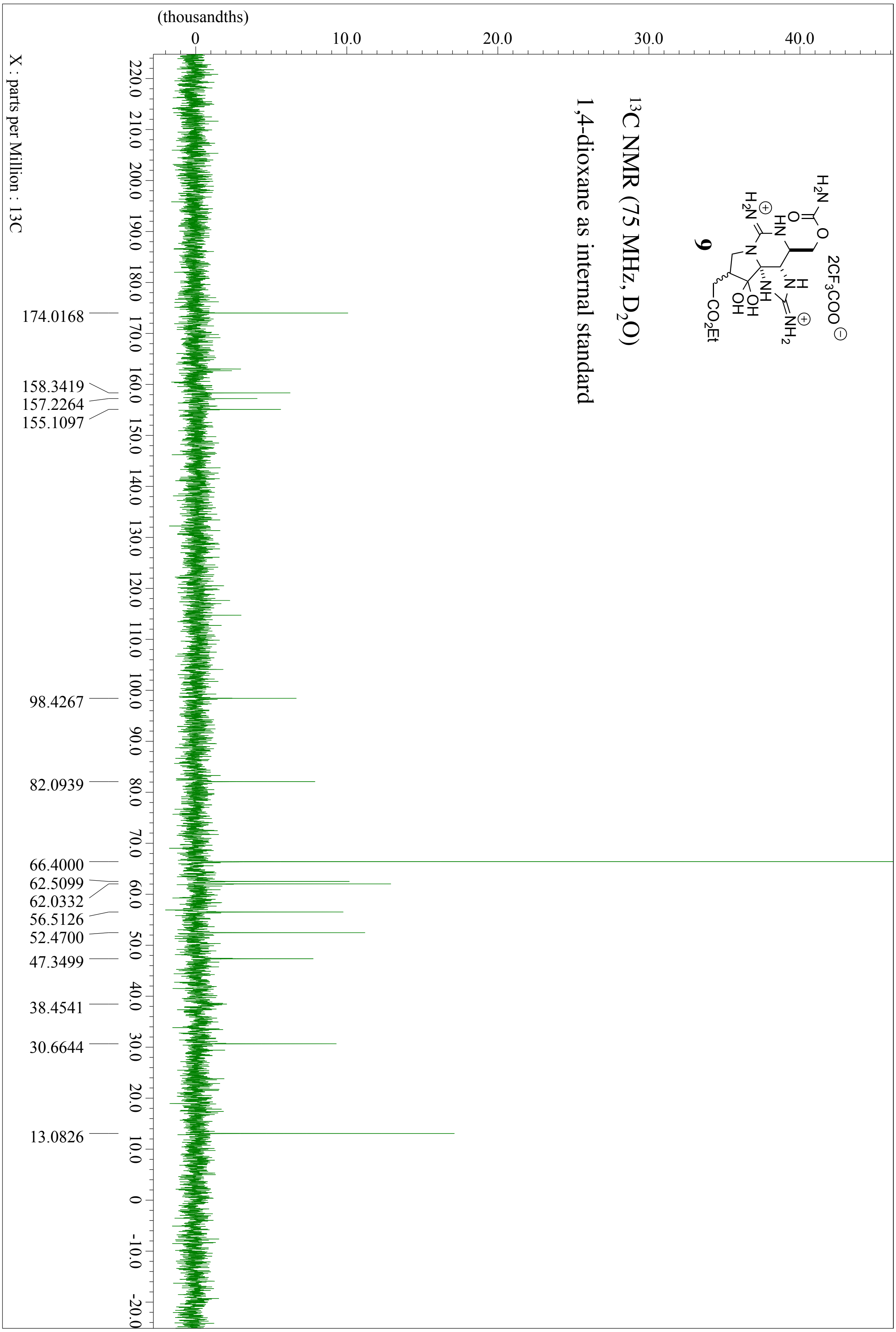
Precise assignment of 9





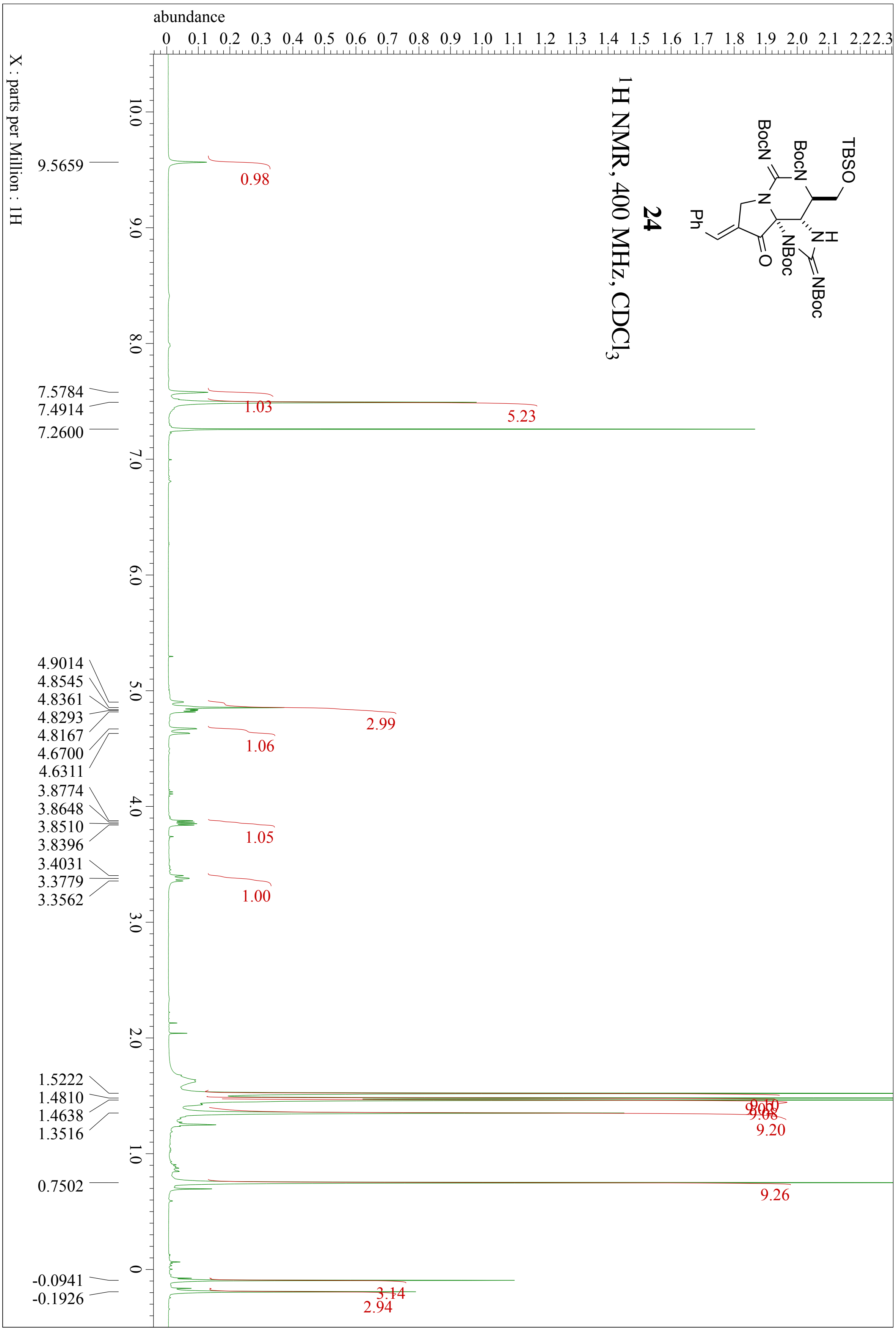


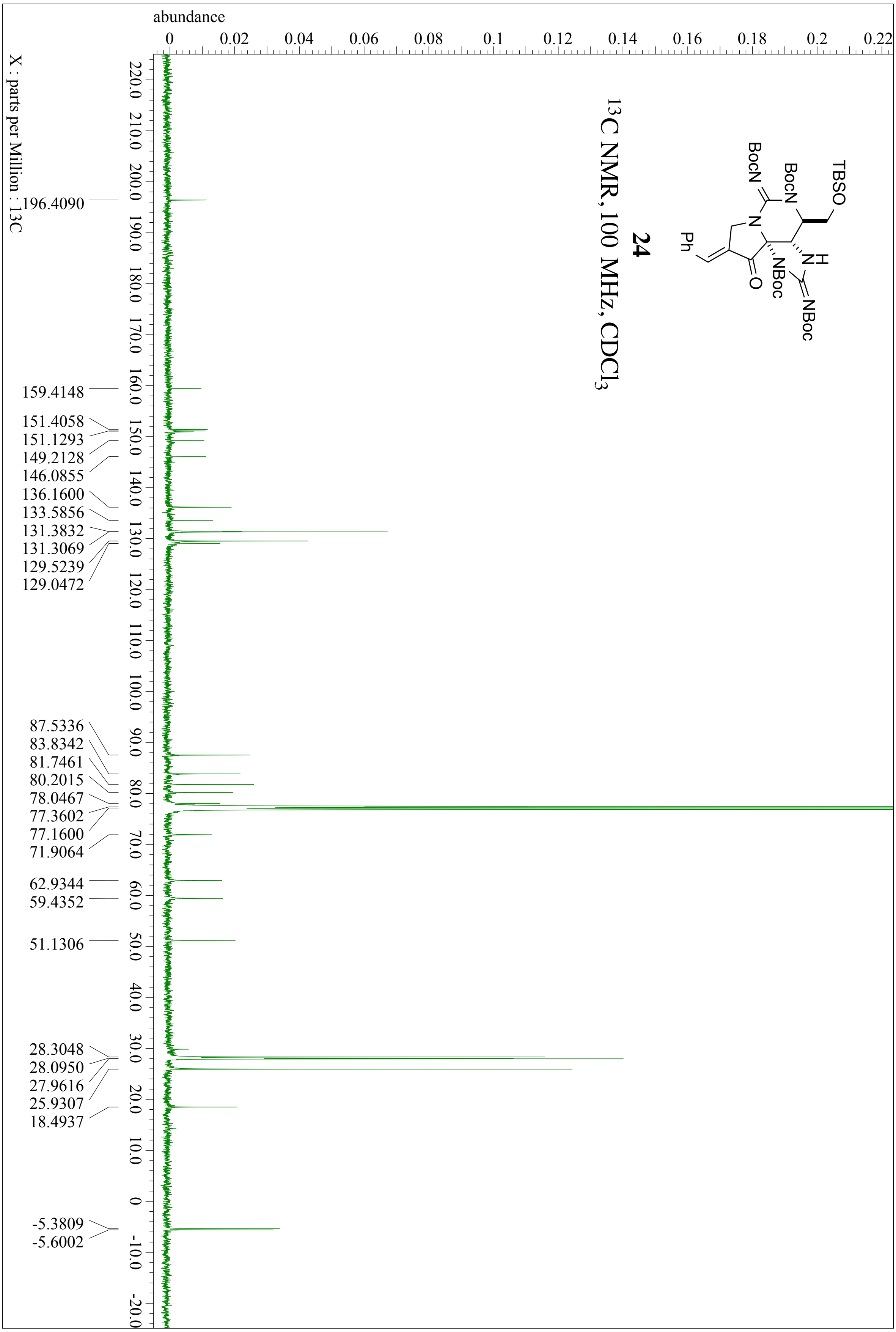




^{13}C NMR (75 MHz, D_2O)

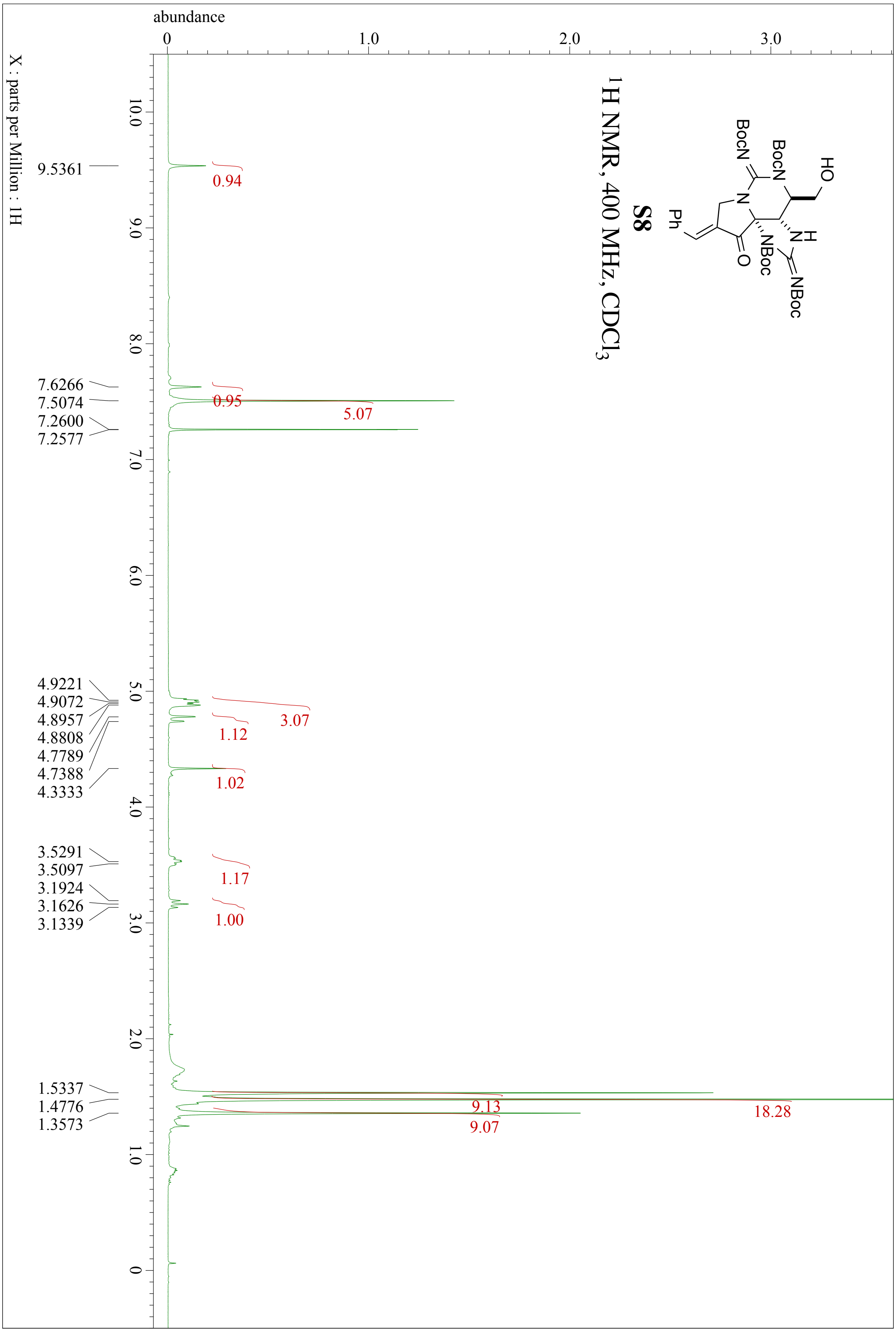
1,4-dioxane as internal standard


TBSO
BocN
BocN
N
H
N
NBoc
NBoc
O
Ph
24
^{1}H NMR, 400 MHz, CDCl$_3$
abundance
X : parts per Million : 1H
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
9.10
9.08
9.20
9.26
3.14
2.94



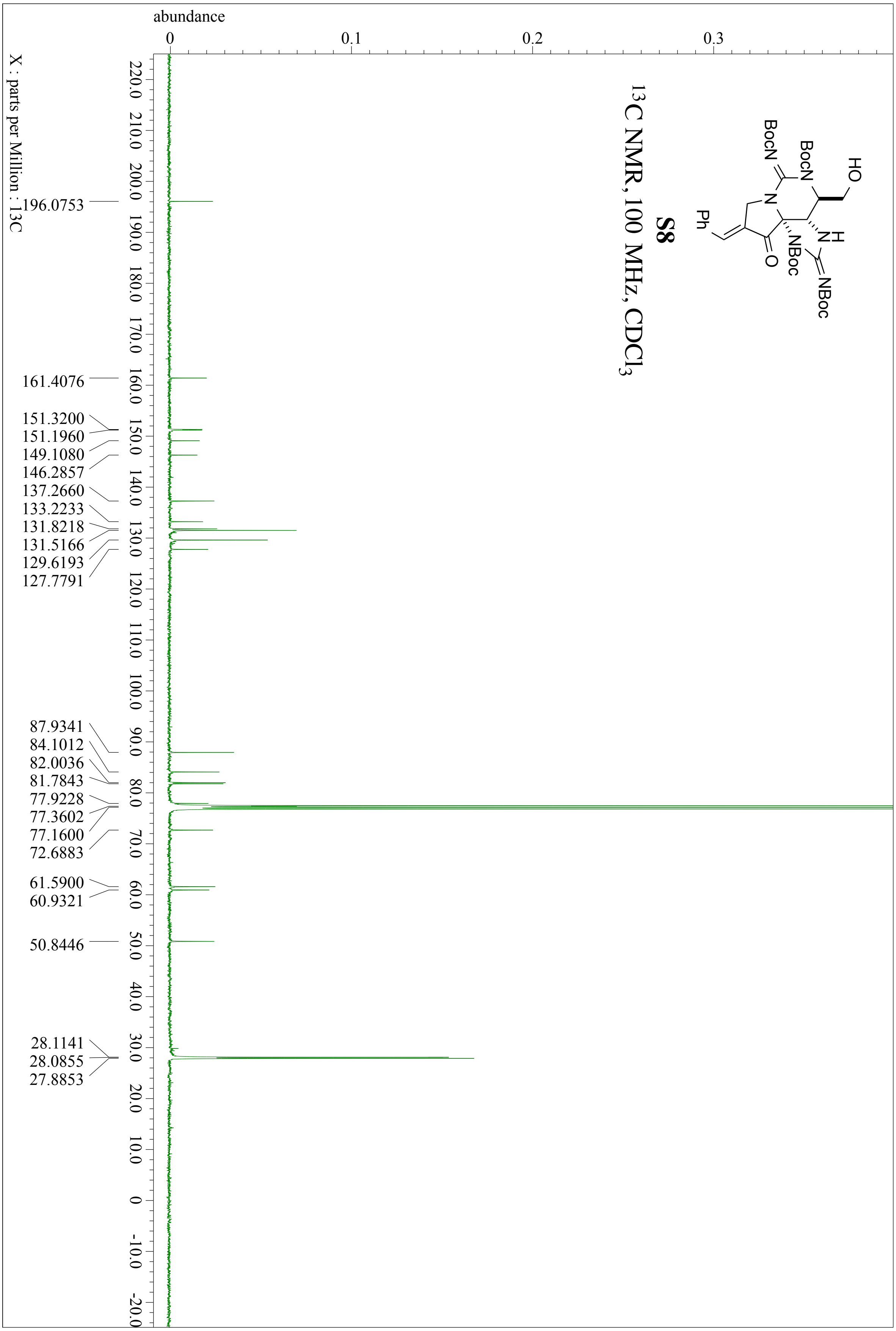
24

^{13}C NMR, 100 MHz, CDCl$_3$



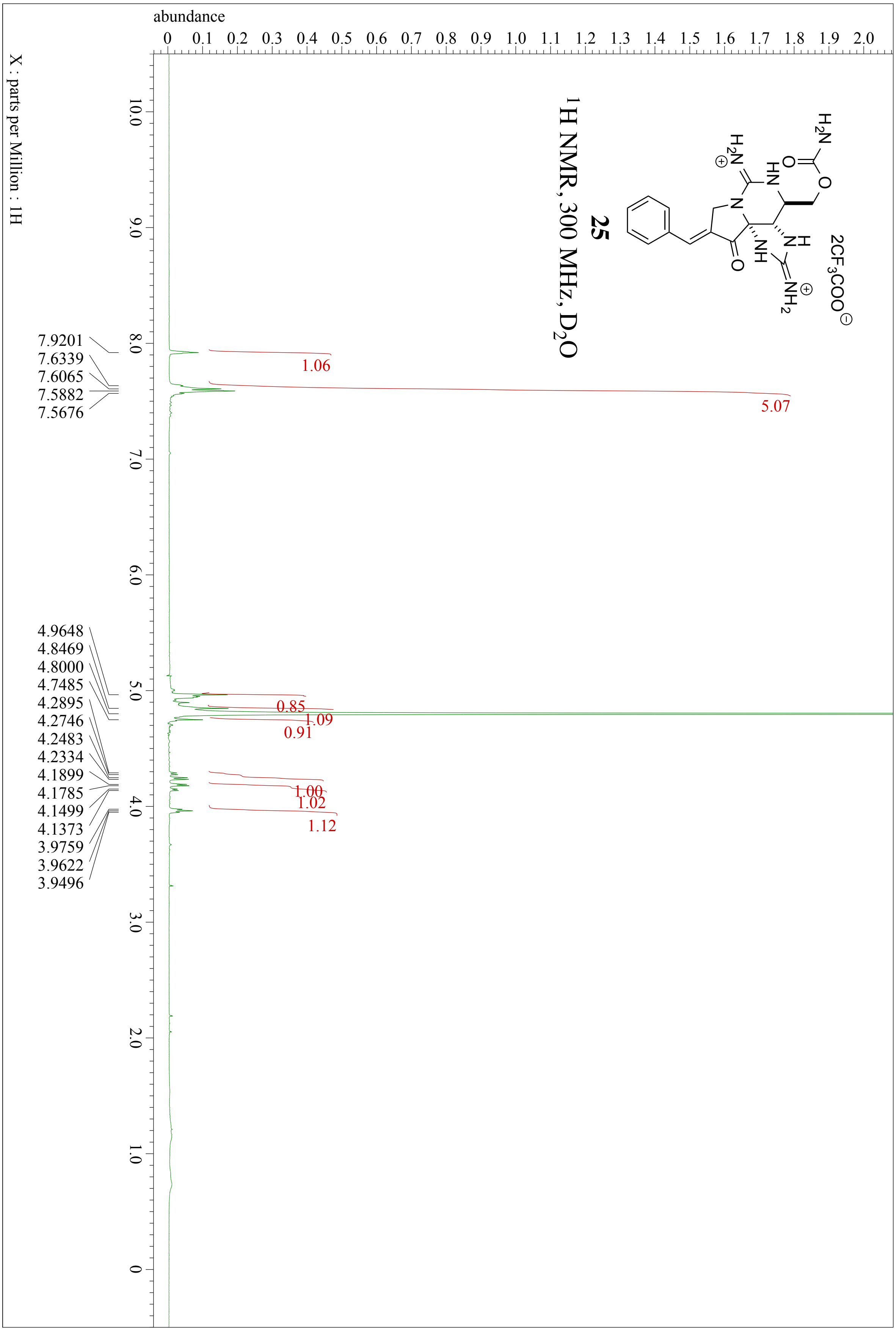
S8

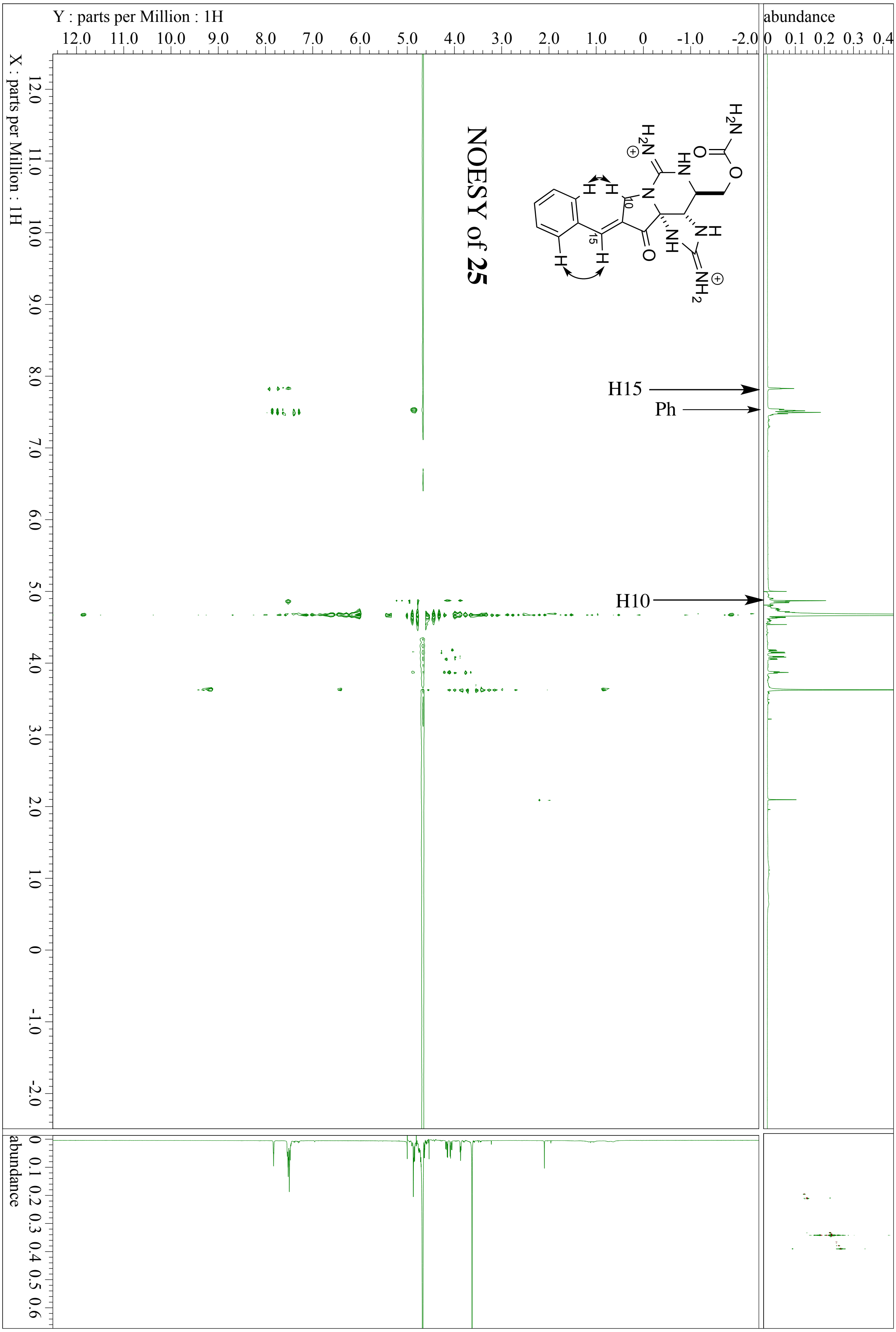
^{1}H NMR, 400 MHz, CDCl$_3$



S8

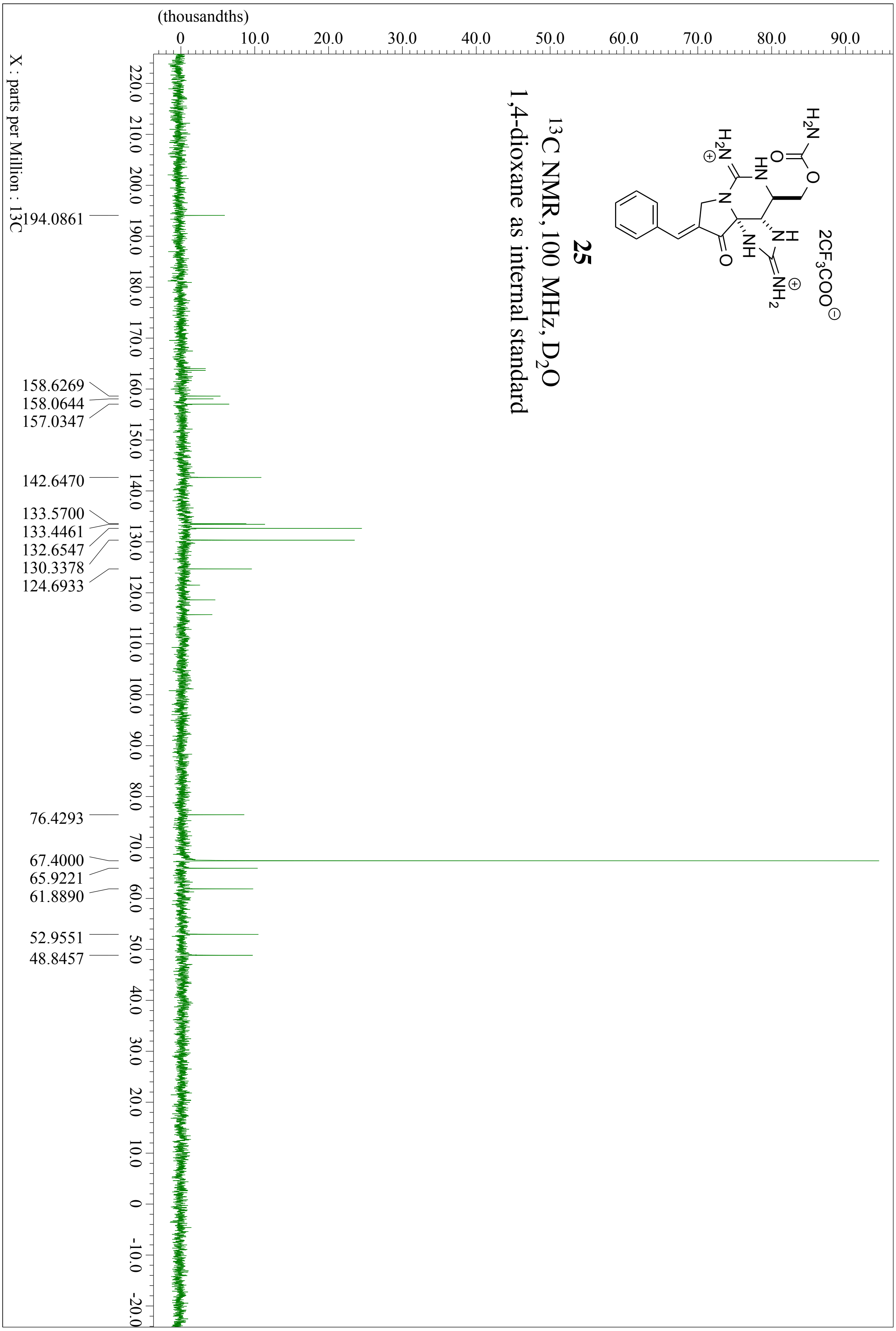
^{13}C NMR, 100 MHz, $CDCl_3$


25
¹H NMR, 300 MHz, D₂O
2CF₃COO⁻
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 1.8 1.9 2.0
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
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
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
-1.0
-2.0
0.1
0.2
0.3
0.4
0.5
0.6
H15
Ph
H10
H_2N
O
HN
N
NH
H
NH_2
H_2N
10
15
H



25

^{13}C NMR, 100 MHz, D$_2$O
1,4-dioxane as internal standard