Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting information

Rapid Mild Macrocyclization of Depsipeptides under Continuous Flow: Total Syntheses of Five Cyclodepsipeptides

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1. General procedures

All commercially available reagents including the substrates were used as received. Dry dichloromethane were purchased from Energy-Chemical. Column chromatography purifications were performed by flash chromatography using Merck silica gel 60. The reversed-phase medium pressure liquid chromatography (RP-MPLC) performed on Santai Science Inc. SepaBean® machine T with SW-5222-040-SP C18 26 × 185 mm column. The semi-preparative high-performance liquid chromatography (SP-HPLC) performed on Agilent 1260 with Nouryon Kromasil® C18 10 × 250 mm column. ^{1}H NMR, and ^{13}C NMR spectra were recorded using Q.One Instruments Quantum-I 400M spectrometer. ^{1}H NMR and ^{13}C NMR chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane. Coupling constants (*J*) are reported in Hertz (Hz). The residual solvent peak was used as an internal reference: ^{1}H NMR (chloroform δ 7.26) and ^{13}C NMR (chloroform δ 77.16). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. HRMS were obtained on Waters Xevo G2-XS QTof. UPLC-MS spectra were acquired on an Agilent Technologies 1290 Infinity LC equipped with an Agilent Technologies 6270 Quadrupole mass spectrometer.

2. Preparation for the solid-phase synthesis of cyclization precursors

2.1 General method 1 for immobilization of Fmoc-AA-OH onto trityl chloride resin

The 2-chlorotrityl chloride (2-CTC) resin was swollen in dry DCM for 15 min. Then, the swollen resin was treated with a solution of Fmoc-AA-OH (2eq., 0.100 M) and DIEA (5 eq., 0.250 M) in dry DCM (10.0 mL/ g resin) at room temperature and then shaken at the same temperature. After being shaken for 2 h, MeOH (0.1 mL/ g resin) was added to the reaction mixture. After being shaken for 15 min, the reaction mixture was filtered. The resulting lantern was rinsed with DMF (1 min × 3), DCM (1 min × 3), and then washed with MeOH (1 min × 3). The resin was dried in vacuo to afford polymer-supported Fmoc-AA-OH.

2.2 General method 2 for removal of *N*-Fmoc-protecting group:

The peptidyl resin was treated with a solution of 20 vol % 4-methylpiperidine in DMF and the mixture agitated at room temperature for 10 min, filtered and repeated once for a further 10 min. The resin was filtered and washed with DMF (1 min × 3).

2.3 General method 3 using HATU/HOAt for solid-phase peptide synthesis (SPPS):

The peptidyl resin was added a mixture of Fmoc-AA-OH (3 eq., 0.250 M), HATU (3 eq., 0.250 M), HOAt (3 eq., 0.250 M) and DIPEA (6 eq., 0.5 M) in DMF. The reaction mixture was agitated at room temperature for 2 h, filtered and repeated again with fresh reagents. The resin was filtered and washed with DMF (1 min × 3) and DCM (1 min × 3). In the case of *N*-methylamino residues resin, this step was repeated again with fresh reagents.

2.4 General method 4 for capping the free amino groups:

Fmoc-protected peptidyl resin was treated with a solution of 10 vol % acetic anhydride in pyridine and the mixture was agitated at room temperature for 5 mins. The resin was filtered and washed with DMF (1 min × 3).

2.5 General method 5 for attachment of Fmoc-βAla-OH onto α-hydroxy carboxylic acid:

The peptidyl resin was washed with dry DCM (1 min × 3), and then added a mixture of Fmoc-AA-OH (3 eq., 0.250 M), DIC (3 eq., 0.250 M), DMAP (0.9 eq., 0.075 M), HOAt (3 eq., 0.250 M) and DIPEA (6 eq., 0.5 M) in dry DCM. The reaction mixture was agitated at room temperature for 12 h. The resin was filtered and washed with DMF (1 min × 3) and DCM (1 min × 3).

2.6 General method 6 for HFIP-mediated resin cleavage:

Resin-bound peptide was cleaved from the resin by gentle agitation in a mixture of 20 vol % HFIP in DCM for 1 h. The filtrate was partially concentrated under a gentle stream of N_2 to obtain the crude product.

2.7 General method 7 for bromophenol blue test monitoring of peptide coupling and capping:

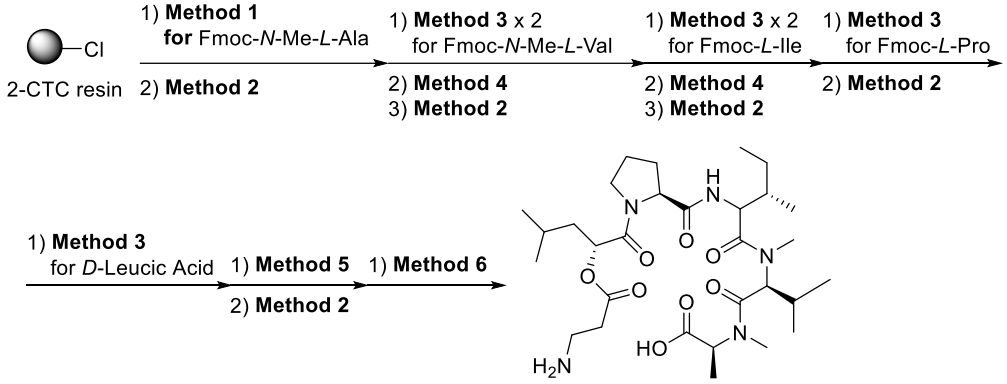
3 mg of bromophenol blue was dissolve in 3 mL of DMF to obtian the bromophenol blue test solution.

A trace amount of peptidyl resin beads was added into a small test tube. 1 to 2 drops of bromophenol blue test solution were added in to the tube[1].

Positive: If the beads are blue to blue-green, the coupling reaction is not complete and a second coupling may be required.

Negative: If the beads are yellow with a trace of green, the coupling reaction is complete.

2.8 Synthesis of Destruxin B linear precursor (1a):

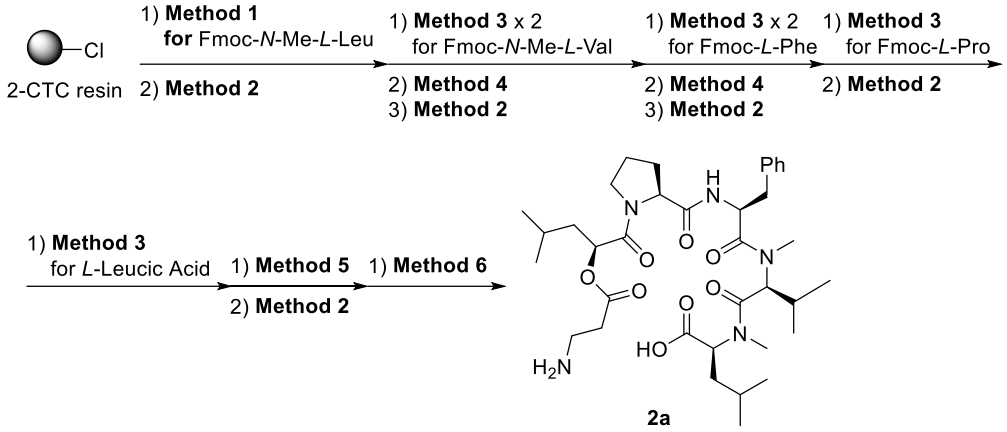


1a

Initial approach began by attaching Fmoc-N-Me-*L*-Ala to 2-CTC resin (0.55 mmol/g, 0.501 g, loading: 0.24 mmol) using **Method 1**. The *N*-Fmoc protecting group was removed using **Method 2**, this method was used for subsequent Fmoc-removals. Throughout the sequence all couplings to resin bound peptide with appropriate Fmoc-AA-OH where achieved using **Method 3**. The coupling was monitor by using **Method 7**, and another coupling was carry out once again when positive result was obtained. Unreacted amino groups was capped using **Method 4**. Attachment of Fmoc-β-Ala-OH onto *D*-Leucic Acid was achieved using **Method 5**. Resulting crude peptide was cleaved from resin by using **Method 6**, which was furthor purified by RP-MPLC using a linear gradient of 5% A to 95% A over 60 min (A: MeOH, B: H_2O) with a flow rate of 15 mL/min. Fractions were collected and analysed by UPLC-MS. Fractions identified with correct m/z were combined and lyophilised to afford the title compound **1a** as a white amorphous solid (24.4 mg, 17 % yield).

HRMS (ESI): (m/z [M+Na]+ calcd for $C_{30}H_{53}N_5O_8$: 634.3787; found: 634.3791)

2.9 Synthesis of Pseudestruxin B linear precursor (2a):

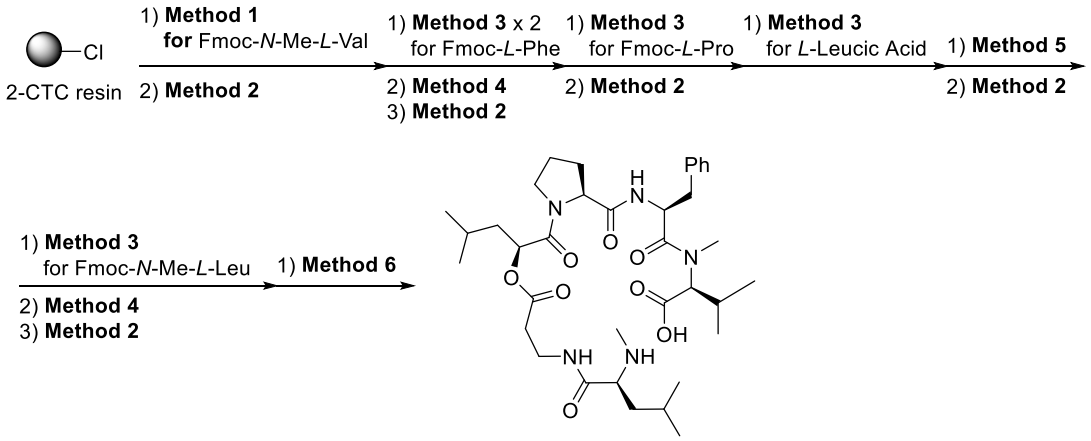


2a

Initial approach began by attaching Fmoc-*N*-Me-*L*-Leu to 2-CTC resin (0.55 mmol/g, 0.500 g, loading: 0.22 mmol) using **Method 1**. The *N*-Fmoc protecting group was removed using **Method 2**, this method was used for subsequent Fmoc-removals. Throughout the sequence all couplings to resin bound peptide with appropriate Fmoc-AA-OH where achieved using **Method 3**. The coupling was monitor by using **Method 7**, and another coupling was carry out once again when positive result was obtained. Unreacted amino groups was capped using **Method 4**. Attachment of Fmoc-β-Ala-OH onto *L*-Leucic Acid was achieved using **Method 5**. Resulting crude peptide was cleaved from resin by using **Method 6**, which was furthor purified by RP-MPLC using a linear gradient of 5% A to 95% A over 60 min (A: MeOH, B: H_2O) with a flow rate of 15 mL/min. Fractions were collected and analysed by UPLC-MS. Fractions identified with correct m/z were combined and lyophilised to afford the title compound **2a** as a white amorphous solid (19.6 mg, 13 % yield).

HRMS (ESI): (m/z [M+H]+ calcd for $C_{36}H_{57}N_5O_8$: 688.4280; found: 688.4283)

2.10 Synthesis of Pseudestruxin B linear precursor (2b):

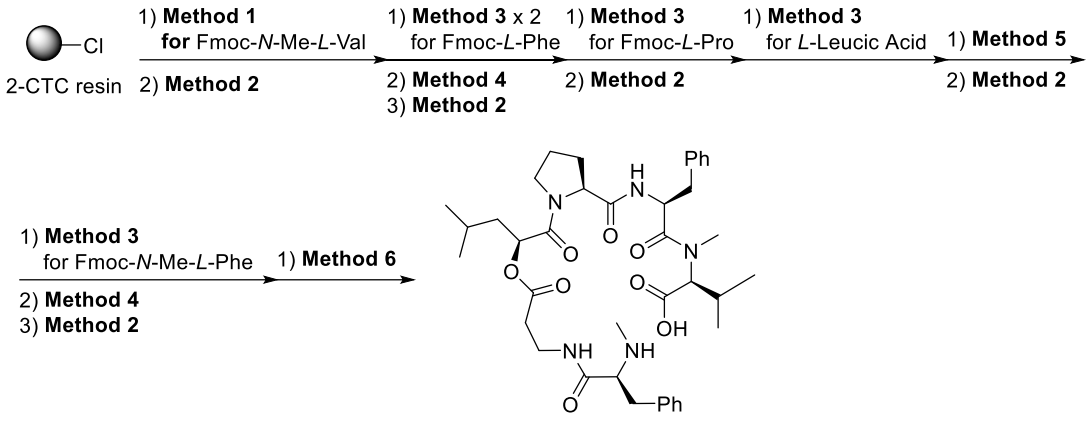


2b

Initial approach began by attaching Fmoc-*N*-Me-*L*-Val to 2-CTC resin (0.55 mmol/g, 0.500 g, loading: 0.25 mmol) using **Method 1**. The *N*-Fmoc protecting group was removed using **Method 2**, this method was used for subsequent Fmoc-removals. Throughout the sequence all couplings to resin bound peptide with appropriate Fmoc-AA-OH where achieved using **Method 3**. The coupling was monitor by using **Method 7**, and another coupling was carry out once again when positive result was obtained. Unreacted amino groups was capped using **Method 4**. Attachment of Fmoc-β-Ala-OH onto *L*-Leucic Acid was achieved using **Method 5**. Resulting crude peptide was cleaved from resin by using **Method 6**, which was furthor purified by RP-MPLC using a linear gradient of 5% A to 95% A over 60 min (A: MeOH, B: H_2O) with a flow rate of 15 mL/min. Fractions were collected and analysed by UPLC-MS.

Fractions identified with correct m/z were combined and lyophilised to afford the title compound **2b** as a white amorphous solid (91.0 mg, 53 % yield).
HRMS (ESI): (m/z [M+H]+ calcd for $C_{36}H_{57}N_5O_8$: 688.4280; found: 688.4275)

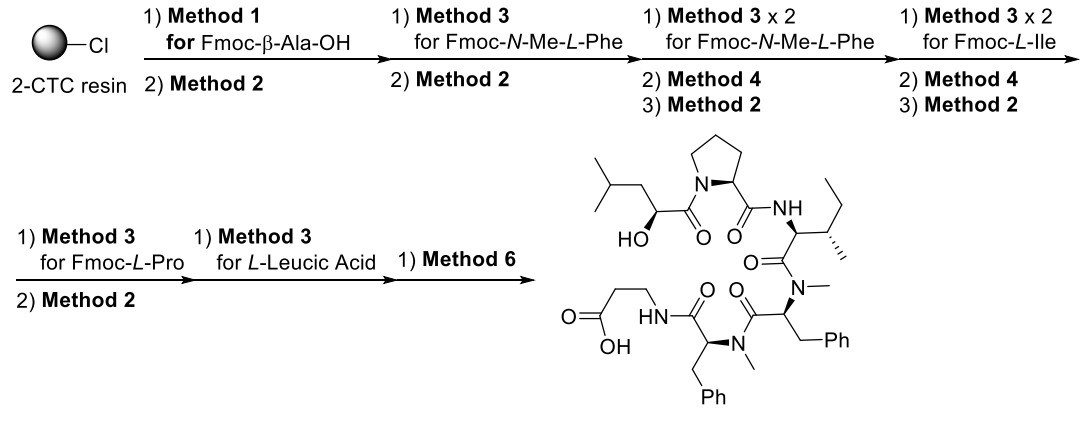
2.11 Synthesis of Isaridin A linear precursor (3a):



3a

Initial approach began by attaching Fmoc-*N*-Me-*L*-Val to 2-CTC resin (0.55 mmol/g, 0.500 g, loading: 0.24 mmol) using **Method 1**. The *N*-Fmoc protecting group was removed using **Method 2**, this method was used for subsequent Fmoc-removals. Throughout the sequence all couplings to resin bound peptide with appropriate Fmoc-AA-OH where achieved using **Method 3**. The coupling was monitor by using **Method 7**, and another coupling was carry out once again when positive result was obtained. Unreacted amino groups was capped using **Method 4**. Attachment of Fmoc-β-Ala-OH onto *L*-Leucic Acid was achieved using **Method 5**. Resulting crude peptide was cleaved from resin by using **Method 6**, which was furthor purified by RP-MPLC using a linear gradient of 5% A to 95% A over 60 min (A: MeOH, B: H_2O) with a flow rate of 15 mL/min. Fractions were collected and analysed by UPLC-MS. Fractions identified with correct m/z were combined and lyophilised to afford the title compound **3a** as a white amorphous solid (95.2 mg, 55 % yield).
HRMS (ESI): (m/z [M+H]+ calcd for $C_{39}H_{55}N_5O_8$:722.4124; found:722.4125)

2.12 Synthesis of Cladoamide A linear precursor (4a):

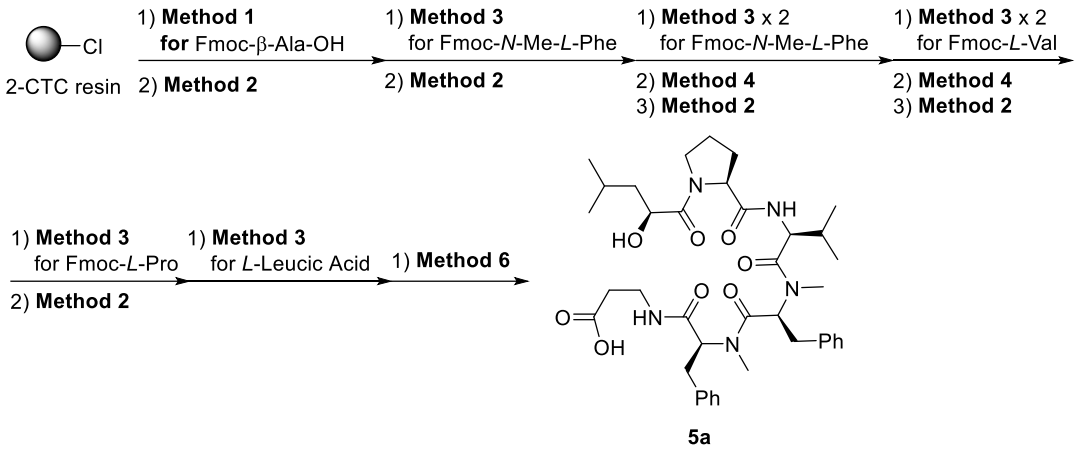


4a

Initial approach began by attaching Fmoc-β-Ala-OH to 2-CTC resin (0.55 mmol/g, 1.20 g, loading: 0.59 mmol) using **Method 1**. The *N*-Fmoc protecting group was removed using **Method 2**, this method was used for subsequent Fmoc-removals. Throughout the sequence all couplings to resin bound peptide with appropriate Fmoc-AA-OH where achieved using **Method 3**. The coupling was monitor by using

Method 7, and another coupling was carry out once again when positive result was obtained. Unreacted amino groups was capped using **Method 4**. Resulting crude peptide was cleaved from resin by using **Method 6**, which was furthor purified by RP-MPLC using a linear gradient of 5% A to 95% A over 60 min (A: MeOH, B: H_2O) with a flow rate of 15 mL/min. Fractions were collected and analysed by UPLC-MS. Fractions identified with correct m/z were combined and lyophilised to afford the title compound **4a** as a white amorphous solid (187.4 mg, 43 % yield).
HRMS (ESI): (m/z [M+Na]+ calcd for $C_{40}H_{57}N_5O_8$:758.4100; found:758.4106)

2.13 Synthesis of Cladoamide B linear precursor (5a):



5a

Initial approach began by attaching Fmoc-β-Ala-OH to 2-CTC resin (0.55 mmol/g, 1.20 g, loading: 0.61 mmol) using **Method 1**. The *N*-Fmoc protecting group was removed using **Method 2**, this method was used for subsequent Fmoc-removals. Throughout the sequence all couplings to resin bound peptide with appropriate Fmoc-AA-OH where achieved using **Method 3**. The coupling was monitor by using **Method 7**, and another coupling was carry out once again when positive result was obtained. Unreacted amino groups was capped using **Method 4**. Resulting crude peptide was cleaved from resin by using **Method 6**, which was furthor purified by RP-MPLC using a linear gradient of 5% A to 95% A over 60 min (A: MeOH, B: H_2O) with a flow rate of 15 mL/min. Fractions were collected and analysed by UPLC-MS. Fractions identified with correct m/z were combined and lyophilised to afford the title compound **5a** as a white amorphous solid (176.5 mg, 40 % yield).
HRMS (ESI): (m/z [M+Na]+ calcd for $C_{39}H_{55}N_5O_8$:744.3943; found: 744.3947)

3. Micro-flow reactor setup

Polypropylene (PP) T-shape mixers, PP fittings, PP unions, and Teflon® tubes (inner diameter: 0.8 mm) were purchased from Nanjing Runze Fluid Control Equipment Co., LTD. Solutions were introduced to a micro-flow system with syringe pumps (TYD01, purchased from Lead Fluid Technology Co., Ltd.) equipped PP syringes (10 mL).

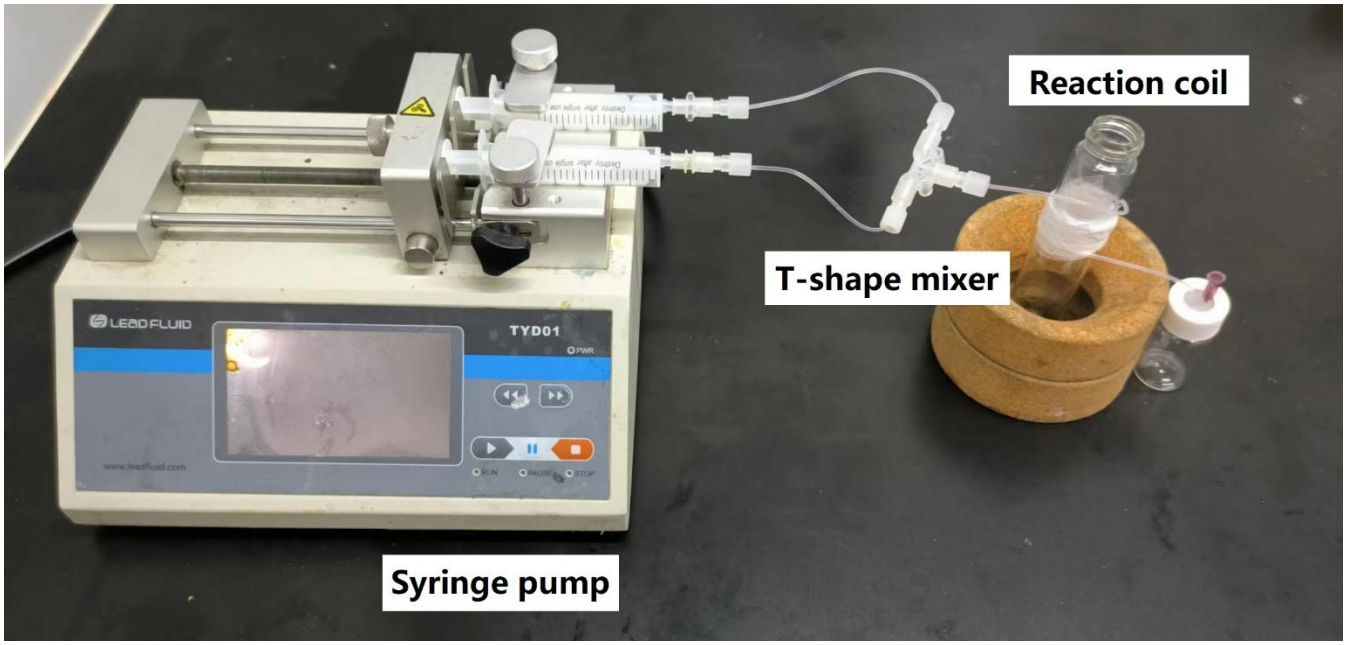


Figure S-1. Micro-flow reactor setup

4. Examination of macrocyclization in micro-flow and batch

4.1 General method 8 for micro-flow macrocyclization:

The macrocyclization flow reactor was constituted of two syringe pumps, a T-shaped mixer, and several Teflon tubes (Figure S-). A solution of linear precursors in a solvent was introduced into the T-shaped mixer via **syringe pump A**. A solution of coupling reagents and base in the solvent was also introduced into the mixer via **syringe pump B**.

4.2 General method 9 for batch type macrolactamization:

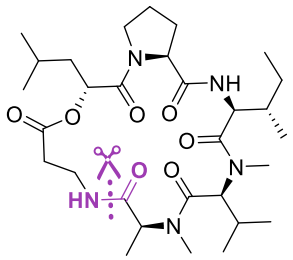
Linear precursor was dissolved in MeCN (2 mM, 8 mL), and the solution of TCFH (6 mM, 4 mL) and DIPEA (12 mM, 4 mL) in MeCN were subsequently added into it. The mixture was allowed to stir at room temperature for 0.5 h and then quenched with saturated aqueous solution of NH_4Cl (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product was performed by RP-MPLC using a linear gradient of 40% A to 90% A over 40 min (A: MeOH, B: H_2O) with a flow rate of 20 mL/min.

4.3 General method 10 for batch type macrolactonization:

A solution of linear precursor in dry CH_2Cl_2 (1.35 mM, 10 mL) was added dropwise into a solution of MNBA (6 mM) and DMAP (12 mM) in dry solvent (3.5 mL) under an argon atmosphere over 12 h

with syringe-pump. The mixture was allowed to stir at room temperature for 12 h and then quenched with saturated aqueous solution of $NaHCO_3$ (2 mL). The mixture was extracted with CH_2Cl_2 (10 mL) and the organic layers were washed with and brine (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product was performed by RP-MPLC using a linear gradient of 40% A to 90% A over 40 min (A: MeOH, B: H_2O) with a flow rate of 20 mL/min.

4.4 Procedure for synthesis of Destruxin B (1):



The batch reactions were carried out to a solution of linear precursors **1a** (9.8 mg, 16 µmol) in MeCN (8 mL, 2 mM) by using **Method 9**. The flow reactions were carried out to a solution of linear precursors **1a** (9.8 mg, 16 µmol) in DMF or MeCN (8 mL, 2 mM) by using **Method 8** on flow rate of 0.05 mL/min with different coupling reagents.

Destruxin B (**1**): as white solid (8.5 mg for TCFH-flow, 8.3 mg for HATU-flow, 8.1 mg for batch);

$[\alpha]_D^{28}$: -194 (*c* = 0.210 , CH_2Cl_2);

IR (CH_2Cl_2, ν_{max}, cm^{-1}) 3386, 3295, 2962, 2931, 2875, 1729, 1663, 1627, 1539, 1518, 1446, 1412, 1381, 1239, 1182, 727, 668, 656;

HRMS (ESI): (m/z [M+Na]+ calcd for $C_{36}H_{55}N_5O_7$: 616.3681; found: 616.3684);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.2 Hz, 1H), 7.19 (d, *J* = 9.2 Hz, 1H), 5.19 (q, *J* = 6.9 Hz, 1H), 4.94 (d, *J* = 10.9 Hz, 1H), 4.92 – 4.83 (m, 2H), 4.67 (d, *J* = 7.1 Hz, 1H), 4.11 – 3.99 (m, 1H), 3.96 – 3.86 (m, 1H), 3.52 – 3.36 (m, 1H), 3.22 (s, 3H), 3.07 (td, *J* = 11.3, 10.8, 1.9 Hz, 1H), 2.72 (s, 3H), 2.71 – 2.61 (m, 1H), 2.61 – 2.51 (m, 1H), 2.50 (d, *J* = 6.1 Hz, 1H), 2.31 (dt, *J* = 10.8, 6.6 Hz, 1H), 2.11 – 2.01 (m, 1H), 1.94 (tt, *J* = 6.8, 3.7 Hz, 4H), 1.90 – 1.82 (m, 1H), 1.47 – 1.35 (m, 3H), 1.38 – 1.32 (m, 2H), 1.30 (d, *J* = 6.8 Hz, 5H), 0.99 (d, *J* = 6.7 Hz, 4H), 0.93 (t, *J* = 6.1 Hz, 8H), 0.88 (d, *J* = 6.6 Hz, 7H), 0.89 – 0.81 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 173.5, 171.1, 170.9, 169.7, 169.7, 71.9, 60.7, 58.1, 55.4, 53.7, 46.5, 38.9, 37.5, 34.4, 33.2, 30.8, 28.9, 28.1, 27.2, 24.4, 24.4, 24.1, 23.4, 21.4, 20.0, 19.7, 15.4, 15.2, 11.4.

Spectral data of ^{1}H and ^{13}C NMR were identical to those previously reported[2].

4.5 Procedure for synthesis of Pseudodestruxin B (2) and isomer (2'):

The batch reactions were carried out to a solution of linear precursors **2a** or **2b** (11.0 mg, 16 µmol) in MeCN (8 mL, 2 mM) by using **Method 9**. The flow reactions were carried out to a solution of linear precursors **2a** or **2b** (11.0 mg, 16 µmol) in DMF or MeCN (8 mL, 2 mM) by using **Method 8** on flow rate of 0.05 mL/min with different coupling reagents.

Pseudodestruxin B (**2**): as white solid (8.7 mg for TCFH-flow, 1.0 mg for HATU-flow, 9.0 mg for batch);

$[\alpha]_D^{28}$: -108 (*c* = 0.030 , CH_2Cl_2);

IR (CH_2Cl_2, ν_{max}, cm^{-1}) 3439, 3335, 2938, 2933, 2924, 2877, 2861, 1647, 1505, 1496, 1489, 1457, 1438, 1411, 1256, 1094, 1062, 661;

HRMS (ESI): (m/z [M+K]+ calcd for $C_{36}H_{55}N_5O_7$: 708.3733; found: 708.3734);

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 173.7, 171.5, 169.8, 169.7, 168.3, 136.2, 128.8, 128.7, 127.2, 73.0, 60.8, 58.4, 57.6, 53.2, 47.1, 39.0, 38.9, 35.6, 35.4, 35.3, 32.1, 30.0, 29.7, 28.8, 27.3, 25.3, 24.6, 23.5, 23.4, 21.9, 21.6, 20.6, 19.7, 19.1.

Table S-1. ^{1}H spectral data comparison of Pseudodestruxin B (2) in $CDCl_3$

Assignment	Pseudodestruxin B (**2**)	Lit.[3]	Error
	δH	δH	$\Delta\delta$H/ppm
Pro CO			
α-CH	4.07, br d (7.0)	4.07, br d (8.4)	0
β-CH_2 a	2.32, m	2.22, m	0.1
β-CH_2 b	2.09, m	2.09, m	0
γ-CH_2 a	1.73, m	1.73, m	0
γ-CH_2 b	1.23, m	1.22, m	0.01
δ-CH	3.47, m	3.47, m	0
Phe CO			0
α-CH	4.73, m	4.73, m	0
β-CH_2 a	3.02, dd (14, 5.0)	3.01, dd (14, 4.8)	0.01
β-CH_2 b	2.91, dd (13.3, 10.7)	2.91, dd (14, 11)	0
Ar-1			0
Ar-2/6	7.27, dd (7.9, 1.6)	7.26, dd (7.8, 1.2)	0.01
Ar-3/5	7.18, m	7.19, br t (7.5)	-0.01
Ar-4	7.2, m	7.22, m	-0.02
NH	8.1, d (7.5)	8.1, d (8.0)	0
MeVal CO			0
α-CH	5.14, d (9.9)	5.15, d (11)	-0.01
β-CH	2.22, m	2.2, m	0.02
β-Me a	0.87, d (6.5)	0.86, d (6.6)	0.01
β-Me b	0.85, d (6.6)	0.84, d (6.6)	0.01
N-Me	3.16, s	3.16, s	0
MeLeu CO			0
α-CH	4.94, dd (11.5, 2.4)	4.95, dd (13, 2.4)	-0.01
β-CH_2 a	2.38, dd (12.3, 4.4)	2.38, m	0
β-CH_2 b	0.98, m	0.99, m	-0.01
γ-CH	1.54, m	1.55, m	-0.01
γ-Me	0.95, d (6.6)	0.95, d (6.0)	0
γ-Me	0.94, d (6.6)	0.94, d (6.0)	0
N-Me	2.85, s	2.85, s	0
β-Ala CO			0
α-CH_2 a	2.6, dt (15, 3)	2.61, dt (15, 3.0)	-0.01
α-CH_2 b	2.55, ddd (15,12, 3.6)	2.55, m	0
β-CH_2 a	4.13, m	4.13, m	0
β-CH_2 b	3.14, m	3.14, m	0
N-H	7.46, d (9.7)	7.45, d (10)	0.01
Oleu CO			0
α-CH	5.12, d (9.3)	5.12, br d (11)	0
β-CH_2 a	1.94, m	1.93, m	0.01
β-CH_2 b	1.18, m	1.19, m	-0.01
γ-CH	1.9, m	1.89, m	0.01
γ-Me	0.94, d (6.6)	0.94, d (6.0)	0
γ-Me	0.89, d (6.5)	0.89, d (7.2)	0

$\Delta\delta(^1H)$ values of six amino acids in synthetic **2** in $CDCl_3$. $\Delta\delta$ = δsynthetic **2** (ppm) − δnatural (ppm). ^{1}H NMR (chloroform δ 7.24)

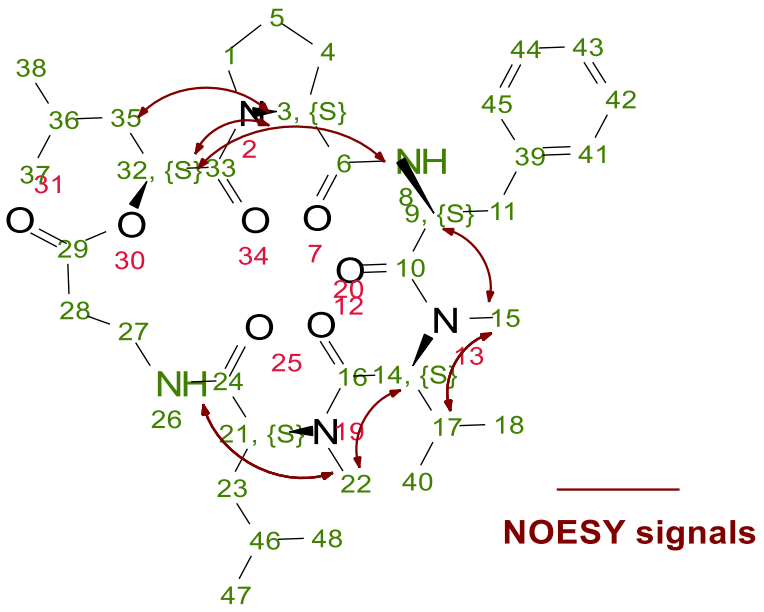


Figure S-2. NOEs signals for Pseudodestruxin B isomer (2')

Pseudodestruxin B isomer (**2'**): as pale yellow solid (1.1 mg for TCFH-flow, yield : 10%; 9.1 mg for HATU-flow, yield : 85%; 1.1 mg for batch, yield : 10%);

$[\alpha]_D^{28}$: -74 (*c* = 0.213, CH_2Cl_2);

IR (CH_2Cl_2, ν_{max}, cm^{-1}) 3331, 3056, 2960, 2929, 2873, 1728, 1637, 1514, 1469, 1438, 1420, 1388, 1370, 1348, 1264, 1184, 1078, 1022, 801, 732, 701;

HRMS (ESI): (m/z [M+Na]+ calcd for $C_{36}H_{55}N_5O_7$: 692.4007; found: 692.4002);

Table S-2. ^1H and ^{13}C spectral data of Pseudodestruxin B isomer (2') in $CDCl_3$

Assignment	2'		2	ΔδH/ppm
	δC	δH	δH	
Pro CO	169.9			
α-CH	60.9	4.07	4.08	-0.01
β-CH_2 a	31.5	2.32	2.14	0.18
β-CH_2 b		2.09	1.85	0.24
γ-CH_2 a	21.5	1.73	1.63	0.1
γ-CH_2 b		1.23	0.98	0.25
δ-CH	46.7	3.47	3.36	0.11
Phe CO	172.3			
α-CH	51.2	4.73	5.17	-0.44
β-CH_2 a	38.3	3.02	3.21	-0.19
β-CH_2 b		2.91	2.99	-0.08
Ar-1	136.3			
Ar-2/6	129.8	7.27	7.24	0.03
Ar-3/5	128.5	7.18	7.19	-0.01
Ar-4	127.1	7.2	7.22	-0.02
NH		8.1	7.54	0.56
MeVal CO	172.8			
α-CH	59.8	5.14	4.71	0.43
β-CH	27.9	2.22	2.26	-0.04
β-Me a	19.0	0.87	0.92	-0.05
β-Me b	20.0	0.85	0.84	-0.01

N-Me	30.9	3.16	3.14	0.02
MeLeu CO	170.6			
α-CH	55.3	4.94	5.23	-0.29
β-CH_2 a	36.5	2.38	1.92	0.46
β-CH_2 b		0.98	1.51	-0.53
γ-CH	25.0	1.54	1.36	0.18
γ-Me	23.7	0.95	0.92	0.03
γ-Me	21.2	0.94	0.89	0.05
N-Me	31.3	2.85	3.02	-0.17
β-Ala CO	173.8			
α-CH_2 a	33.5	2.60	2.60	0
α-CH_2 b		2.55	2.51	0.04
β-CH_2 a	35.1	4.13	3.47	0.66
β-CH_2 b		3.14	3.47	-0.33
N-H		7.46	6.68	0.78
Oleu CO	169.9			
α-CH	71.5	5.12	4.65	0.47
β-CH_2 a	39.4	1.94	1.79	0.15
β-CH_2 b		1.18	1.16	0.02
γ-CH	24.6	1.90	1.75	0.15
γ-Me	23.4	0.94	0.92	0.02
γ-Me	21.2	0.89	0.88	0.01

Δδ(^{1}H) values of six amino acids in **2'** in $CDCl_3$. Δδ = δ**2** (ppm) – δ**2'** (ppm). ^{1}H NMR (chloroform δ 7.24)

4.6 Procedure for synthesis of Isaridin A (3) and isomer (3'):

The batch reactions were carried out to a solution of linear precursors **3a** (11.6 mg, 16 μmol) in MeCN (8 mL, 2 mM) by using **Method 9**. The flow reactions were carried out to a solution of linear precursors **3a** (11.6 mg, 16 μmol) in DMF or MeCN (8 mL, 2 mM) by using **Method 8** on flow rate of 0.05 mL/min with different coupling reagents.

Isaridin A (**3**): as white solid (9.4 mg for TCFH-flow, 1.1 mg for HATU-flow, 9.0 mg for batch);

$[\alpha]_D$: -127 (*c* = 0.43, CH_2Cl_2);

IR (CH_2Cl_2, ν_{max}, cm^{-1}) 3522, 3363, 3352, 3285, 3029, 3028, 2960, 2960, 2937, 2873, 2872, 1724, 1664, 1618, 1524, 1496, 1448, 1420, 1370, 1344, 1235, 1173, 1124, 1083, 1031, 979, 917, 827, 732, 700, 658;

HRMS (ESI): (m/z [M+H]+ calcd for $C_{39}H_{53}N_5O_7$: 704.4018; found: 704.4021);

Table S-3. ^{1}H and ^{13}C NMR spectral data comparison of Isaridin A (3) in $CDCl_3$[4].

Assignment	Isaridin A (3)		Lit.[4]		Error
	*δ*C	*δ*H	*δ*C	*δ*H	Δ*δ*/ppm
Pro CO	171.8		-		
α-CH	60.9	4.05, m	-	4.05	0
β-CH_2 a	32.3	2.21, m	-	2.22	-0.01
β-CH_2 b		2.09, m	-	2.1	-0.01
γ-CH_2 a	22.0	1.75, m	-	1.74	0.01
γ-CH_2 b		1.29, m	-	1.29	0
δ-CH	47.2	3.46, m	-	3.41	0.05

Phe CO	173.7		-		
α-CH	53.3	4.71, ddd (11,7.7, 5.2)	-	4.72	-0.01
β-CH_2 a	35.8	2.98, dd (14, 5.3)	-	2.99	-0.01
β-CH_2 b		2.89, dd (14, 11)	-	2.9	-0.01
Ar-1	136.3		-		
Ar-2/6	128.9	7.27, m	-	7.27	0
Ar-3/5	129.1	7.17, m	-	7.18	-0.01
Ar-4	127.4		-		
NH		8.04, d (7.7)	-	8.04	0
MeVal CO	170.0		-		
α-CH	57.6	5.11, d (11)	-	5.12	-0.01
β-CH	27.4	2.31, m	-	2.3	0.01
β-Me a	19.1	0.86, d (6.5)	-	0.87	-0.01
β-Me b	19.4	0.77, d (7.0)	-	0.78	-0.01
N-Me	29.1	3.12, s	-	3.13	-0.01
MePhe CO	167.9		-		
α-CH	62.0	5.07, br d (10)	-	5.07	0
β-CH a	36.7	3.6, dd (13, 10)	-	3.61	-0.01
β-CH b		2.64, dd (13, 4)	-	2.64	0
Ar-1	137.2		-		
Ar-2/6	128.8	7.27, m	-	7.27	0
Ar-3/5	128.9	7.2, m	-	7.2	0
Ar-4	127.0		-		
N-Me	29.0	3.01, s	-	3.02	-0.01
β-Ala CO	173.9		-		
α-CH_2 a	35.2	2.52, dt (15, 3.1)	-	2.52	0
α-CH_2 b		2.29, m	-	2.44	-0.15
β-CH_2 a	35.6	4.08, m	-	4.08	0
β-CH_2 b		3.14, m	-	3.14	0
N-H		7.44, d (8.2)	-	7.42	0.02
Oleu CO	169.9		-		
α-CH	73.0	5.06, d (10)	-	5.07	-0.01
β-CH_2 a	38.8	1.86, ddd (15,12, 3.4)	-	1.87	-0.01
β-CH_2 b		1.14, ddd (15,11, 1.8)	-	1.15	-0.01
γ-CH	24.4	1.66, m	-	1.66	0
γ-Me	23.5	0.93, d (6.7)	-	0.94	-0.01
γ-Me	20.2	0.79, d (7.0)	-	0.8	-0.01

$\Delta\delta(^1H)$ values of six amino acids in synthetic **3** in $CDCl_3$. $\Delta\delta = \delta$synthetic **3** (ppm) − δnatural (ppm)

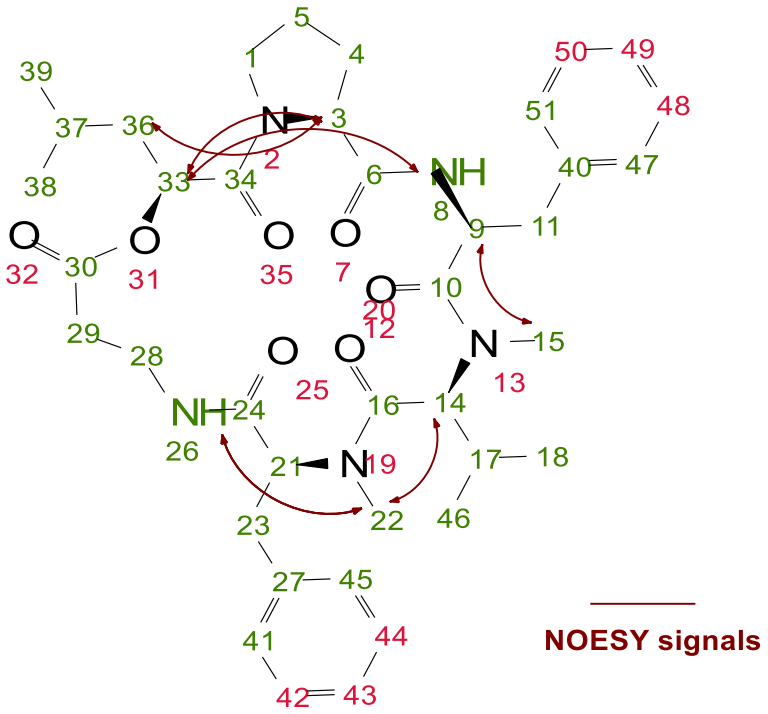


Figure S-3. NOEs signals for Isaridin A isomer (3')

Isaridin A isomer (**3'**): as pale yellow solid (0.8 mg for TCFH-flow, yield: 7%; 9.5 mg for HATU-flow, yield: 84%; 1.1 mg for batch, yield: 9%);

$[\alpha]_D^{28}$: -93 (*c* = 0.177, CH_2Cl_2);

IR (CH_2Cl_2, ν_{max}, cm^{-1}) 3532, 3330, 2959, 2935, 2871, 1726, 1635, 1618, 1514, 1498, 1468, 1454, 1419, 1347, 1265, 1184, 1125, 1103, 1079, 1031, 981, 920, 870, 826, 734, 699, 672, 656;

HRMS (ESI): (m/z [M+K]+ calcd for $C_{39}H_{53}N_5O_7$: 704.4018; found: 704.4023);

Table S-4. ^{1}H and ^{13}C NMR spectral data comparison of 3 and 3' in $CDCl_3$

Assignment	Isaridin A		Isomer		ΔδC/ppm	ΔδH/ppm
	δC	δH	δC	δH		
Pro CO	171.8		169.9		1.9	
α-CH	60.9	4.05, m	60.9	4.10, m	0.0	-0.05
β-CH_2 a	32.3	2.21, m	31.3	2.18, m	1.0	0.03
β-CH_2 b		2.09, m		1.93, m		0.16
γ-CH_2 a	22.0	1.75, m	21.5	1.64, m	0.5	0.11
γ-CH_2 b		1.29, m		1.04, m		0.25
δ-CH	47.2	3.46, m	46.7	3.39, m	0.5	0.07
Phe CO	173.7		172.2		1.5	
α-CH	53.3	4.71, ddd (11,7.7, 5.2)	51.1	5.18, q (7.2, 7.1)	2.2	-0.47
β-CH_2 a	35.8	2.98, dd (14, 5.3)	38.4	3.20, dd (14, 6.9)	-2.6	-0.22
β-CH_2 b		2.89, dd (14, 11)		3.00, dd (14, 6.8)		-0.11
Ar-1	136.3	-	136.2	-	0.1	0.00
Ar-2/6	128.9	7.27, m	128.7	7.27, m	0.2	0.00
Ar-3/5	129.1	7.17, m	129.8	7.17, m	-0.7	0.00
Ar-4	127.4	-	127.1	-	0.3	0.00
NH		8.04, d (7.7)		7.54, d (8.0)		0.50
MeVal CO	170.0		172.9		-2.9	
α-CH	57.6	5.11, d (11)	59.7	4.49, d (10.9)	-2.1	0.62
β-CH	27.4	2.31, m	27.7	1.94, m	-0.3	0.37

β-Me a	19.1	0.86, d (6.5)	17.7	0.06, d (6.6)	1.4	0.80
β-Me b	19.4	0.77, d (7.0)	19.9	0.67, d (6.5)	-0.5	0.10
N-Me	29.1	3.12, s	30.9	3.09, s	-1.8	0.03
MePhe CO	167.9		169.9		-2.0	0.00
α-CH	62.0	5.07, br d (10)	57.7	5.70, dd (12, 4.7)	4.3	-0.63
β-CH_2 a	36.7	3.6, dd (13, 10)	34.2	3.69, dd (15, 12)	2.5	-0.09
β-CH_2 b		2.64, dd (13, 4)		2.79, dd (15, 4.5)		-0.15
Ar-1	137.2		137.6		-0.4	
Ar-2/6	128.8	7.27, m	128.4	7.27, m	0.4	0.00
Ar-3/5	128.9	7.2, m	129.0	7.20, m	-0.1	0.00
Ar-4	127.0		126.8		0.2	0.00
N-Me	29.0	3.01, s	31.7	3.07, s	-2.7	-0.06
β-Ala CO	173.9		173.7		0.2	
α-CH_2 a	35.2	2.52, dt (15, 3.1)	33.5	2.67, ddd (17, 5.9, 3.4)	1.7	-0.15
α-CH_2 b		2.29, m		2.61, ddd (17, 8.6, 3.8)		-0.32
β-CH_2 a	35.6	4.08, m	35.2	3.54, m	0.4	0.54
β-CH_2 b		3.14, m		3.54, m		-0.40
N-H		7.44, d (8.2)		6.76, t (6.2)		0.68
Oleu CO	169.9		169.5		0.4	
α-CH	73.0	5.06, d (10)	71.5	4.69, d (11)	1.5	0.37
β-CH_2 a	38.8	1.86, ddd (15,12, 3.4)	39.4	1.82, m	-0.6	0.04
β-CH_2 b		1.14, ddd (15,11, 1.8)		1.19, m		-0.05
γ-CH	24.4	1.66, m	24.7	1.82, m	-0.3	-0.16
γ-Me	23.5	0.93, d (6.7)	23.4	0.94, d (7.0)	0.1	-0.01
γ-Me	20.2	0.79, d (7.0)	21.3	0.92, d (7.0)	-1.1	-0.13

$\Delta\delta(^1H)$ and $\Delta\delta(^{13}C)$ values of six amino acids in **3'** in $CDCl_3$. $\Delta\delta = \delta$**3** (ppm) – δ**3'** (ppm)

4.7 Additional conditions of *N*-Me macrolactamization under flow:

Table S-5. Additional conditions for synthesis of Pseudestruxin B

Entry	Reagent	Base	Solvent	Equiv.[a]	Conc. [mM]	% p:p*[b]
1	HATU	DIPEA	DMF	3-6	1 (50 °C)	8:92
2	HATU	DIPEA	DMF	3-6	1 (-10 °C)	9:90
3	HATU	DIPEA	DMF	3-6	0.5	10:90
4	HATU	DIPEA	DMF	3-6	1	11:89
5	TCFH	NMI	DMF	1.5-3	1	89:11
6	TCFH	NMI	MeCN	1.5-3	1	90:10
7	TCFH	NMI	MeCN	1.5-3	0.5	89:11
8	TCFH	NMI	MeCN	1.5-3	2	88:12
9	TCFH	NMI	MeCN	1.5-1.5	1	23:4

[a] The ratio of Reagent-Base was shown. [c] Ratio of p and p' was determined by HPLC-UV analysis against biphenyl as internal standard, and p' means conform isomer.

4.8 Procedure for synthesis of Cladoamide A (4):

The batch reactions were carried out to a solution of linear precursors **4a** (10.0 mg, 13.9 µmol) in dry CH_2Cl_2 (10 mL, 1.39 mM) by using **Method 10**. The flow reactions were carried out to a solution of linear precursors **4a** (10 mg, 13.9 µmol) in in dry CH_2Cl_2 or MeCN (6.9 mL, 2 mM) by using **Method 8** on flow rate of 0.005 mL/min with different coupling reagents. The reactions at 0.1 mM were carried out by diluting previous 2 mM solution 10 times.

$[M + H]^+$ calculated for **dimer 4'** $C_{78}H_{107}N_{10}O_{14}$: 1407.8; observed 1407.5.
Cladoamide A **(4)**: white solid (4.7 mg for flow, 3.0 mg for batch)
$[\alpha]_D^{28}$: -142 (*c* = 0.033, CH_2Cl_2);
IR (CH_2Cl_2, ν_{max}, cm^{-1}) 3479, 3357, 2956, 2925, 2872, 2851, 1728, 1663, 1641, 1615, 1497, 1452, 1439, 1414, 1372, 1255, 1232, 1181, 1125, 1084, 1066, 991, 777, 749, 733, 698, 671, 661;
HRMS (ESI): (m/z [M+Na]+ calcd for $C_{40}H_{55}N_5O_7$: 740.3994; found: 740.4000);

Table S-6. ^{1}H and ^{13}C NMR spectral data comparison of 4 in CD_3OD

Assignment	Cladoamide A		Lit.[5]		Error	Δδ/ppm
	δC	δH	δC	δH	δC	δH
Oleu CO	172.5		172.4			0.1
α-CH	74.3	4.92(overlapped)	74.2	4.92(overlapped)	0.1	0
β-CH2 a	39.3	1.46, dd (10.7,14)	39.3	1.46, dd (11.0,14.7)	0	0
β-CH2 b		1.79(overlapped)		1.79(overlapped)		0
γ-CH	26.0	1.86(overlapped)	26.0	1.86(overlapped)	0	0
γ-Me	21.5	0.99, d (6.6)	21.5	0.99, d (6.5)	0	0
γ-Me	23.9	1.04, d (6.6)	23.8	1.04, d (6.6)	0.1	0
Pro CO	173.9		173.8		0.1	
α-CH	62.6	4.28, d (7.9)	62.6	4.28, d (7.6)	0	0
β-CH	33.4	2.34, m	33.3	2.34, m	0.1	0
γ-CH a	23.4	1.72, m	23.3	1.72, m	0.1	0
γ-CH b		1.98(overlapped)		1.98(overlapped)		0
δ-CH	48.6	3.55, dd (4.7, 9.4)	48.6	3.55, dd (4.3, 9.6)	0	0
Ile CO	176.1		176.0		0.1	
α-CH	56.8	4.58, m	56.7	4.59, br t (8.2)	0.1	-0.01
β-CH	38.2	1.96(overlapped)	38.1	1.96(overlapped)	0.1	0
β-CH2 a	26.9	1.33, m	26.8	1.33, (overlapped)	0.1	0
β-CH2 b		1.53,m		1.53,m		0
β-Me	11.5	0.9, t (7.4)	11.4	0.9, t (7.4)	0.1	0
γ-Me	15.5	0.84, d (7.0)	15.5	0.84, d (7.0)	0	0
N-H		7.96Disappeared		7.97, d (8.3)		x
MePhe1 CO	173.3		173.2		0.1	
α-CH	53.4	5.5, dd (6.5, 9.4)	53.4	5.49, dd (6.4, 9.4)	0	0.01
β-CH a	34.8	1.84(overlapped)	34.8	1.84(overlapped)	0	0
β-CH b		2.84, dd (9.4, 15.4)		2.85, dd (9.6, 15.6)		-0.01
Ar-1	138.0		138.0		0	
Ar-2/6	129.5	6.98, d (7.5)	129.4	6.98, d (7.5)	0.1	0
Ar-3/5	130.1	7.24, t (7.5)	130.0	7.24, t (7.4)	0.1	0
Ar-4	128.1	7.18, t (7.5)	128.0	7.18, t (7.3)	0.1	0
N-Me	32.1	3.13, s	32.0	3.13, s	0.1	0
MePhe2 CO	170.4		170.3		0.1	
α-CH	64.2	5.08, br t (7.3)	64.2	5.08, br t (7.5)	0	0

β-CH a	35.7	2.28(overlapped)	35.7	2.28(overlapped)	0	0
β-CH b		3.05, dd (6.4, 13.9)		3.05, dd (6.7, 13.9)		0
Ar-1	139.0		138.9		0.1	
Ar-2/6	130.5	7.04, d (7.5)	130.5	7.04, d (7.4)	0	0
Ar-3/5	130.1	7.1(overlapped)	130.0	7.1(overlapped)	0.1	0
Ar-4	128.1	7.08(overlapped)	128.0	7.08(overlapped)	0.1	0
N-Me	29.8	2.81, s	29.7	2.81, s	0.1	0
β-Ala CO	174.9		174.8		0.1	
α-CH2 a	35.7	2.46, ddd (3.8,12.1, 15.6)	35.7	2.46, ddd (4.0, 12.1, 15.9)	0	0
α-CH2 b		2.58, br dt (15.6, 3.0)		2.58, br dt (15.5, 3.1)		0
β-CH2 a	36.7	3.11(overlapped)	36.6	3.1(overlapped)	0.1	0.01
β-CH2 b		3.95, m		3.95, m		0
N-H		8.02, Disappeared		8.03, d (8.7)		x

$\Delta\delta(^{1}H)$ and $\Delta\delta(^{13}C)$ values of six amino acids in synthetic **4** in CD_3OD. $\Delta\delta$ = δsynthetic **4** (ppm) − δnatural (ppm)

4.9 Procedure for synthesis of Cladoamide B (5):

The batch reactions were carried out to a solution of linear precursors **5a** (10.0 mg, 13.6 µmol) in dry CH_2Cl_2 (10 mL, 1.35 mM) by using **Method 10**. The flow reactions were carried out to a solution of linear precursors **5a** (10 mg, 13.6 µmol) in in dry CH_2Cl_2 or MeCN (6.8 mL, 2 mM) by using **Method 8** on flow rate of 0.005 mL/min with different coupling reagents. The reactions at 0.1 mM were carried out by diluting previous 2 mM solution 10 times.

$[M + H]^+$ calculated for **dimer 5'** $C_{80}H_{111}N_{10}O_{14}$: 1435.8; observed 1435.6.
Cladoamide B **(5)**: white solid (5.8 mg for flow, 3.2 mg for batch);
$[\alpha]_D^{28}$: -183 (*c* = 0.513, CH_2Cl_2);
IR (CH_2Cl_2, ν_{max}, cm^{-1}) ;
HRMS (ESI): (m/z [M+Na]+ calcd for $C_{39}H_{53}N_5O_7$: 726.3837; found: 726.3840);

Table S-7. ^{1}H and ^{13}C NMR spectral data comparison of 5 in CD_3OD

Assignment	Cladoamide B		Lit.[5]		Error	Δδ/ppm
	δC	δH	δC	δH	δC	δH
Oleu CO	172.6		172.6, C		0	
α-CH	74.3	4.91, overlapped	74.2, CH	4.91, d (10.7)	0.1	0
β-CH_2 a	39.3	1.47, dd (10.2, 14.5)	39.3, CH_2	1.47, dd (10.7, 13.8)	0	0
β-CH_2 b		1.79, overlapped		1.79		0
γ-CH	26.0	1.85, overlapped	26.0, CH	1.85	0	0
γ-Me	21.6	0.99, d (6.6)	21.5, CH_3	0.99, d (6.4)	0.1	0
γ-Me	23.9	1.04, d (6.6)	23.8, CH_3	1.04, d (6.7)	0.1	0
Pro CO	173.9		173.9, C		0	
α-CH	62.6	4.30, dd (8.4, 2.1)	62.6, CH	4.30, d (7.9)	0	0
β-CH	33.4	2.34, m	33.3, CH_2	2.34, m	0.1	0
γ-CH_2 a	23.3	1.73, overlapped	23.3, CH_2	1.73, m	0	0
γ-CH_2 b		1.98, m		1.98, m		0
δ-CH	overlapped	3.56, dd (4.3, 9.3)	48.6, CH_2	3.56, dd (4.7, 9.4)	x	0
Val CO	175.9		175.9, C		0	
α-CH	57.8	4.57, d (7.9)	57.7, CH	4.58	0.1	-0.01
β-CH	31.7	2.17, m	31.6, CH	2.16, m	0.1	0.01

β-Me a	19.2	0.88, d (7.0)	19.2, CH_3	0.88, d (6.9)	0	0
β-Me b	19.3	1.00, d (6.7)	19.2, CH_3	1.00, d (6.6)	0.1	0
N-H		Disappeared		7.97, d (8.1)		x
MePhe1 CO	173.5		174.8, C		-1.3	
α-CH	53.5	5.49, dd (6.5, 9.5)	53.5, CH	5.49, dd (6.3, 9.6)	0	0
β-CH_2 a	34.9	1.86, overlapped	34.9, CH_2	1.86	0	0
β-CH_2 b		2.83, dd (9.4, 15.3)		2.82, dd (9.5, 15.6)		0.01
Ar-1	138.0		138.0, C		0	
Ar-2/6	129.5	6.99, d (7.3)	129.4, CH	6.98, d (7.6)	0.1	0.01
Ar-3/5	130.0	7.24, t (7.2)	130.0, CH	7.24, t (7.3)	0	0
Ar-4	128.1	7.18, t (7.4)	128.1, CH	7.17, t (7.3)	0	0.01
N-Me	32.0	3.13, s	32.0, CH_3	3.13, s	0	0
MePhe2 CO	170.4		170.4, C		0	
α-CH	64.2	5.09, dd (6.9, 8.2)	64.2, CH	5.09, dd (6.4, 8.5)	0	0
β-CH_2 a	35.7	2.29, overlapped	35.6, CH_2	2.29, dd (8.5, 13.9)	0.1	0
β-CH_2 b		3.05, dd (6.5, 14.2)		3.05, dd (6.4, 13.9)		0
Ar-1	139.0		138.9, C		0.1	
Ar-2/6	130.5	7.04, d (7.6)	130.5, CH	7.04, d (7.5)	0	0
Ar-3/5	130.1	7.10 , overlapped	130, CH	7.09	0.1	0.01
Ar-4	128.1	7.08, overlapped	128.1, CH	7.07	0	0.01
N-Me	29.8	2.81, s	29.7, CH_3	2.81, s	0.1	0
β-Ala CO	174.8		174.8, C		0	
α-CH_2 a	35.7	2.46, ddd (3.3, 11.6, 15.3)	35.6, CH_2	2.46, ddd (3.3, 11.8, 15.6)	0.1	0
α-CH_2 b		2.58, dt (3.1, 15.6)		2.58, dt (3.3, 15.6)		0
β-CH_2 a	36.6	3.13, overlapped	36.5, CH_2	3.13	0.1	0
β-CH_2 b		3.94, m		3.94, m		0
N-H		8.02, d (9.2)		8.01, d (9.2)		0.01

$\Delta\delta(^1H)$ and $\Delta\delta(^{13}C)$ values of six amino acids in synthetic **4** in CD_3OD. $\Delta\delta$ = δsynthetic **4** (ppm) − δnatural (ppm)

5. Supporting References

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6. NMR Spectra

6.1 Destruxin B (1)

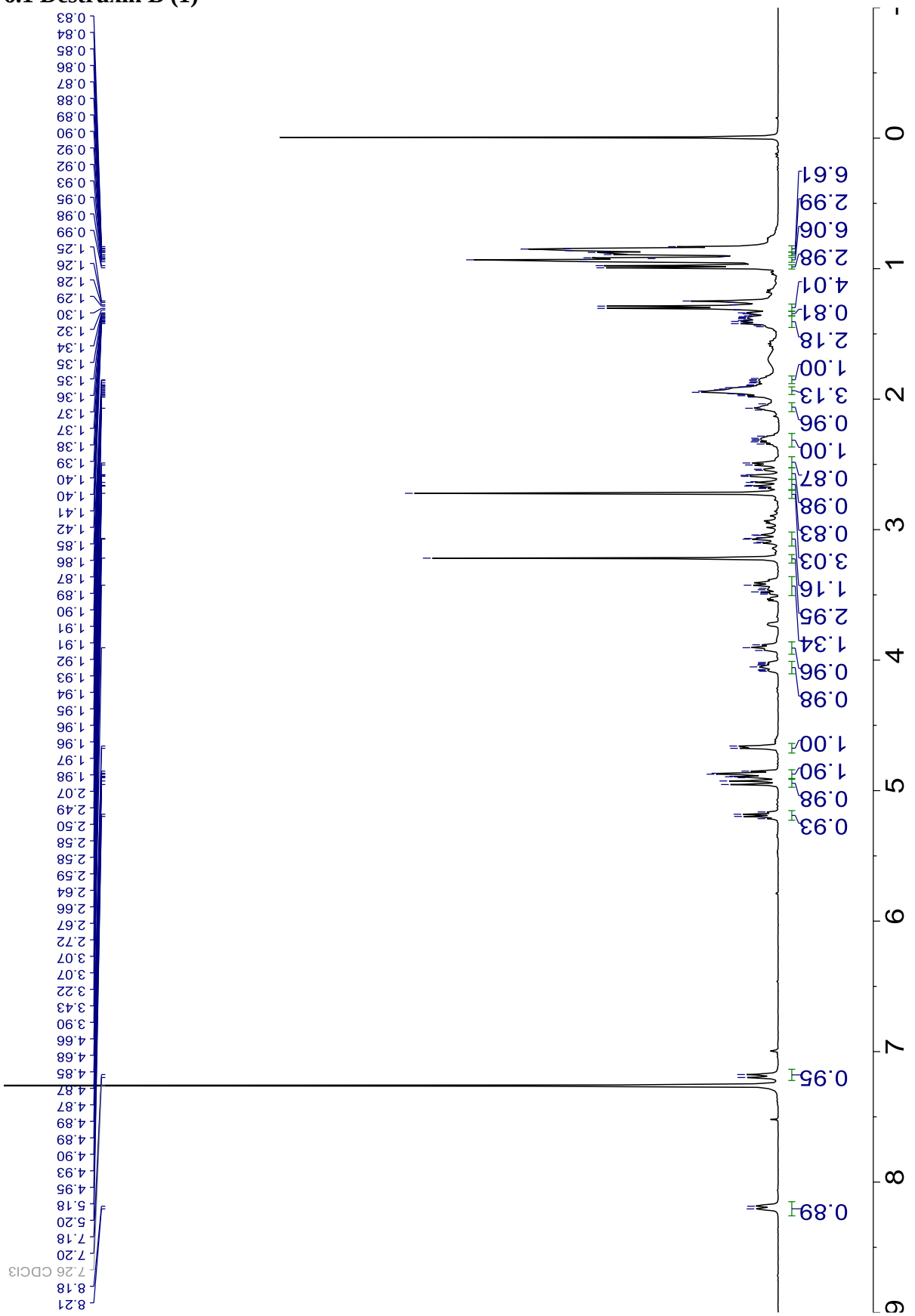

Figure S-4. ^{1}H NMR spectrum of 1 ($CDCl_3$, 298 K, 400 MHz)

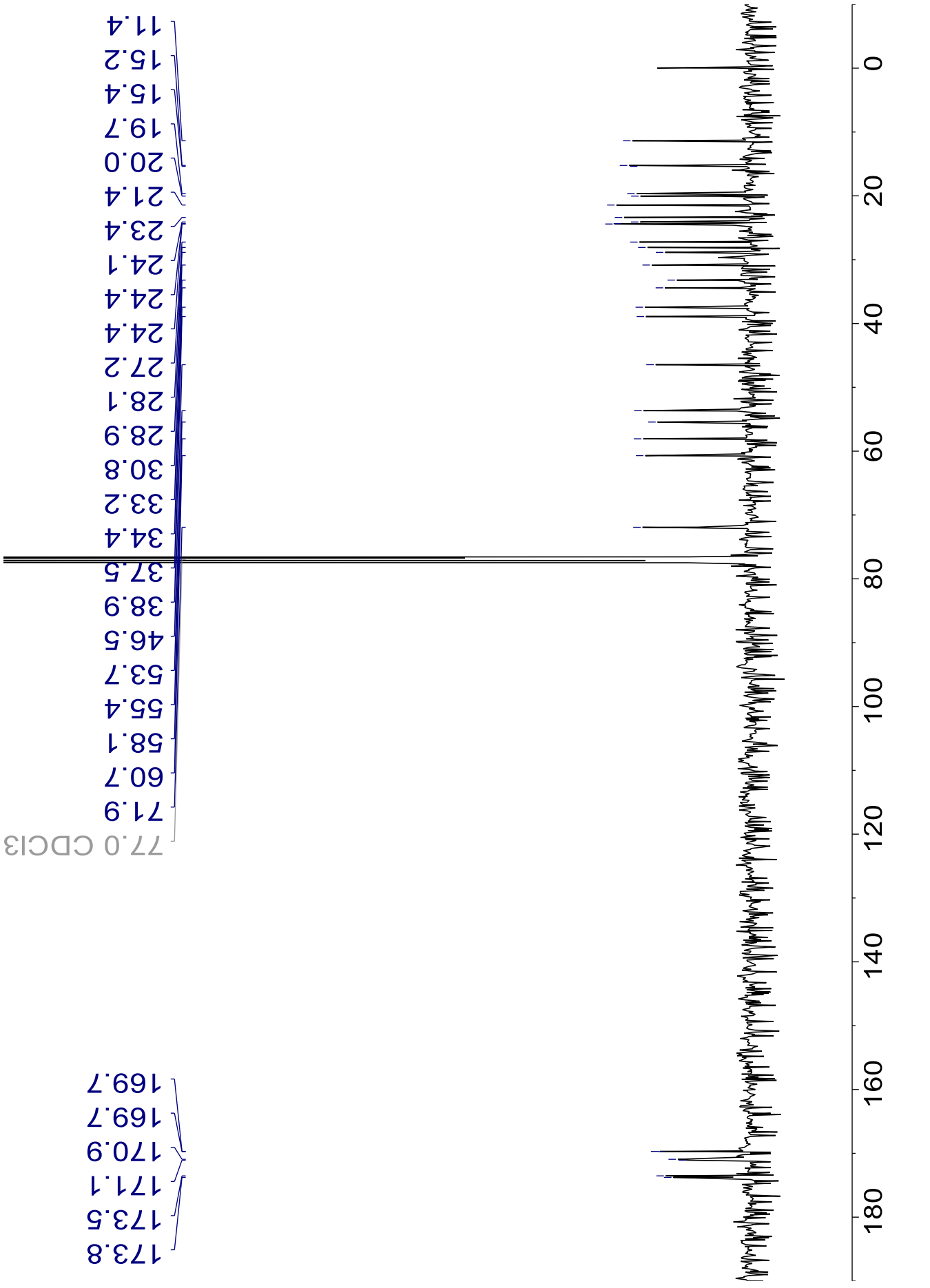

Figure S-5. ^{13}C NMR spectrum of 1 ($CDCl_3$, 298 K, 101 MHz)

6.2 Pseudodestruxin B (2)

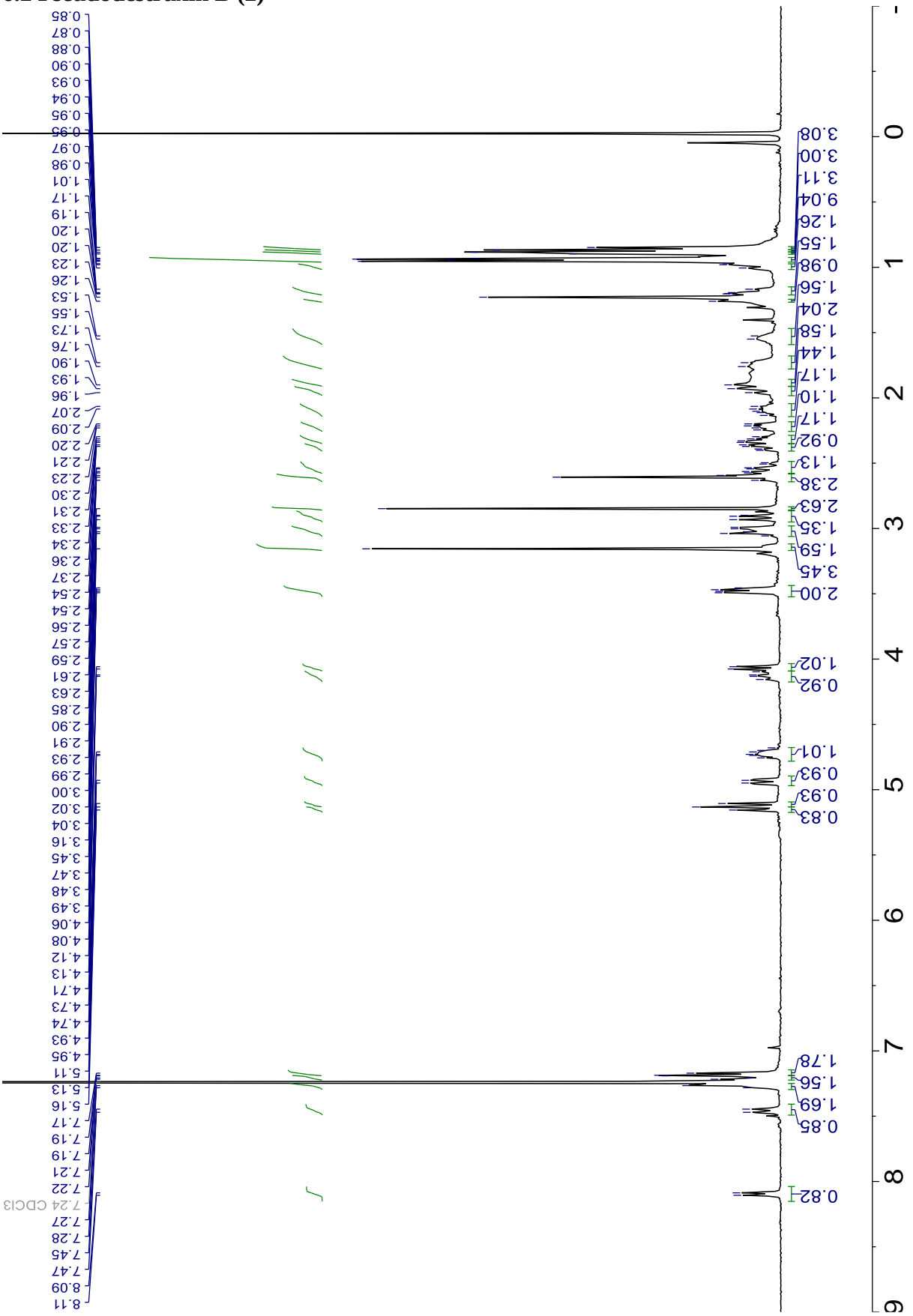

Figure S-6. ^{1}H NMR spectrum of 2 ($CDCl_3$, 298 K, 400 MHz)

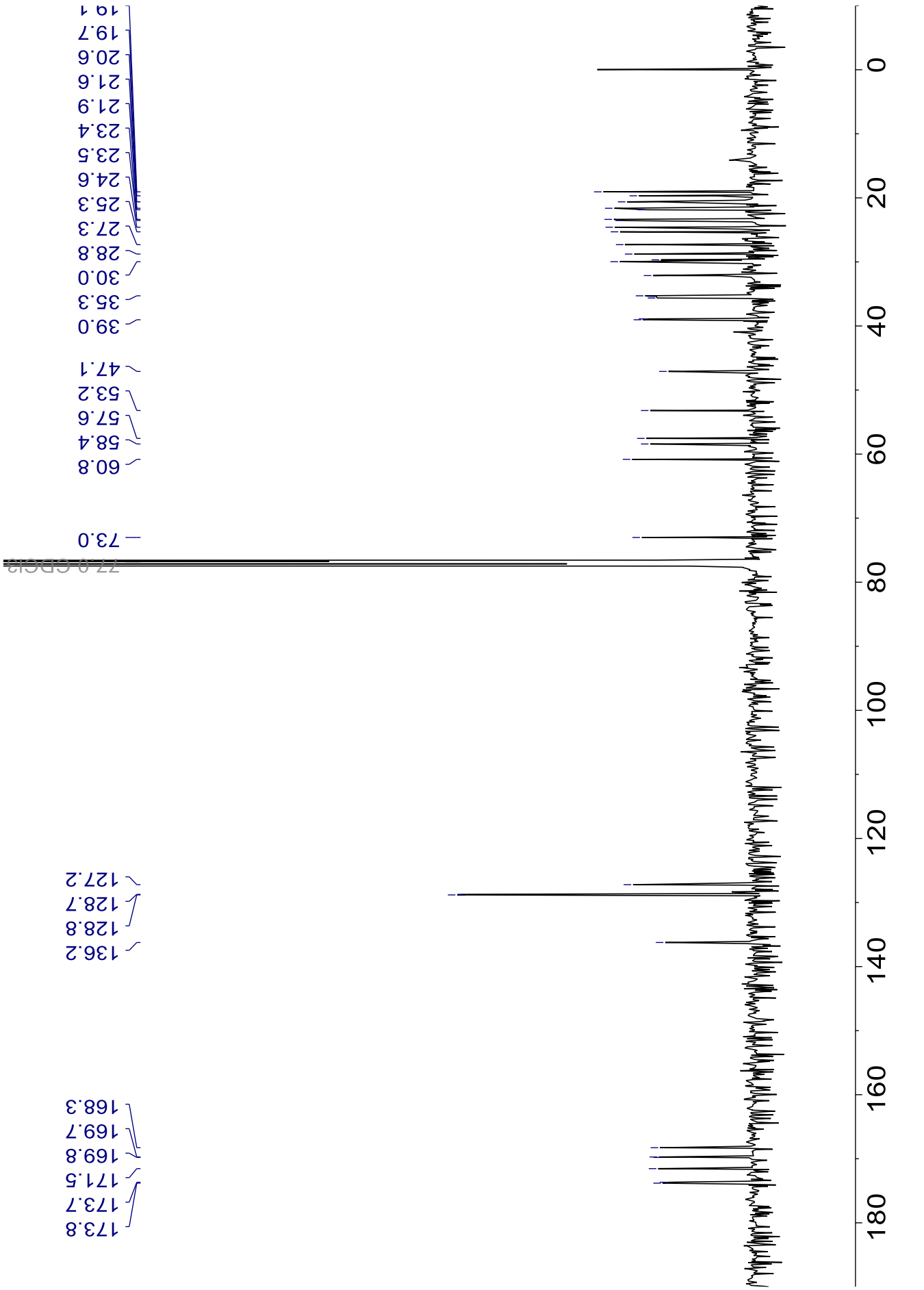

Figure S-7. ^{13}C NMR spectrum of 2 ($CDCl_3$, 298 K, 101 MHz)

6.3 Pseudodestruxin B isomer (2')

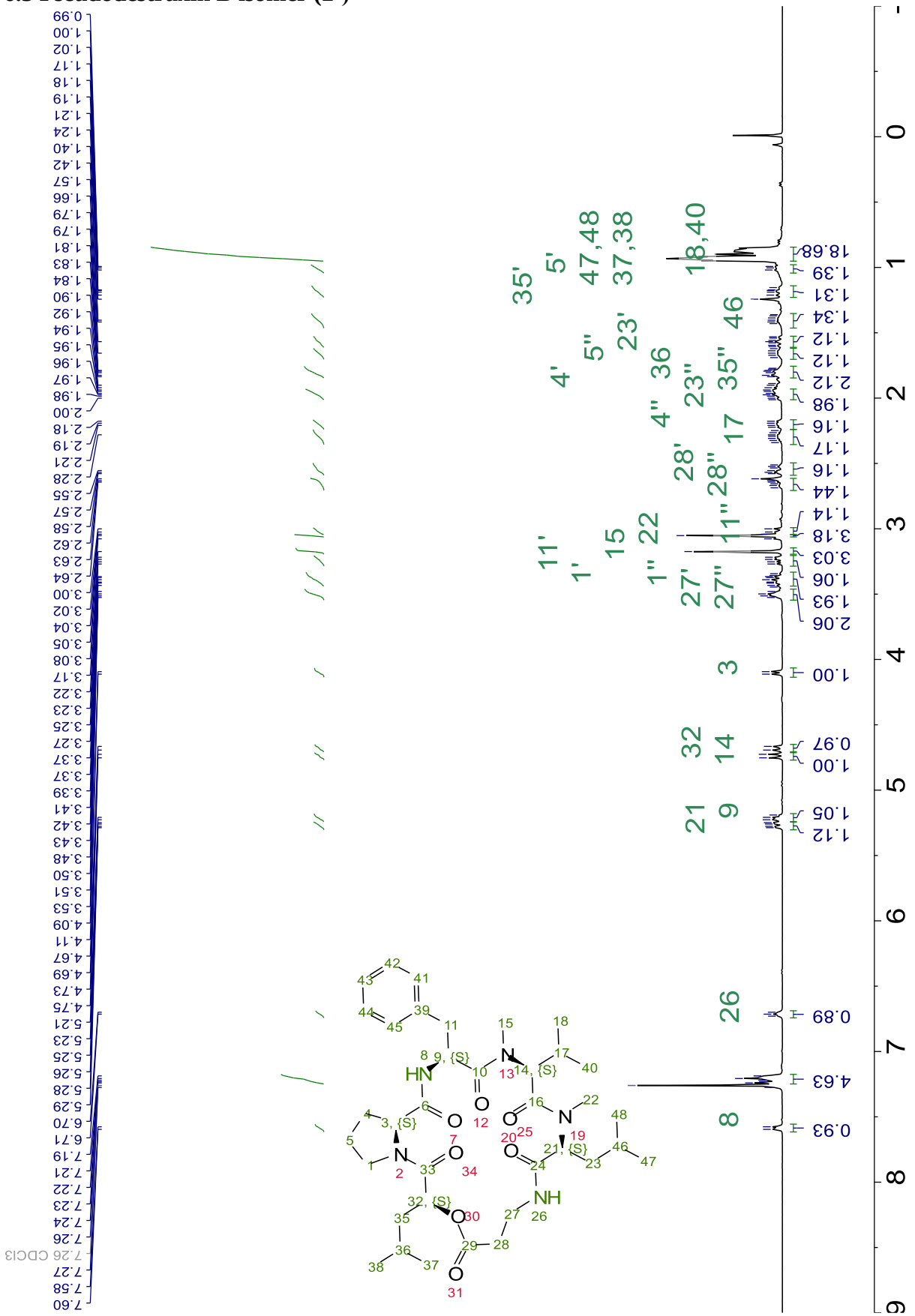

Figure S-8. ^{1}H NMR spectrum of 2' (CDCl$_3$, 298 K, 400 MHz)

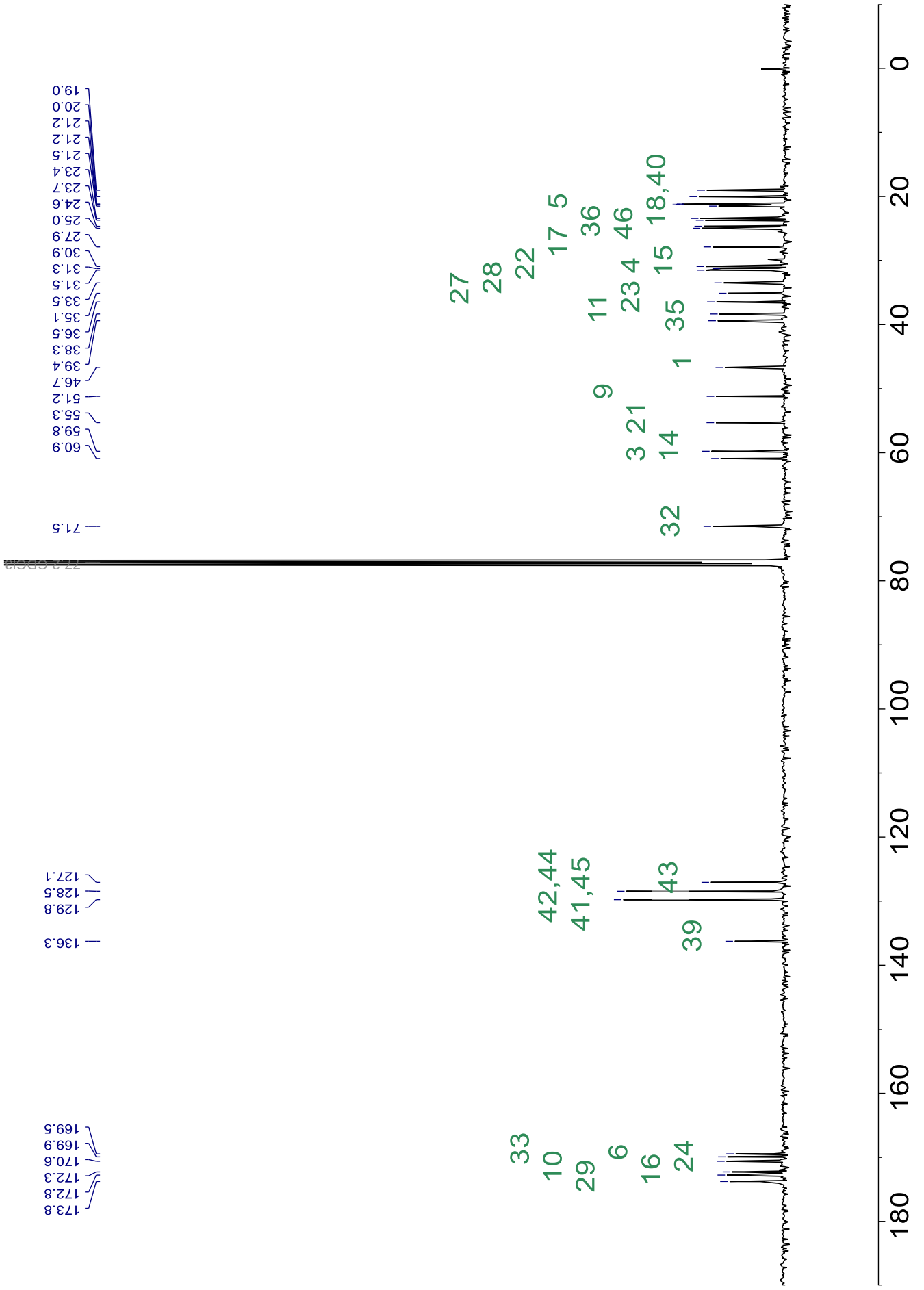

Figure S-9. ^{13}C NMR spectrum of 2' ($CDCl_3$, 298 K, 101 MHz)

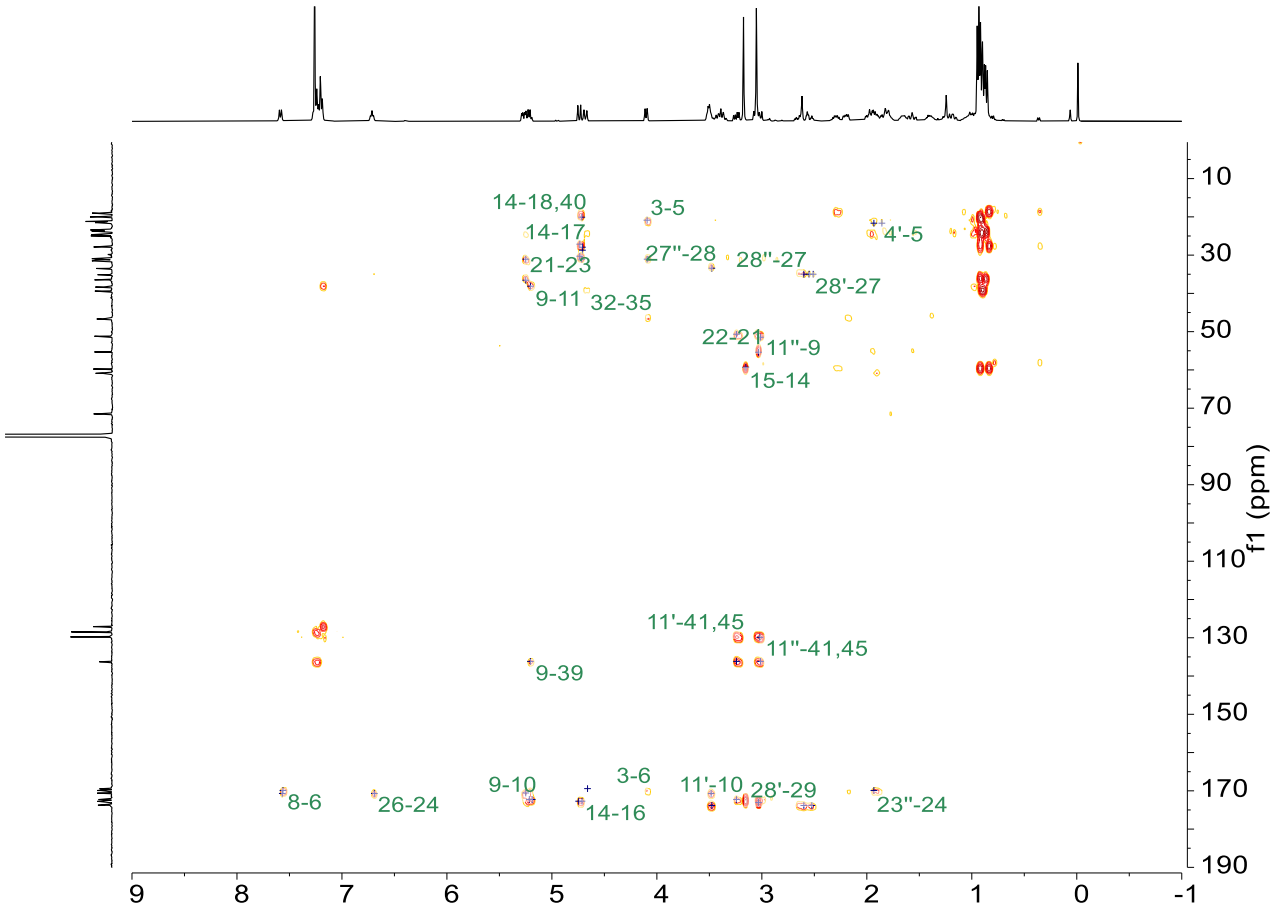

Figure S-10. HMBC spectra for Pseudodestruxin B (2')

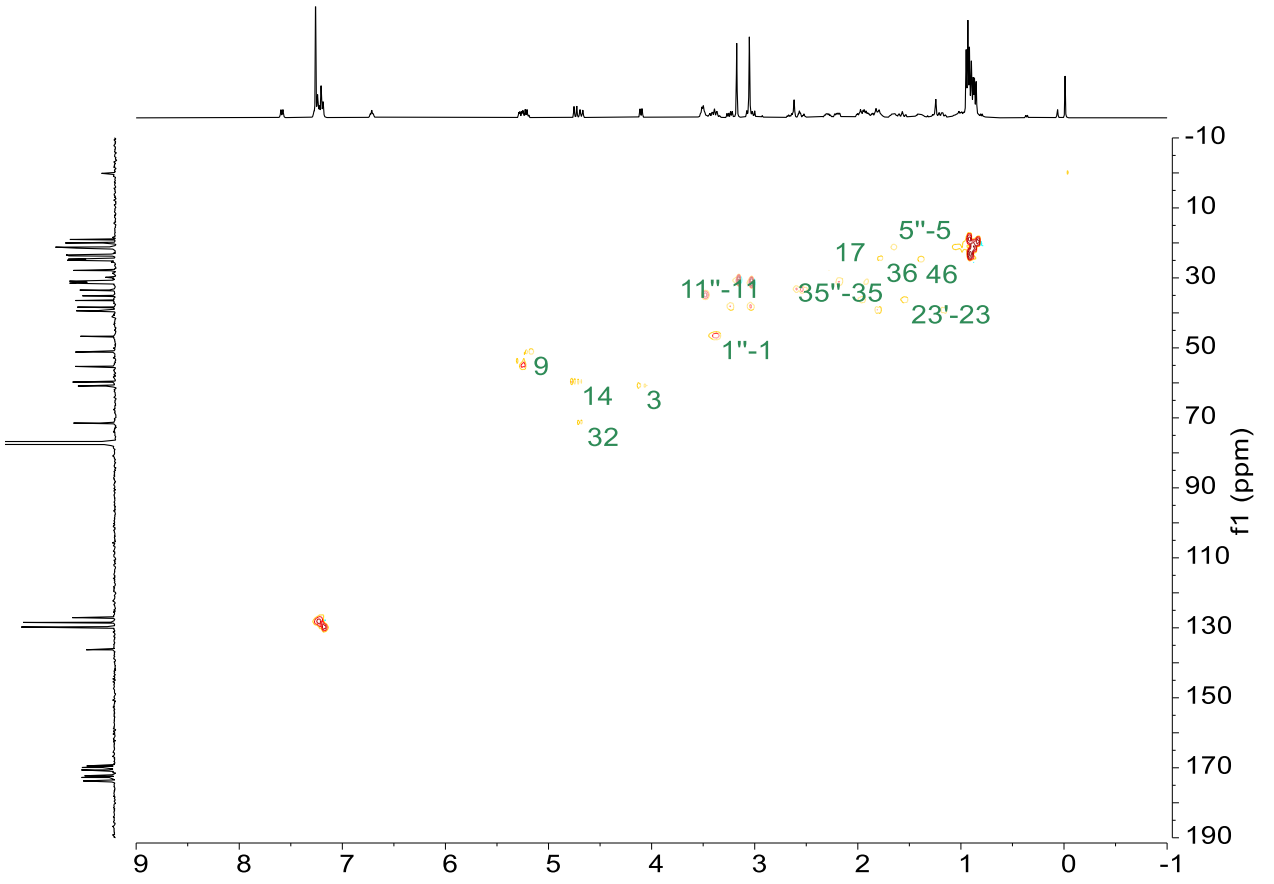

Figure S-11. HSQC spectra for Pseudodestruxin B (2')

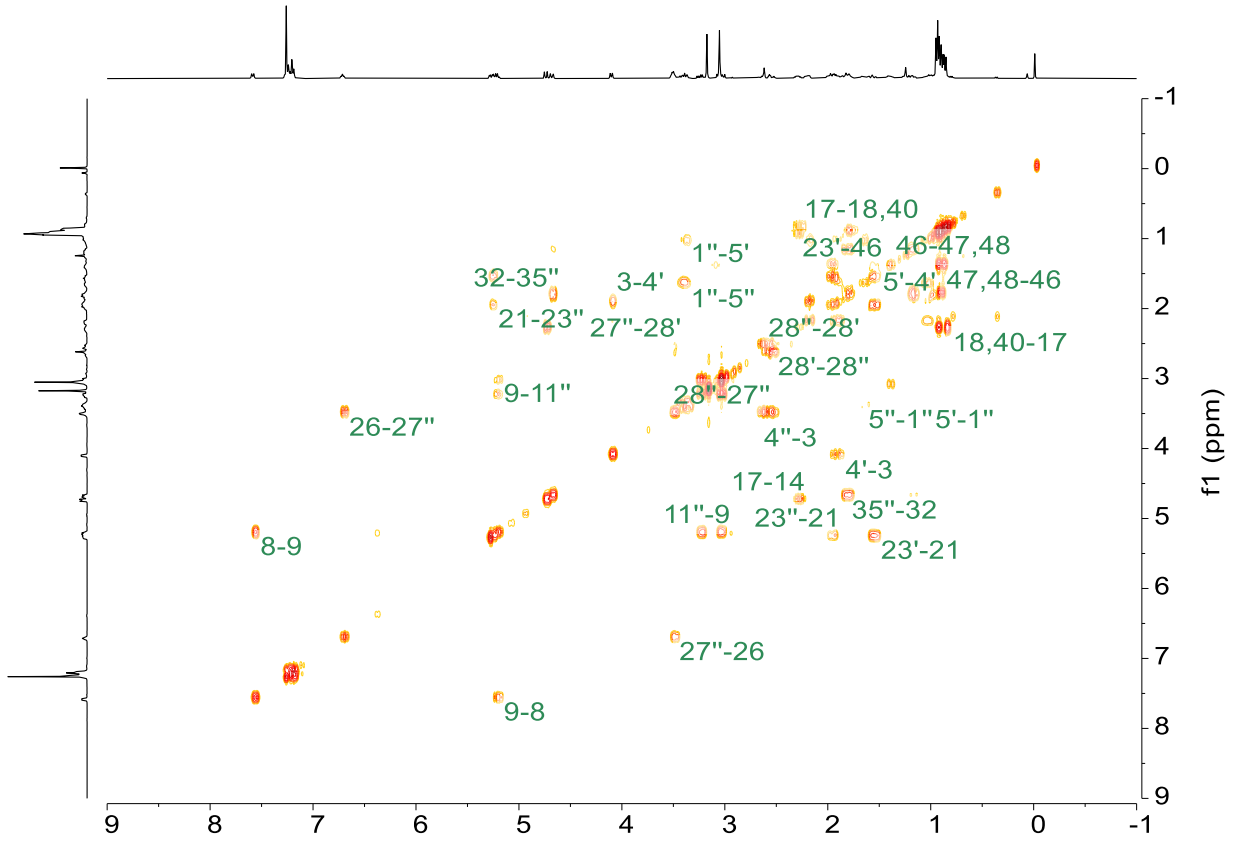

Figure S-12. COSY spectra for Pseudodestruxin B (2')

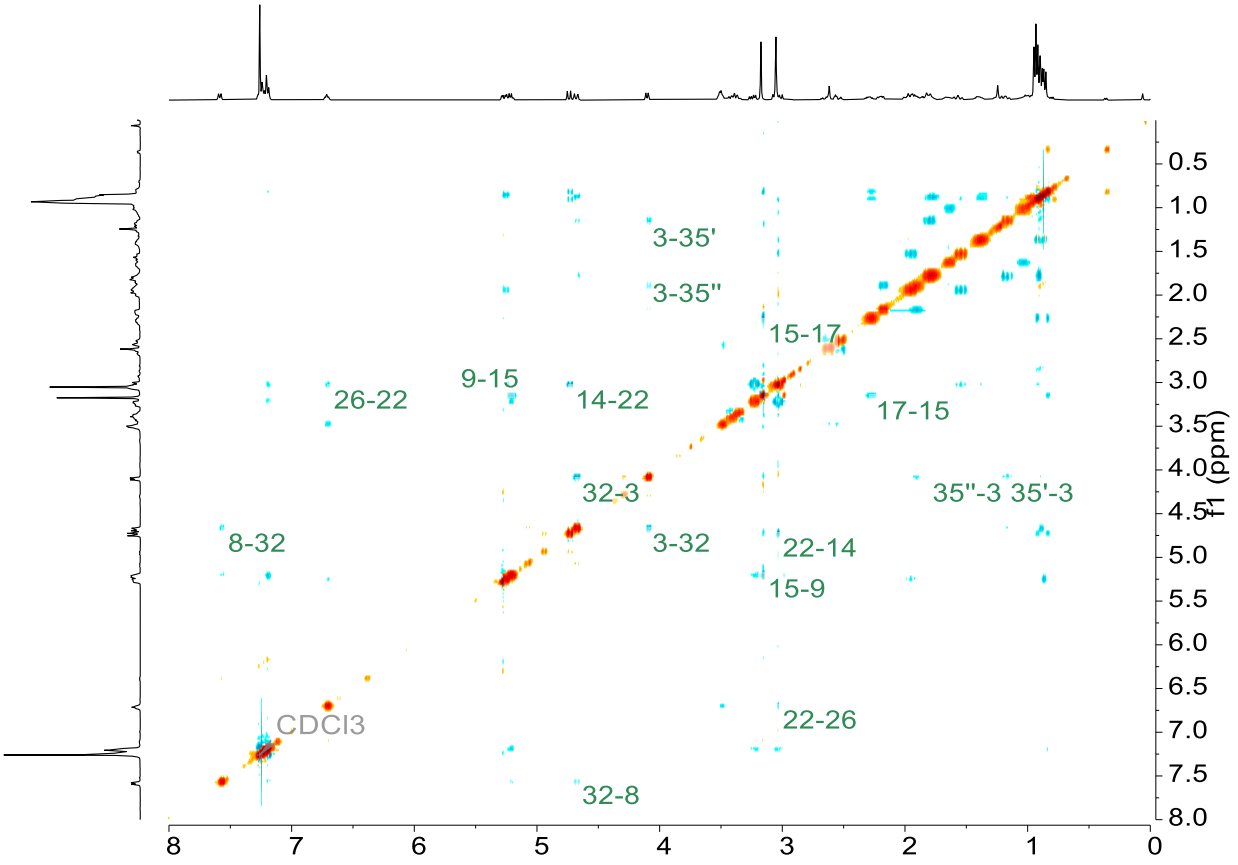

Figure S-13. NOESY spectra for Pseudodestruxin B (2')

6.4 Isaridin A (3)

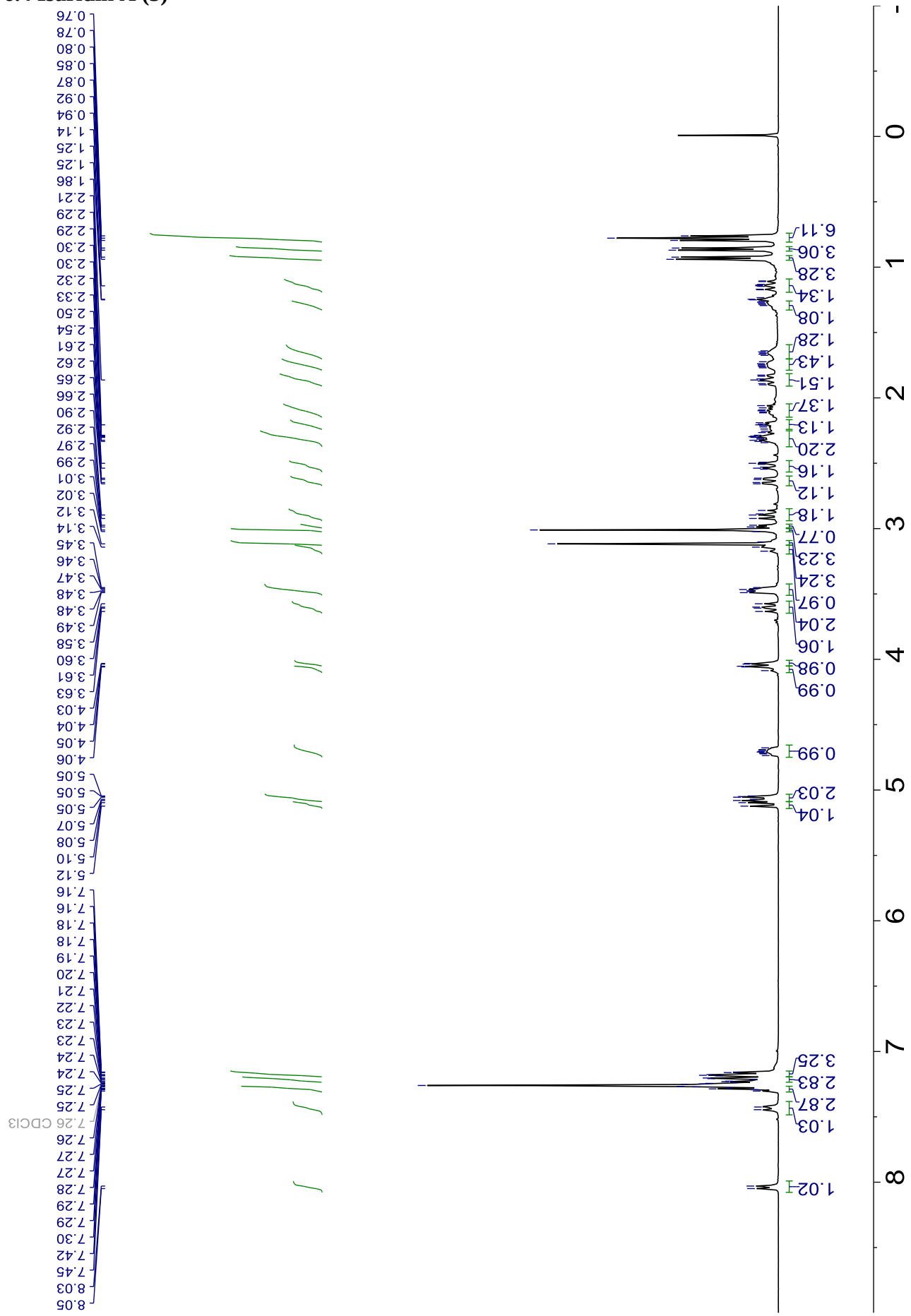

Figure S-14. ^{1}H NMR spectrum of 3 ($CDCl_3$, 298 K, 400 MHz)

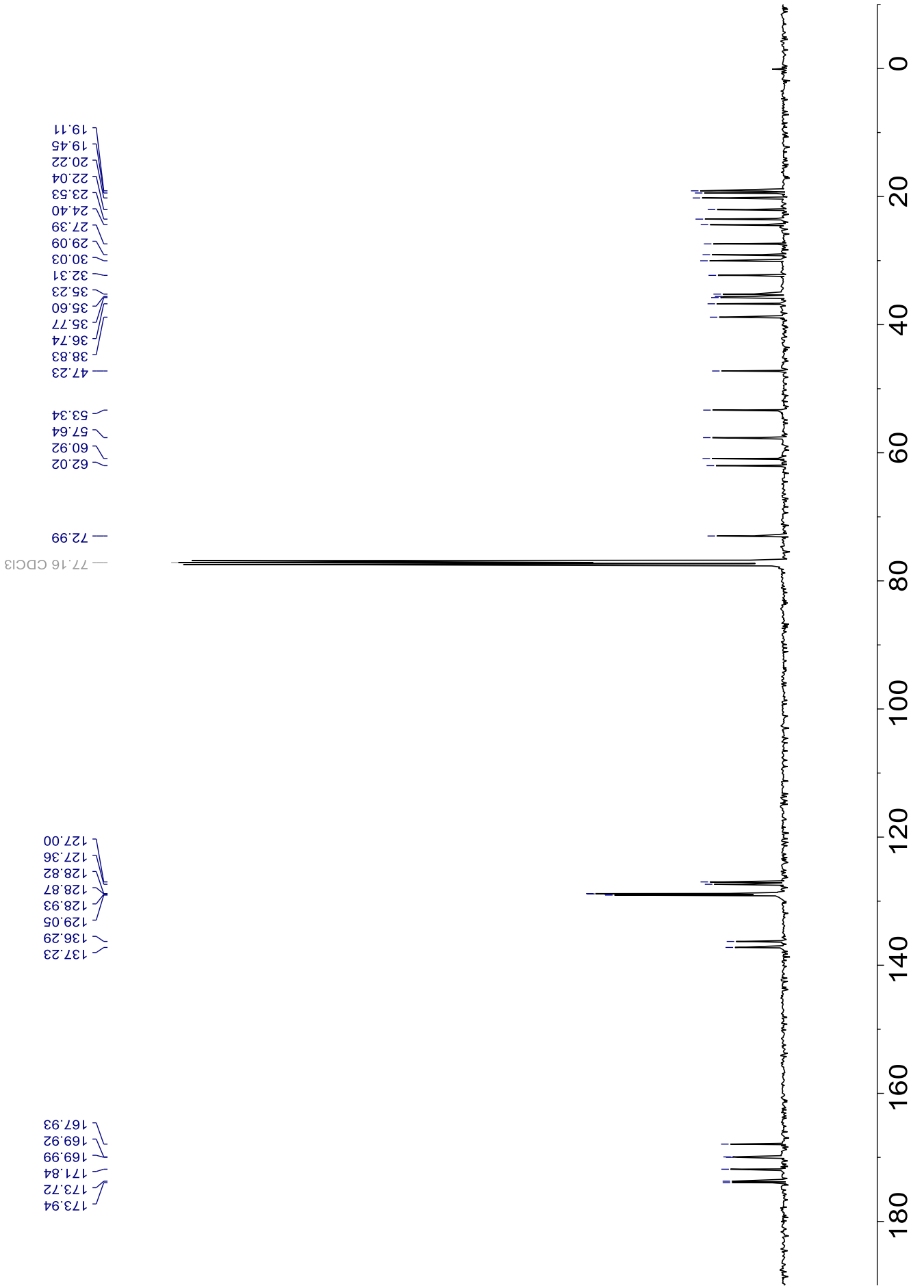

Figure S-15. ^{13}C NMR spectrum of 3 ($CDCl_3$, 298 K, 101 MHz)

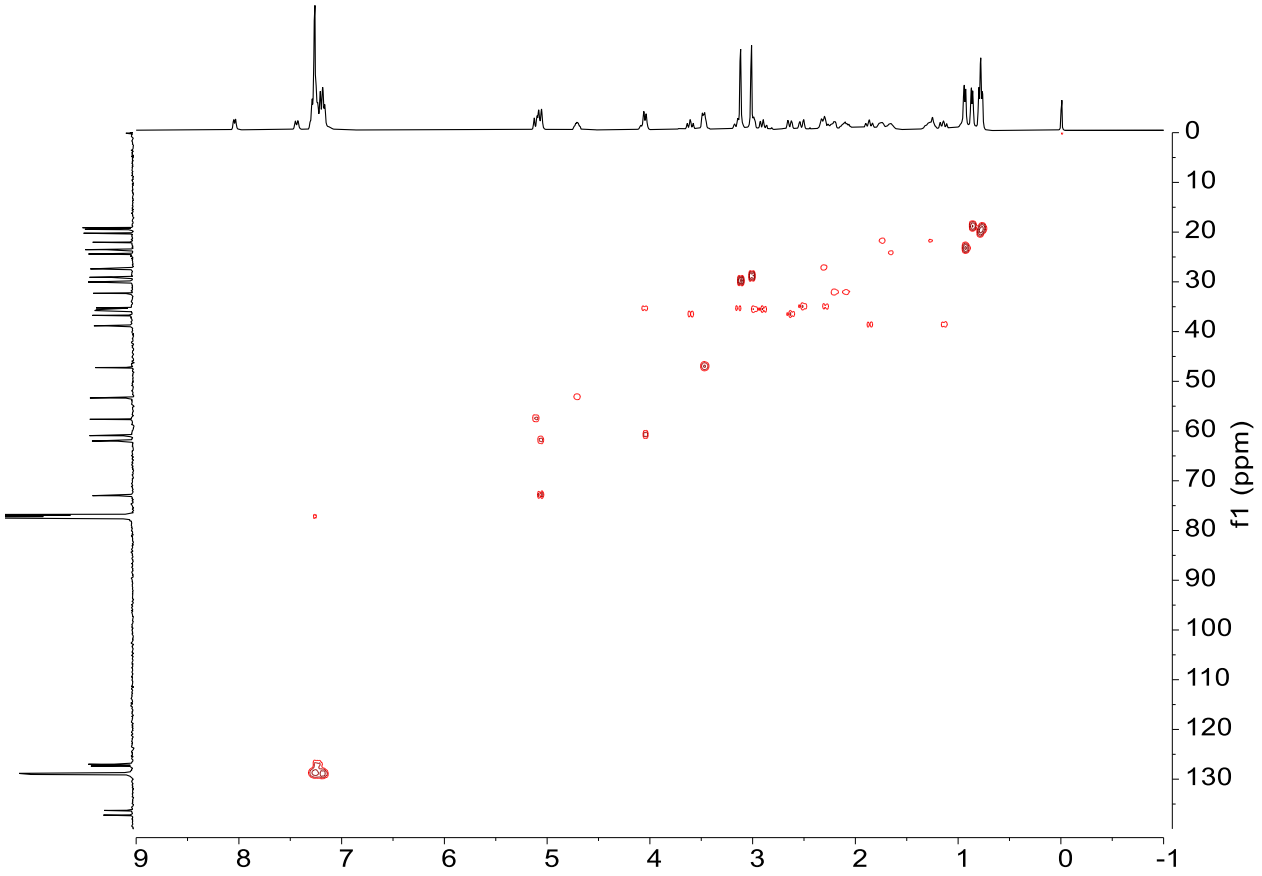

Figure S-16. HSQC spectra for 3

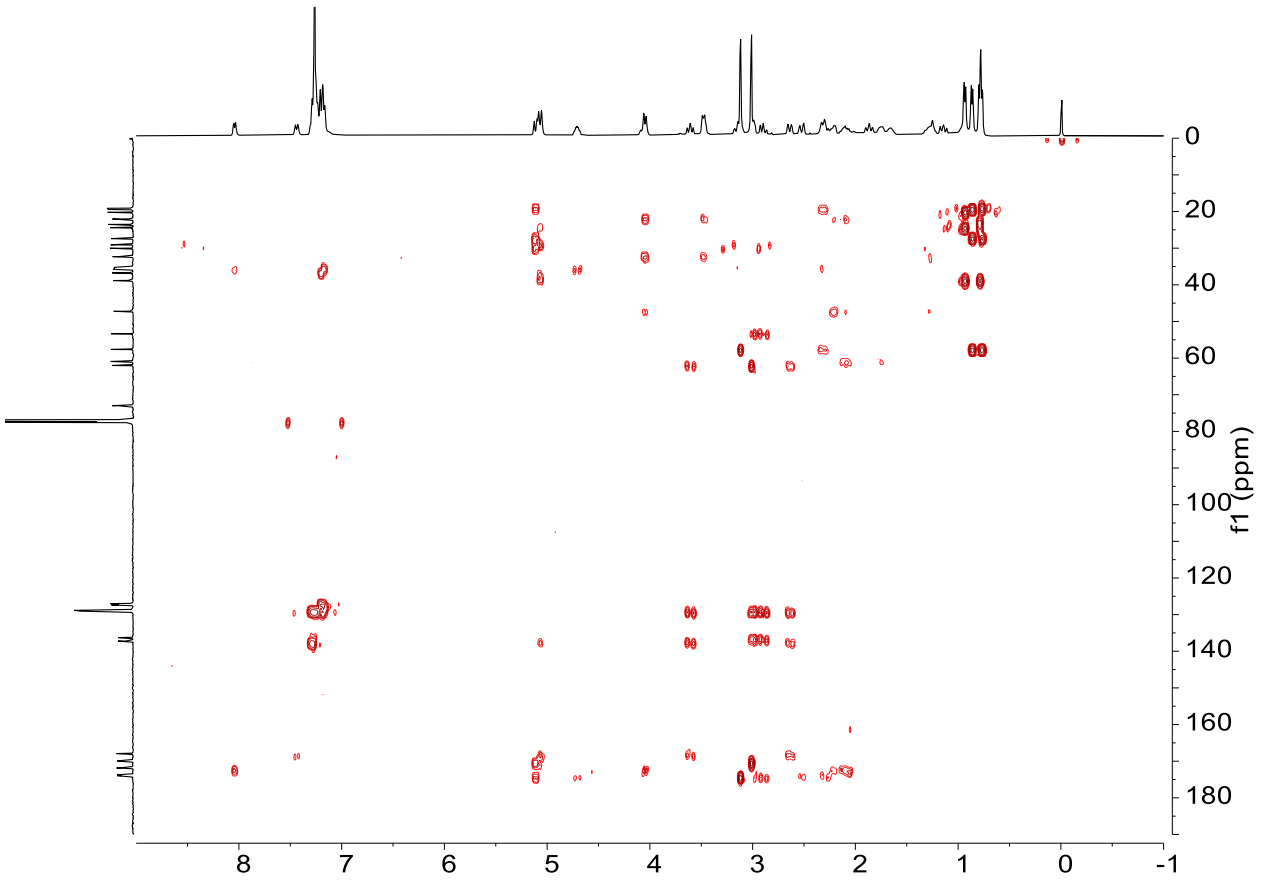

Figure S-17. HMBC spectra for 3

6.5 Isaridin A isomer (3’)

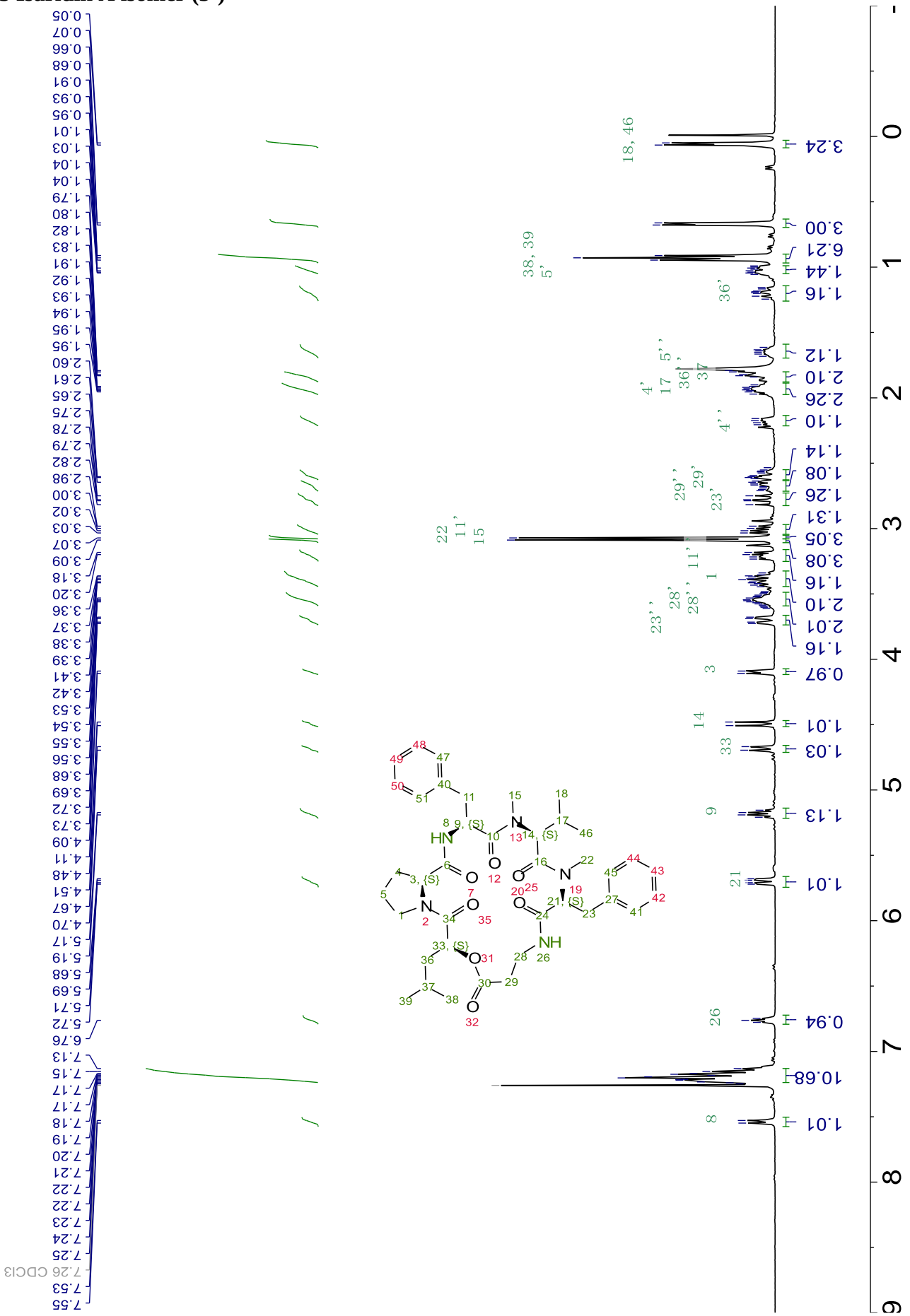

Figure S-18. ^{1}H NMR spectrum of 3’ ($CDCl_3$, 298 K, 400 MHz)

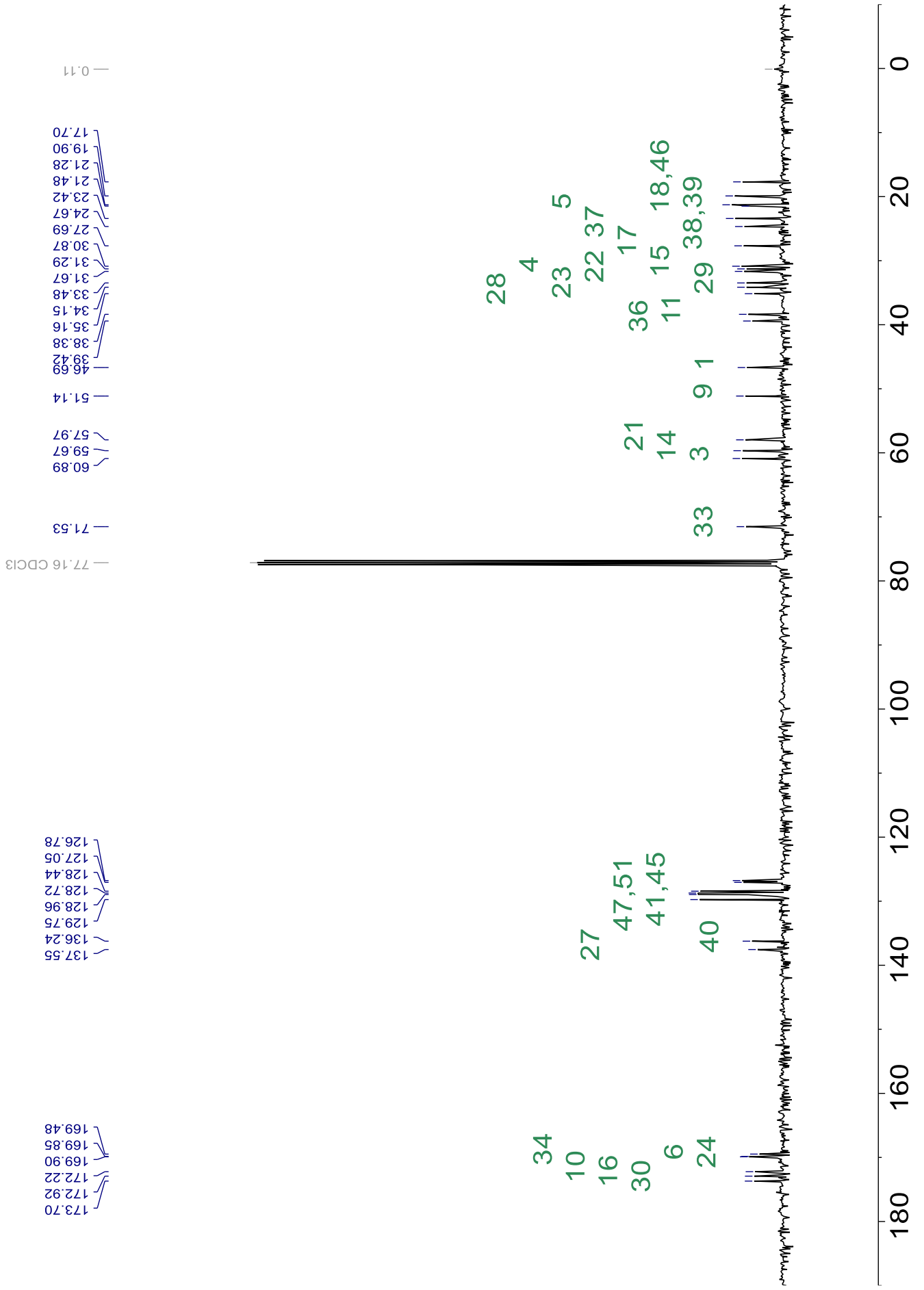

Figure S-19. ^{13}C NMR spectrum of 3' ($CDCl_3$, 298 K, 101 MHz)

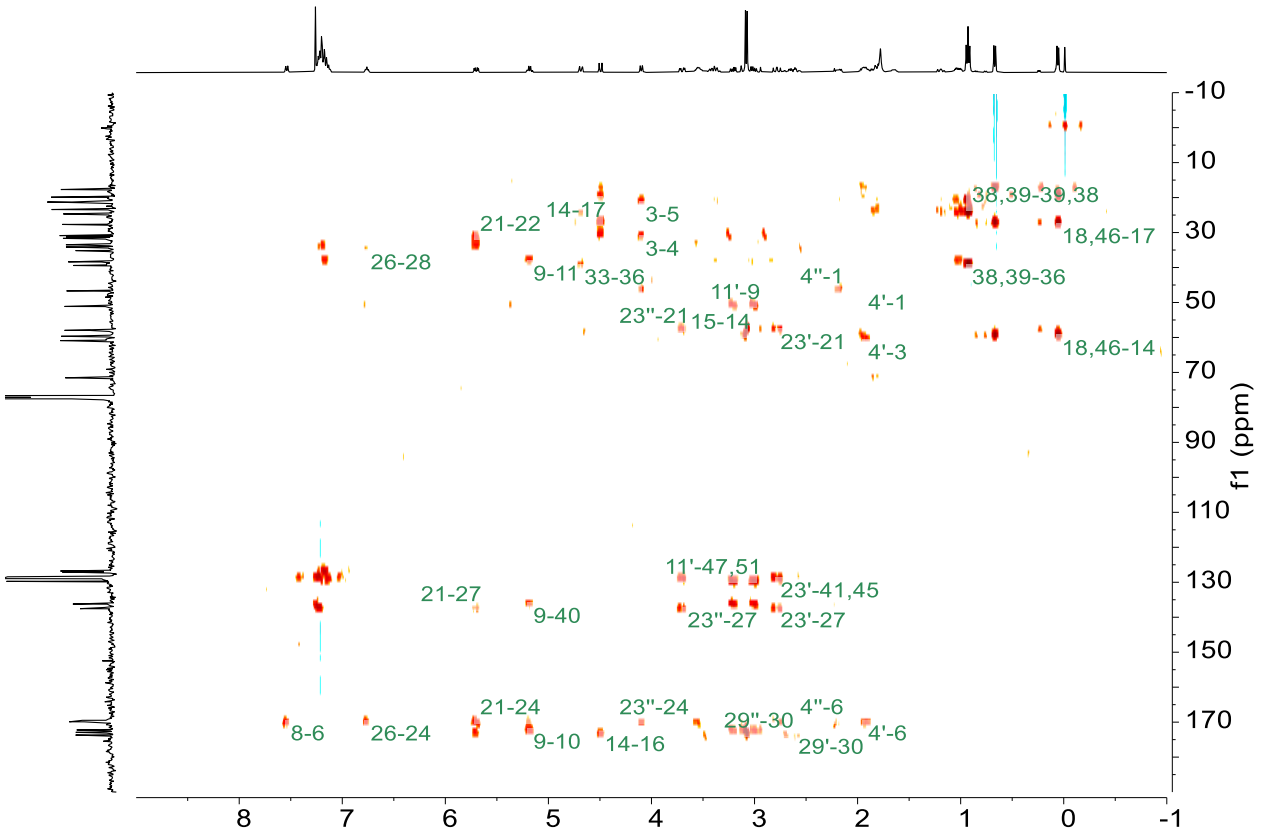

Figure S-20. HMBC spectra for 3'

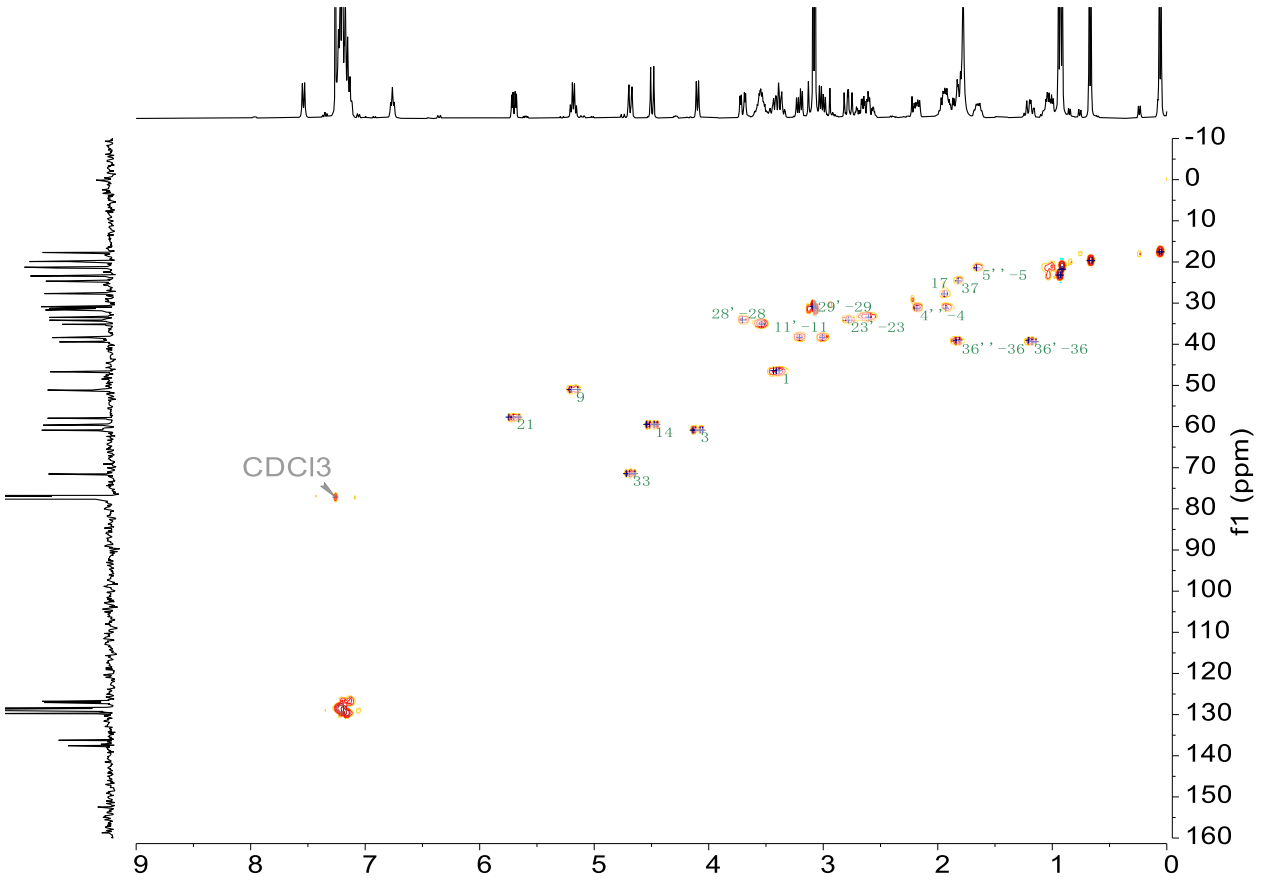

Figure S-21. HSQC spectra for 3'

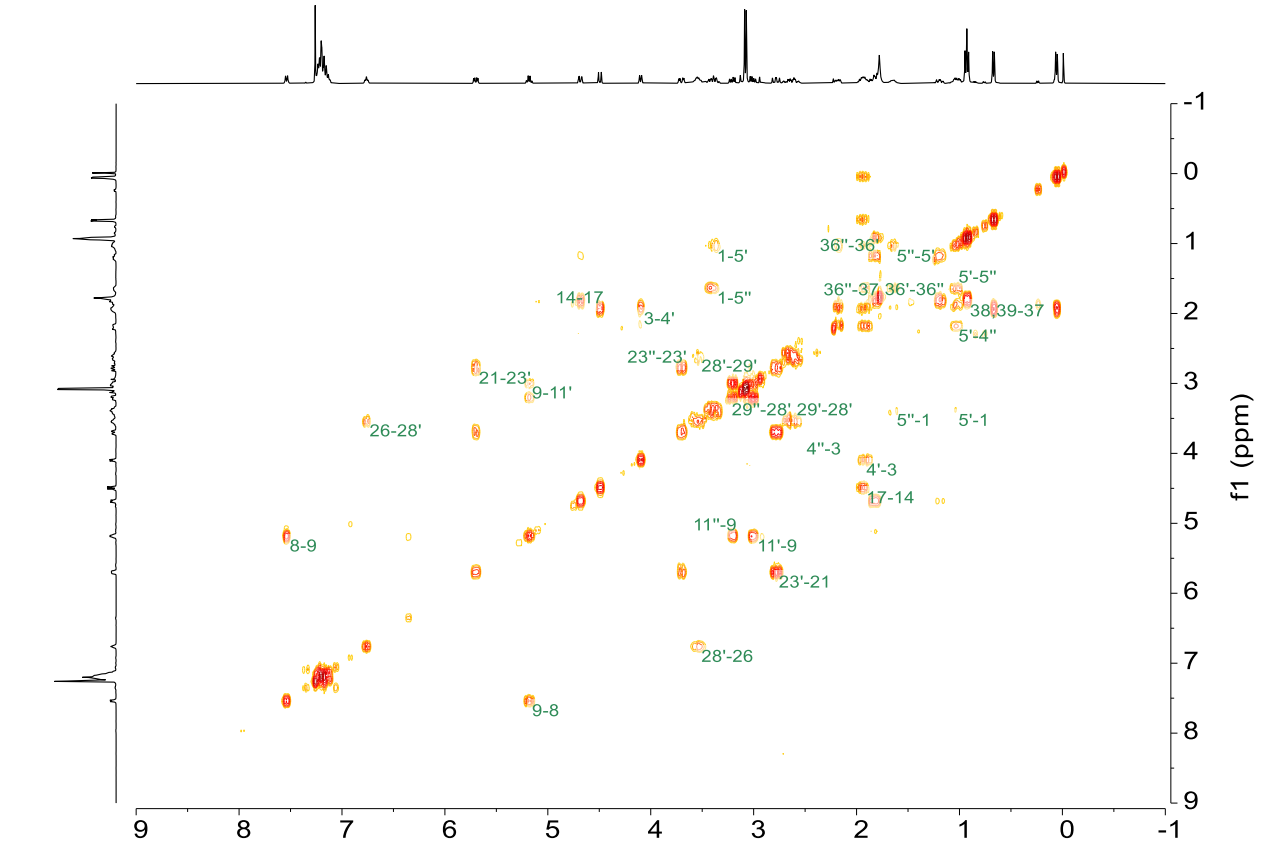

Figure S-22. COSY spectra for 3'

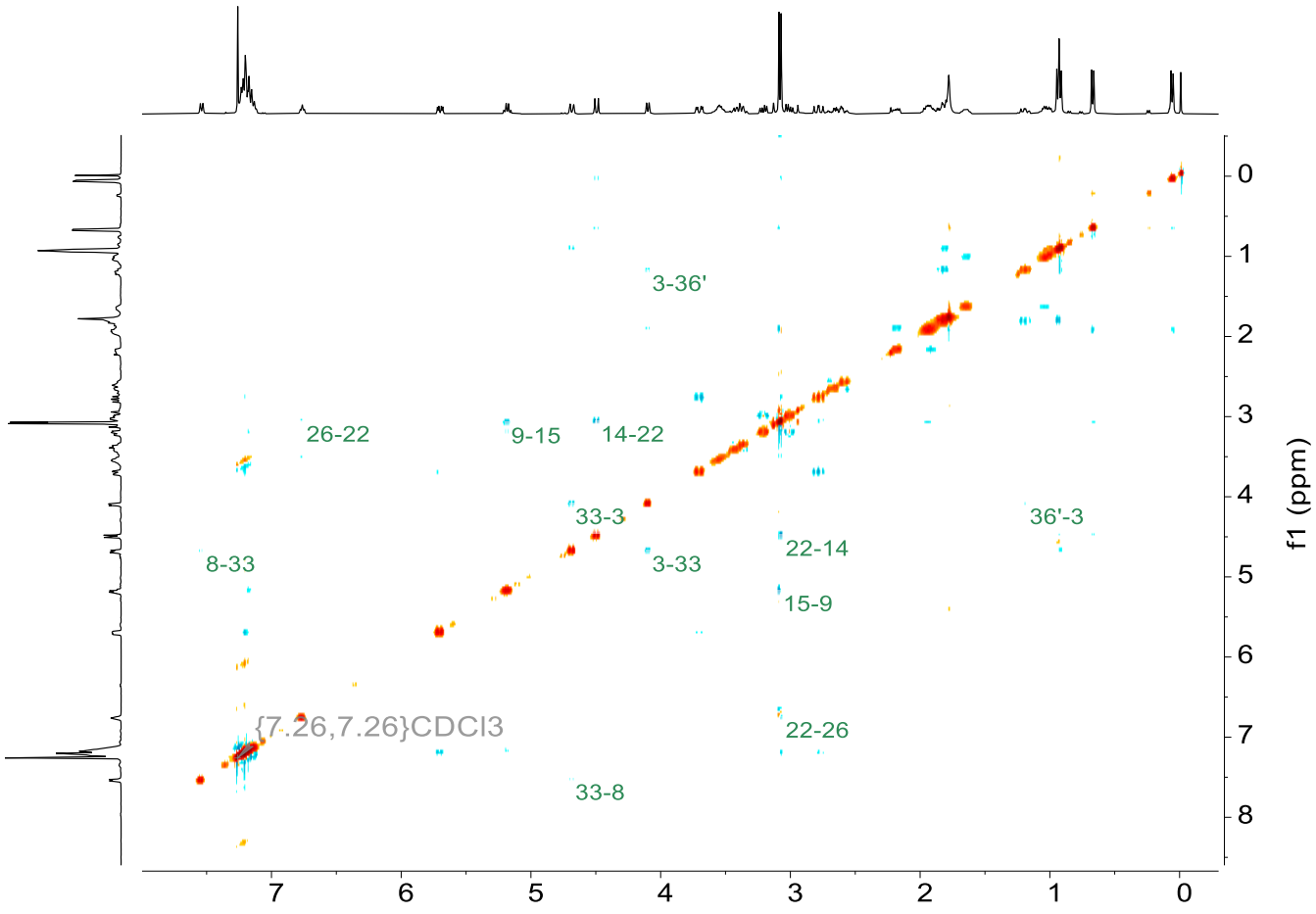

Figure S-23. NOESY spectra for Isaridin A (3')

6.6 Cladoamide A (4)

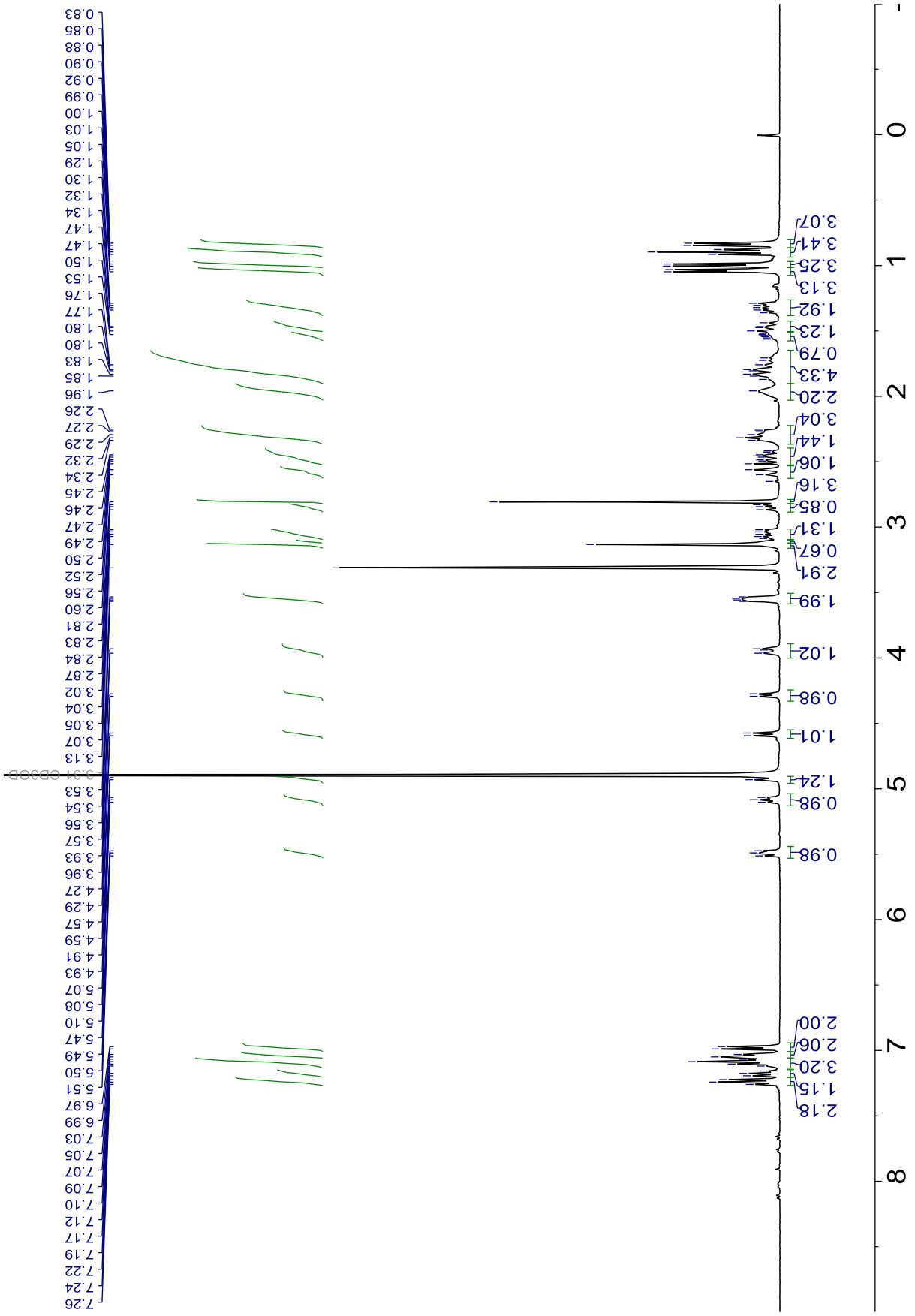

Figure S-24. ^{1}H NMR spectrum of 4 (CD_3OD, 298 K, 400 MHz)

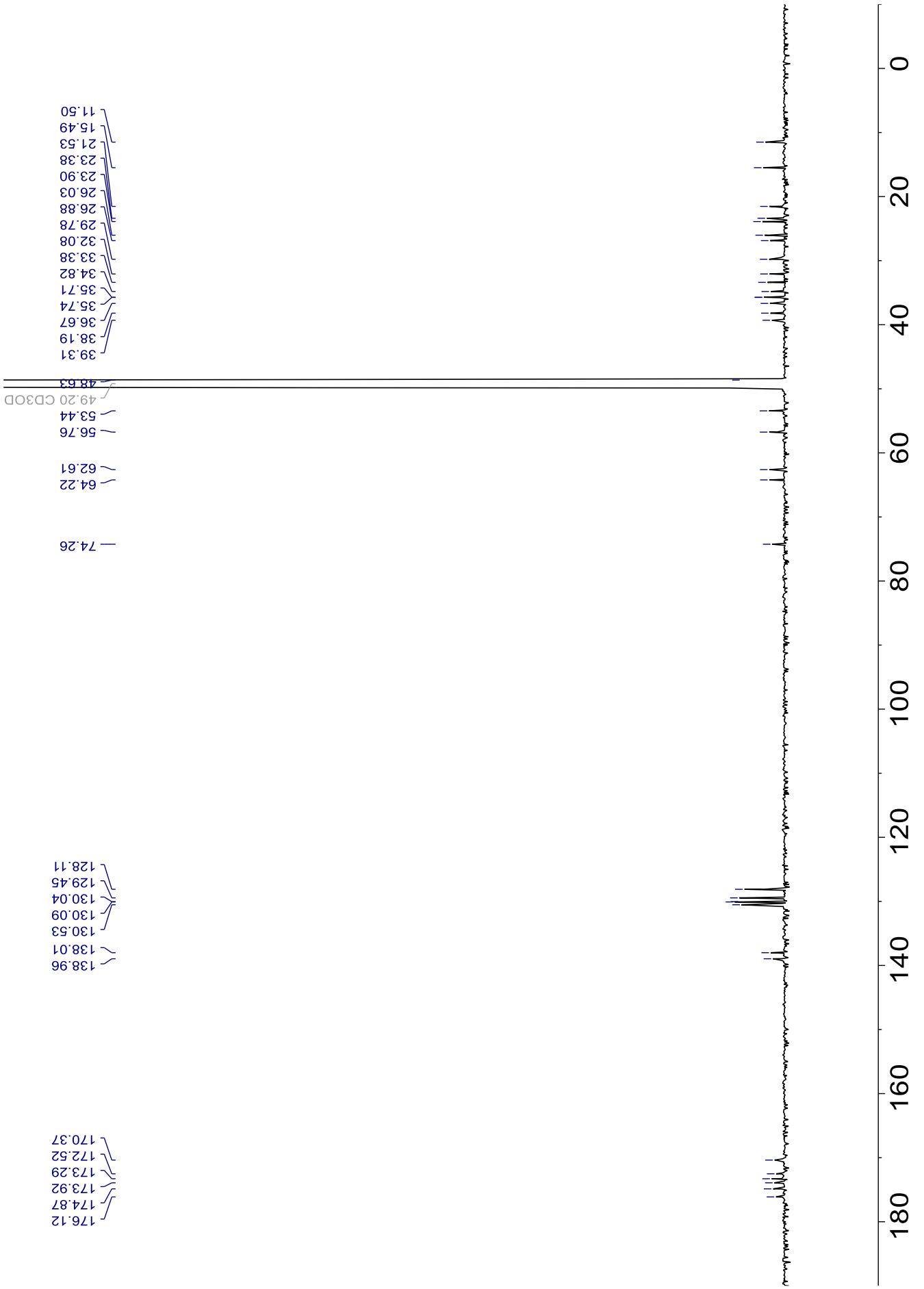

Figure S-25. ^{13}C NMR spectrum of 4 (CD_3OD, 298 K, 101 MHz)

6.7 Cladoamide A (5)

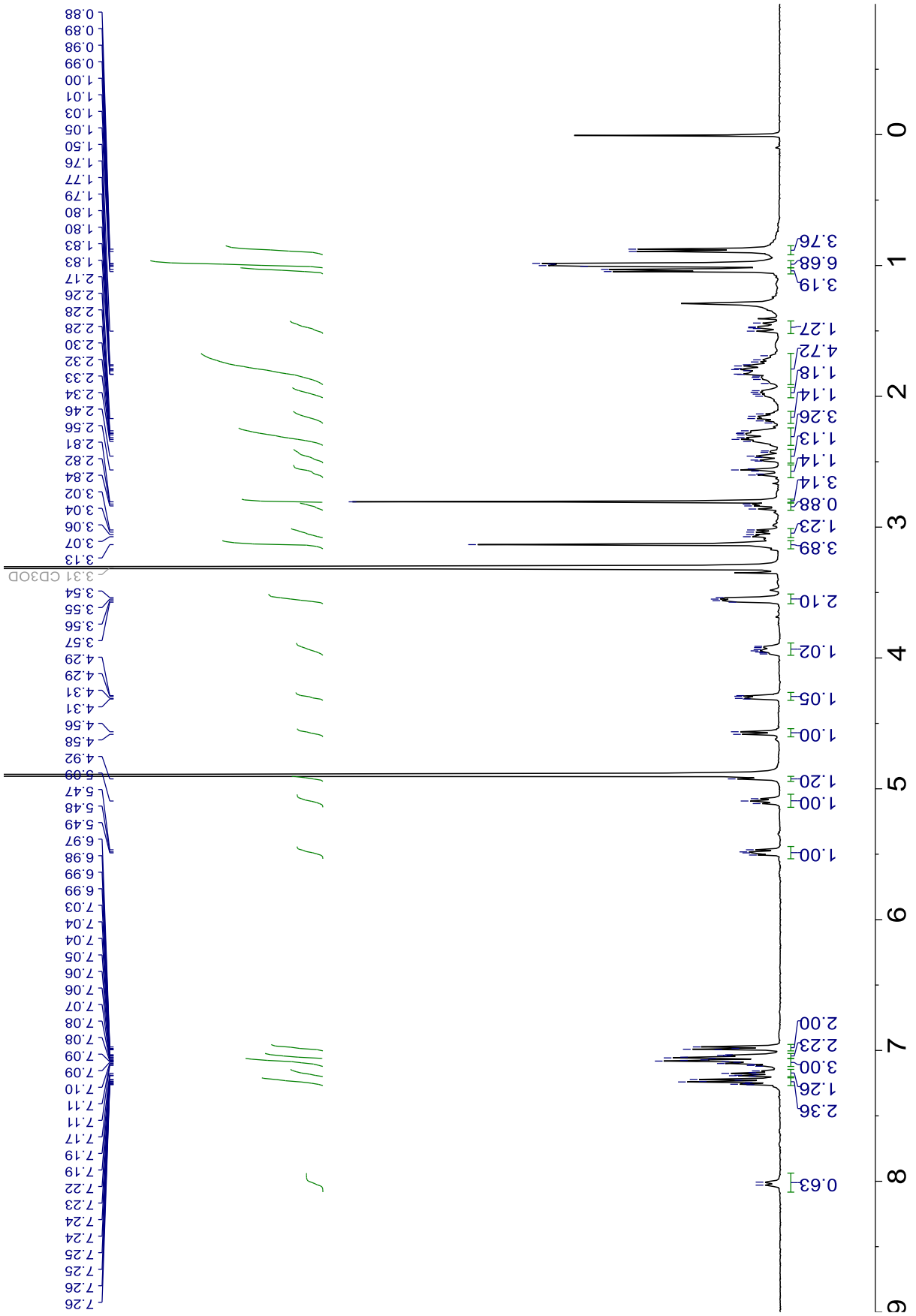

Figure S-26. ^{1}H NMR spectrum of 5 (CD_3OD, 298 K, 400 MHz)

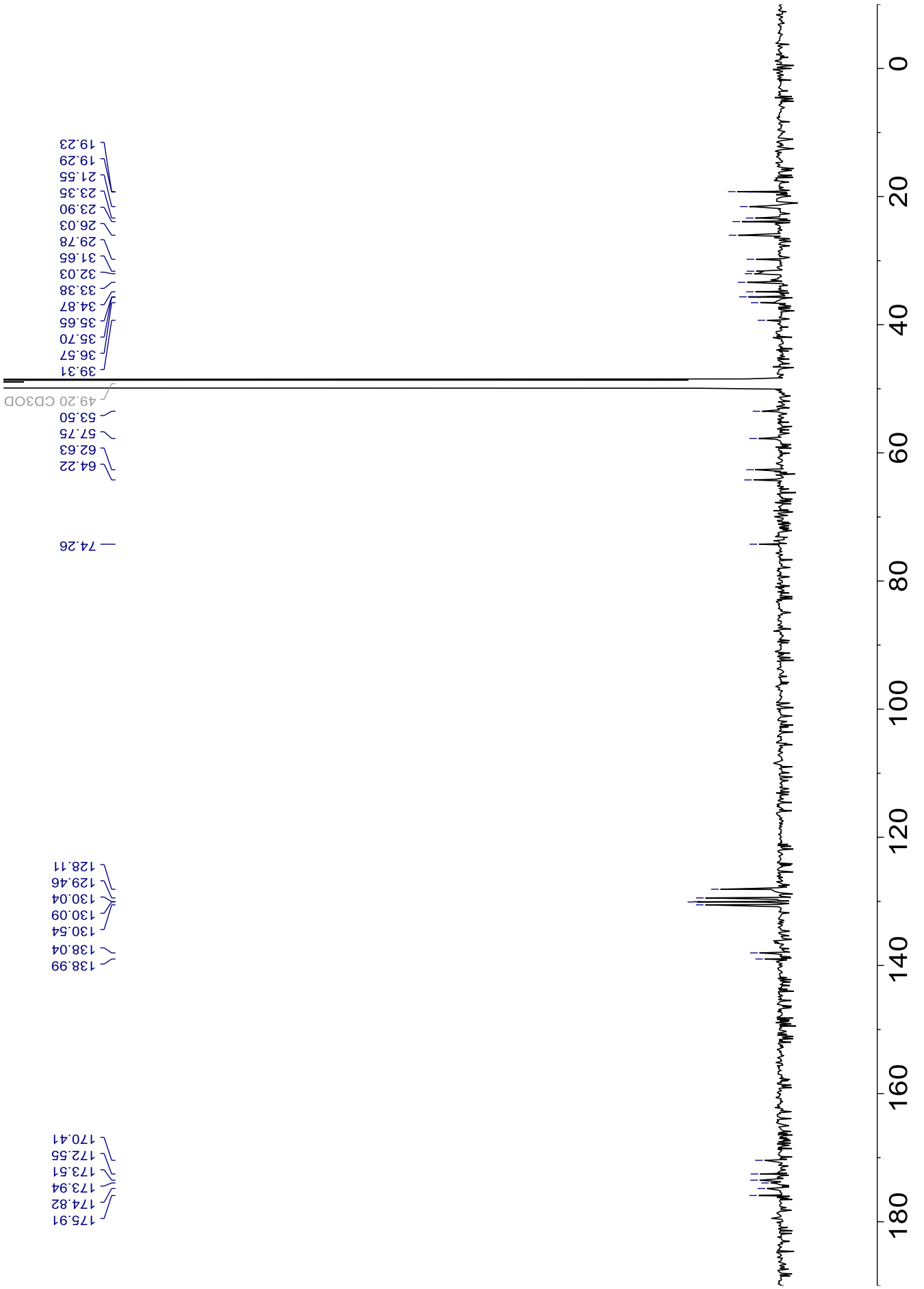

Figure S-27. ^{13}C NMR spectrum of 5 (CD_3OD, 298 K, 101 MHz)