SUPPORTING INFORMATION

Total Synthesis of the Marine Cyclic Depsipeptide Viequeamide A

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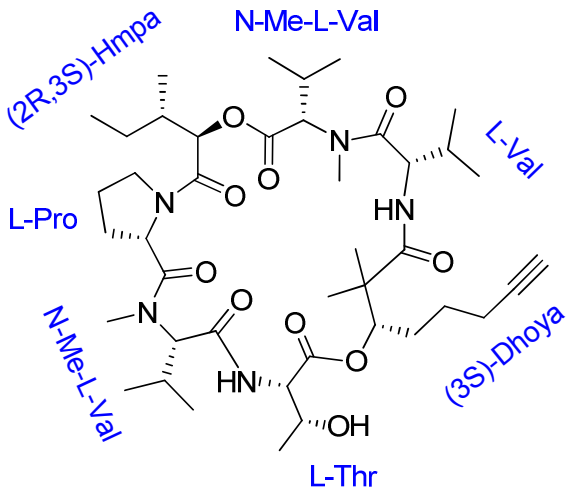
1. **^{1}H NMR and ^{13}C NMR Data (in $CDCl_3$) Comparison of Synthetic with Natural Viequeamide A (1)**



Viequeamide A (1)

		Natural[c]		Synthetic 1[d]	
residue	position	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
Thr	1		169.2		169.2
	2	4.68, dd (10.3,	58.1	4.67, dd (10.3, 3.1)	58.1
	3	3.87, m	68.2	3.87, m	68.1
	4	0.80, d (6.4)	19[a]	0.79, d (6.4)	19[a]
	OH	4.48, d (12.4)		4.50 ,d (12.4)	
	NH	8.04, d (10.4)		8.03, d (10.4)	
N-Me-Val-1	5		168.2		168.2
	6	4.06, d (12.4)	67.4	4.07, d (10.7)	67.4
	7	2.41, m	26.0	2.41, m	25.9
	8	0.84, d (6.7)	19[a]	0.84, d (6.7)	19[a]
	9	0.93-1.00[b]	20.1	0.91-1.01[b]	20.0
	10	2.77, s	29.0	2.77, s	29.0
Pro	11		172.1		172.1
	12	5.01, dd (8.4,	55.7	5.01, d (7.8)	55.7
	13a	2.09, m	29.7	1.95-2.15[b]	29.6
	13b	2.03, m		1.95-2.15[b]	
	14	2.52, m	25.4	2.52, m	25.3
	15a	3.95, m	47.4	3.95, m	47.3
	15b	3.52, m		3.52, m	
Hmpa	16		168.7		168.7
	17	4.82, d (2.0)	74.5	4.82, d (1.7)	74.5
	18	1.72, m	36.6	1.6-1.8[b]	36.6
	19	1.10, d (6.7)	13.8	1.09, d (6.7)	13.8
	20	1.43-1.55[b]	27.3	1.43-1.55[b]	27.2
	21	0.93-1.00[b]	12.0	0.91-1.01[b]	11.9
	22		170.3		170.3

N-Me-Val-2	23	3.91, d (10.7)	63.7	3.91, d (10.7)	63.6
	24	2.28	29.5	2.19-2.32[b]	29.4
	25	0.93-1.00[b]	19[a]	0.91-1.01[b]	19[a]
	26	0.93-1.00[b]	19[a]	0.91-1.01[b]	19[a]
	27	2.98 s	28.3	2.97 s	28.2
Val	28		172.8		172.7
	29	4.89, dd (7.3,	53.9	4.88, d (7.2)	53.9
	30	1.96, m	31.7	1.95-2.15[b]	31.7
	31	0.93-1.00[b]	20.7	0.91-1.01[b]	20.6
	32	0.75, d (6.6)	16.1	0.74, d (6.5)	16.1
	NH	6.83, d (7.4)		6.83, d (7.2)	
Dhoya	33		174.7		174.7
	34		46.7		46.6
	35	1.36, s	17.1	1.36, s	17.0
	36	1.18, s	25.6	1.17, s	25.6
	37	5.55, d (8.5)	77.4	5.53, d (8.7)	77.4
	38a	1.76, m	27.9	1.6-1.8[b]	27.9
	38b	1.43-1.55[b]		1.43-1.55[b]	
	39	1.43-1.55[b]	24.8	1.43-1.55[b]	24.7
	40	2.19-2.32[b]	18.1	2.19-2.32[b]	18.1
	41		84.2		84.1
	42	1.93, t (2.6)	68.9	1.93, t (2.5)	68.9

[a] Synthetic **1:** 18.8, 19.1, 19.3, 19.5 (Natural: 18.9, 19.1, 19.4, 19.6); [b] These proton resonances overlapped.
[c] Recorded at 500 MHz and 125 MHz. [d] Recorded at 300 MHz and 125 MHz.

2. Preparation of compound 3, 4, P1, 5, P2, 6, 7, 8, 9, P3, 10, 12, 13, 14

2-Hydroxy-3-methyl-pentanoic acid allyl ester (3). *L*-Isoleucine (32.75g, 250 mmol) was dissolved in 1.25 M H_2SO_4 (175 mL) and cooled to 0 ^oC. A solution of $NaNO_2$ (25.9g, 375 mmol) in H_2O (125 mL) was added dropwise over 1 h. The resulting reaction mixture was stirred for 2 h at 0 ^oC and then over night at room temperature (rt). The mixture was extracted with EtOAc (3 × 300 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. 2-Hydroxy-3-methyl-pentanoic acid was obtained as a colorless oil, which was then dissolved in DMF (60 mL). To the solution, K_2CO_3 (31.05 g, 225 mmol), allylbromide (26 mL, 49.2 mmol) and TBAB (9.67g, 30 mmol) were added. The obtained mixture was stirred for 16 h at rt, and then diluted with 200 mL of H_2O. The mixture was extracted with EtOAc (2×300 mL), washed with brine, dried over Na_2SO_4 and then concentrated under reduced pressure. Flash chromatography of the residue (petroleum ether/ EtOAc, 30/1) provided **3** as a colorless oil (25.8 g, 62% in two steps). ^1H NMR (300 MHz, $CDCl_3$) δ 6.06–5.88 (1H, m), 5.31 (2H, dd, *J* = 32.7, 13.8 Hz), 4.65 (2H, d, *J* = 5.7 Hz), 4.03 (1H, d, *J* = 4.9 Hz), 1.80 (1H, m), 1.59–1.40 (1H, m), 1.35–1.14 (1H, m), 0.96 (3H, d, *J* = 6.9 Hz), 0.92 (3H, t, *J* = 7.5 Hz).

(S)-Allyl 2-(*tert*-butoxycarbonyl(methyl)amino)-3-methylbutanoate (5). NaH (60% in mineral oil, 4.91 g, 122.7 mmol) was added to a solution of L-*N*-Boc-valine (5.29g, 24.3 mmol) and MeI (12.1 mL, 184 mmol) in THF (100 mL) at 0 ^oC. After stirring at rt for 18 h, the reaction mixture was poured into saturated NH_4Cl solution (500 mL), extracted with EtOAc (3 × 150 mL) and dried over Na_2SO_4. After evaporation of the solvents, the obtained *N*-methyl-*N*-Boc-valine was mixed with K_2CO_3 (6.7 g, 48.6 mmol) and allyl bromide (3.15 mL, 36.5 mmol) in DMSO (60 mL). The mixture was stirred at rt for 12 h, and then partitioned between EtOAc and brine. The organic phase was separated and the aqueous phase was extracted with EtOAc. The combined organic phase was dried over Na_2SO_4 and concentrated. Flash chromatography (petroleum ether/EtOAc, 15/1) gave **5** (5.9 g, 90% in two steps) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 6.03–5.84 (1H, m), 5.28 (2H, dd, *J* = 28.9, 13.8 Hz), 4.66–4.58 (2H, m), 4.21 (1H, m), 2.83 (3H, s), 2.22 (1H, s), 1.45 (9H, s), 0.99 (3H, d, *J* = 6.5 Hz), 0.89 (3H, t, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) δ 171.3, 170.8,

156.2, 155.6, 132.0, 131.8, 118.4, 118.1, 80.3, 80.0, 65.2, 65.1, 63.2, 30.6, 30.5, 28.4, 27.8, 27.7, 20.0, 19.8, 19.0, 18.8.

***(S)*-4-Benzyl-3-((S)-3-hydroxy-2,2-dimethyloct-7-ynoyl)oxazolidin-2-one (6).** The fragment **9** (1.03 g, 4.17 mmol) was dissolved in dry THF (15 mL) and then added dropwise to a solution of LDA (1.5 equiv) in dry THF (10 mL) at –78 °C. After stirring at –78 °C for 30 min, chlorotriisopropoxytitanium IV (1.0 M in THF, 16.68 mL, 16.68 mmol, 4 equiv) was added dropwise, and the resulting mixture was warmed to –40 °C for 1 h. The mixture was then cooled to –78 °C, a solution of hexynal (400 mg, 4.17 mmol) in THF (6 mL) was added, and the reaction mixture was warmed to –40 °C. After stirring at –40 °C for 3 h, the mixture was warmed to 0 °C. The reaction was quenched with NH_4Cl and stirred with Celite for 30 min while warming to rt. The filtrate was extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The product was purified by flash chromatography (petroleum ether/EtOAc, 5/1) yielding **6** as a pale yellow oil (874 mg, 61% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.20 (5H, m), 4.70 (1H, dd, *J* = 9.7, 6.9 Hz), 4.24 – 4.12 (3H, m), 3.26 (1H, d, *J* = 13.4 Hz), 2.76 (1H, dd, *J* = 13.1, 9.9 Hz), 2.57 (1H, s), 2.27 (2H, t, *J* = 5.3 Hz), 1.95 (1H, s), 1.87–1.60 (4H, m), 1.41 (3H, s), 1.37 (3H, s).

(*S*)-3-Hydroxy-2,2-dimethyloct-7-ynoic acid (7). A solution of 30% aqueous H_2O_2 (53.5 µL, 0.524 mmol) was added dropwise to a solution of **6** (45 mg, 0.131 mmol) in a solution of THF : H_2O (4:1, 1mL) at 0 ºC. $LiOH{\cdot}H_2O$ (11 mg, 0.262 mmol) in H_2O (300 µL) was added. After 1 h, Na_2SO_3 (75 mg, 0.59 mmol) was added and THF was removed from the slurry under vacuum. The residue was partitioned between CH_2Cl_2 and H_2O. The aqueous layers were collected and acidified to pH=1 with 1N HCl. The aqueous layer was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered and concentrated to yield the title compound as a colorless oil (23 mg, 95% yield): $[\alpha]_D^{21}$ = -26.8° (*c* 0.424, $CHCl_3$); [Ref: $[\alpha]_D^{21}$ = -26.3° (*c* 1.0, $CHCl_3$)]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 (1H, bs), 3.67 (1H, d, *J* = 10.3 Hz), 2.25 (2H, td, *J* = 6.6, 2.4 Hz), 1.96 (1H, t, *J* = 2.5 Hz), 1.89–1.76 (1H, m), 1.62 (2H, ddd, *J* = 18.8, 12.9, 6.9 Hz), 1.48–1.36 (1H, m), 1.24 (3H, s), 1.20 (3H, s).

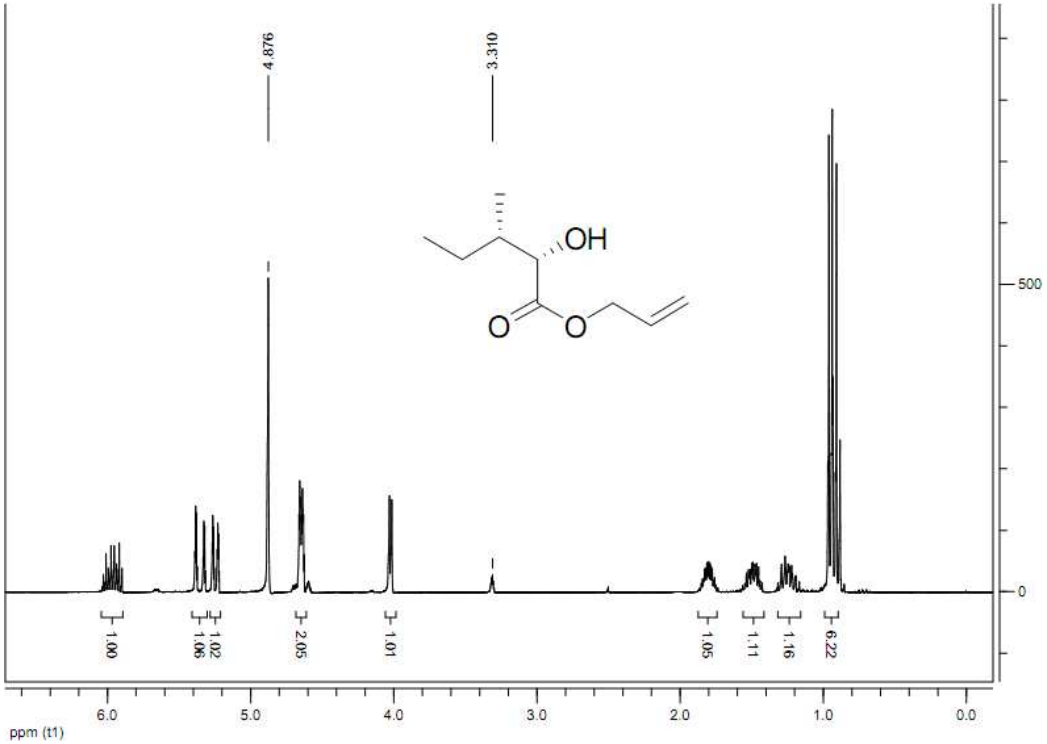
(*S*)-4-Benzyl-3-isobutyryloxazolidin-2-one (9). A solution of (4S)-4-benzyl-3-

propanoyloxazolidin-2-one (700 mg, 3.0 mmol) in THF (6 mL) was added dropwise to a stirred solution of sodium hexamethyldisilazide (2.0 M in THF, 1.65 mL, 3.3 mmol) in THF (15 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 1 h and then iodomethane (0.37 mL, 6.0 mmol) was added dropwise. The mixture was stirred at -78 °C for 4 h, then satd. ammonium chloride solution (15 mL) and water (6 mL) were added and the aqueous phase was acidified to pH = 2 with conc. HCl. The mixture was extracted with EtOAc, and the combined extracts were washed successively with *satd.* sodium hydrogencarbonate, sodium thiosulfate and brine. After dried with magnesium sulfate, filtered and concentrated, the oily residue was purified by column chromatography (petroleum ether/EtOAc, 20/1) to afford title compound **9** in 78% yield (579 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.26 (3H, m), 7.24–7.17 (2H, m), 4.74–4.61 (1H, m), 4.25–4.13 (2H, m), 3.76 (1H, dt, *J* = 13.6, 6.8 Hz), 3.27 (1H, dd, *J* = 13.3, 3.2 Hz), 2.77 (1H, dd, *J* = 13.3, 9.5 Hz), 1.24 (3H, d, *J* = 6.8 Hz), 1.20 (3H, d, *J* = 6.8 Hz).

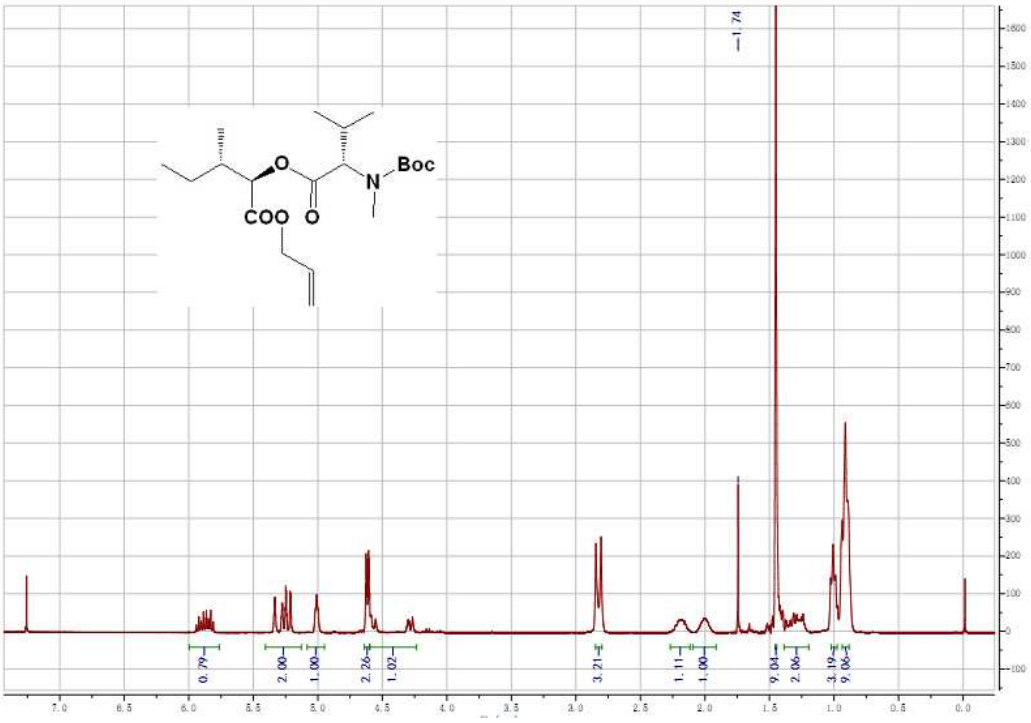
(*6S,9S,12R*)-12-*sec*-Butyl-6,9-diisopropyl-2,2,8-trimethyl-4,7,10-trioxo-3,11-dioxa-5,8-diazatridecan-13-oic acid (10). To a solution of peptide **P1** (420 mg, 0.867 mmol) in CH_2Cl_2 (20 mL) at 0 °C, was added $Pd(PPh_3)_4$ (50 mg, 0.043 mmol) and NMA (0.28 mL, 2.6 mmol). The reaction was stirred at room temperature for 10 h. After evaporation *in vacuo*, the residue was pureed by silica gel chromatography (petroleum ether/ethyl acetate, then CH_2Cl_2/MeOH) to give the carboxyl acid intermediate **10** as yellow oil (328 mg, 85%).

3. Copies of ^{1}H NMR and ^{13}C NMR spectra for New Compounds

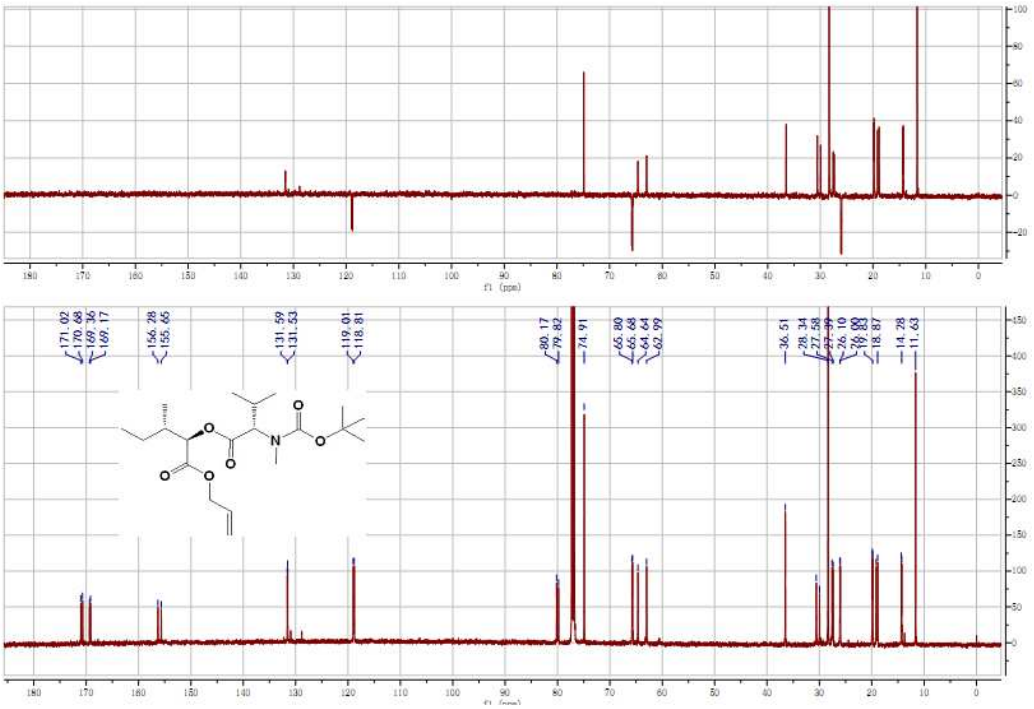
^{1}H NMR (300 MHz, CD_3OD) spectrum of compound **3**



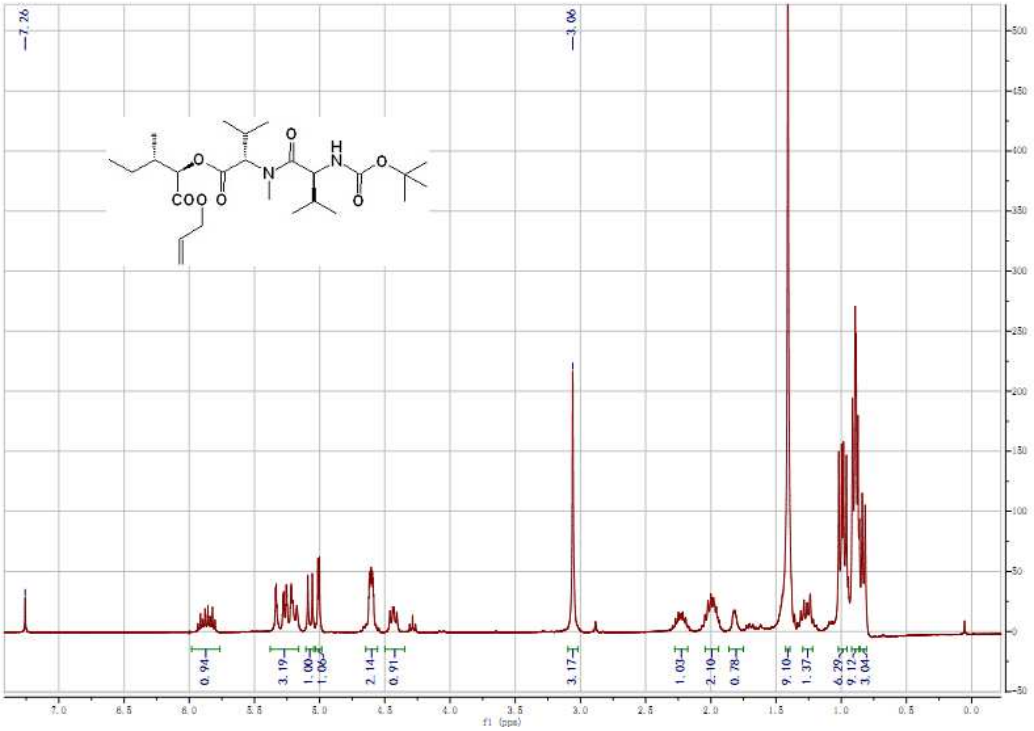
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **4**



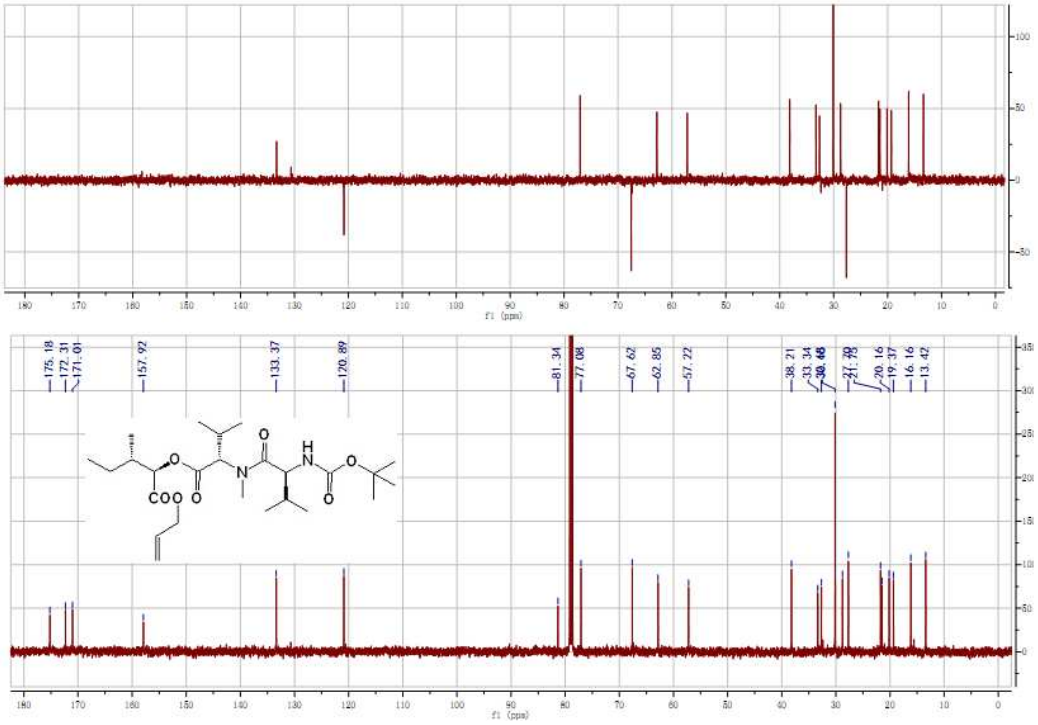
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **4**



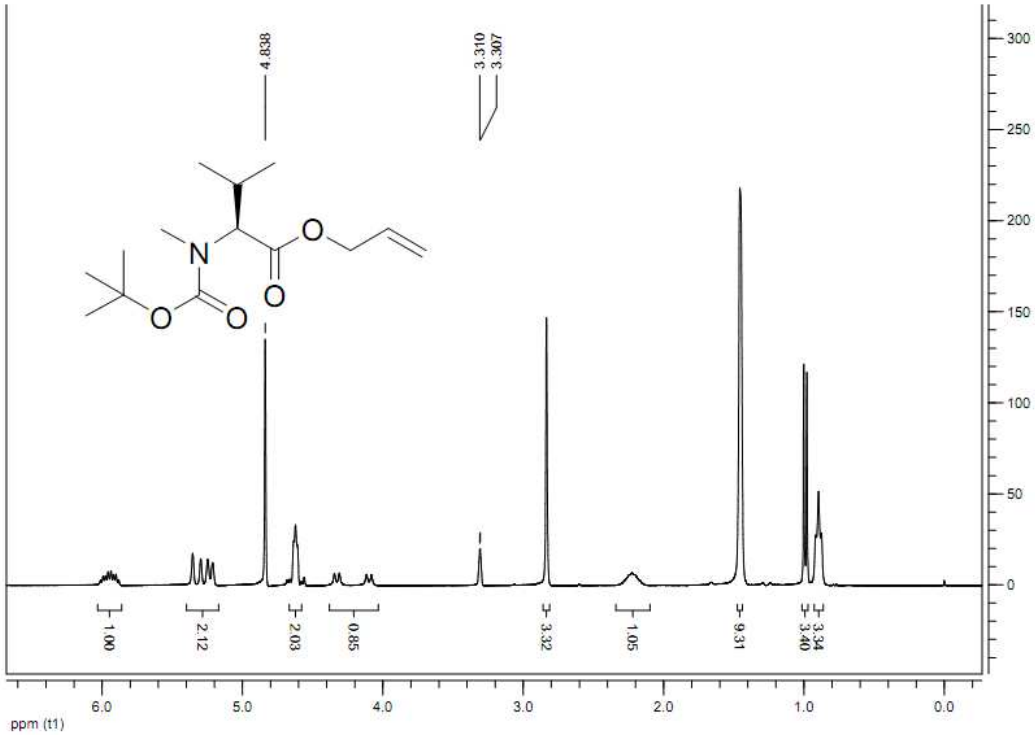
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **P1**



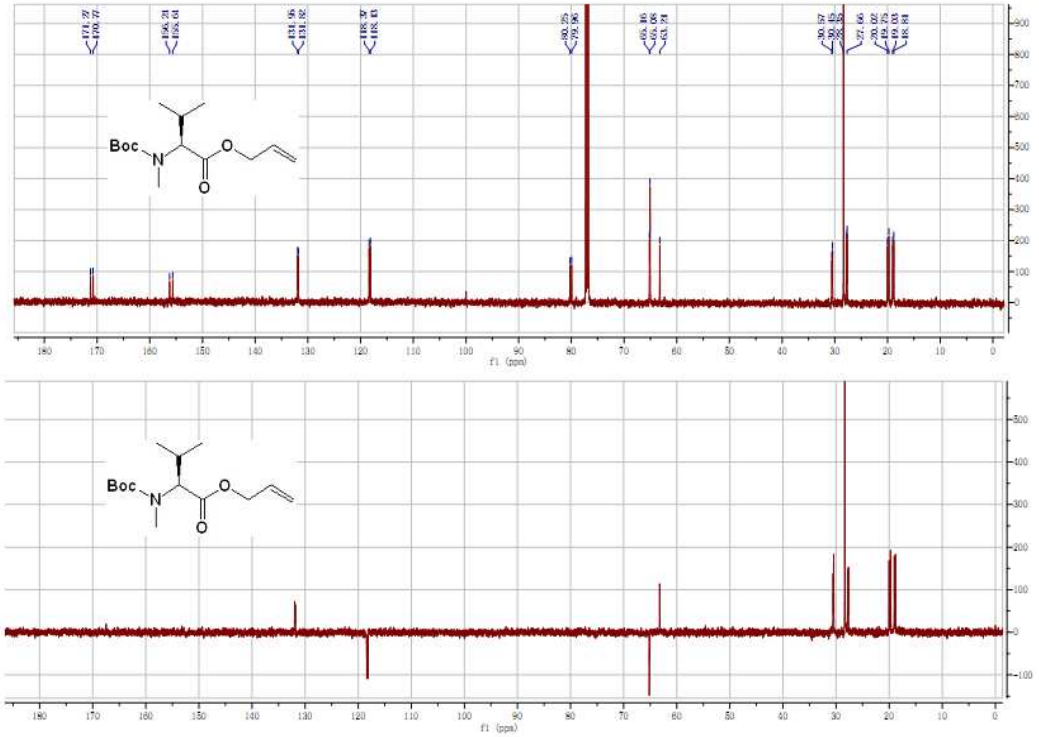
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **P1**



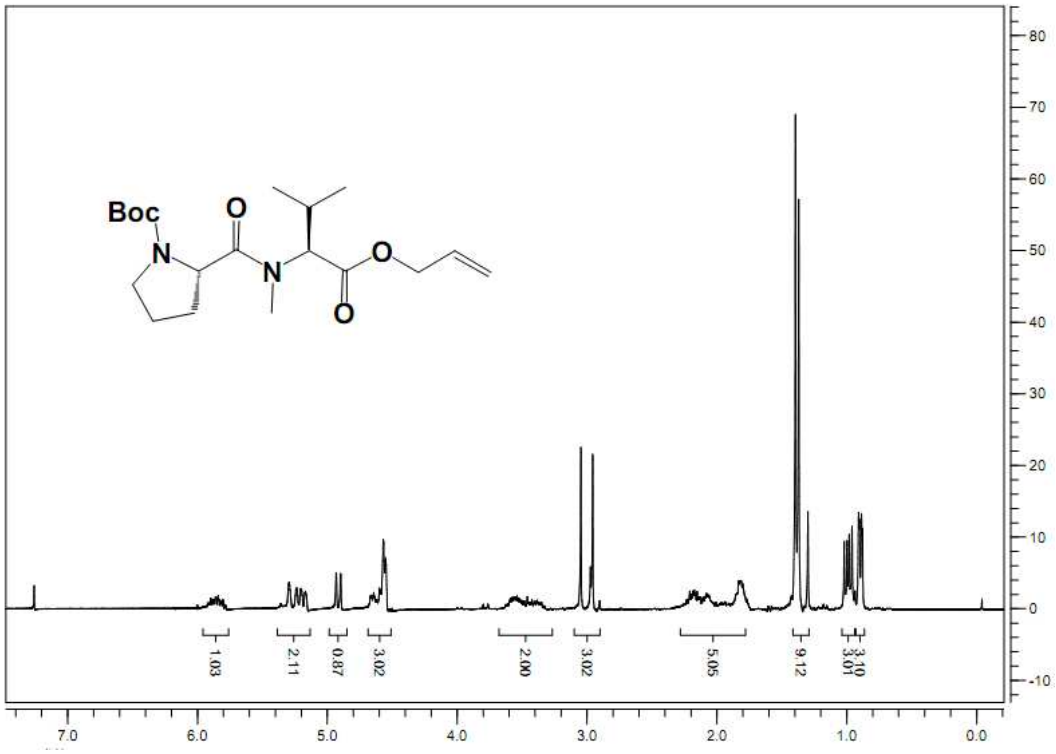
^{1}H NMR (300 MHz, CD_3OD) spectrum of compound **5**



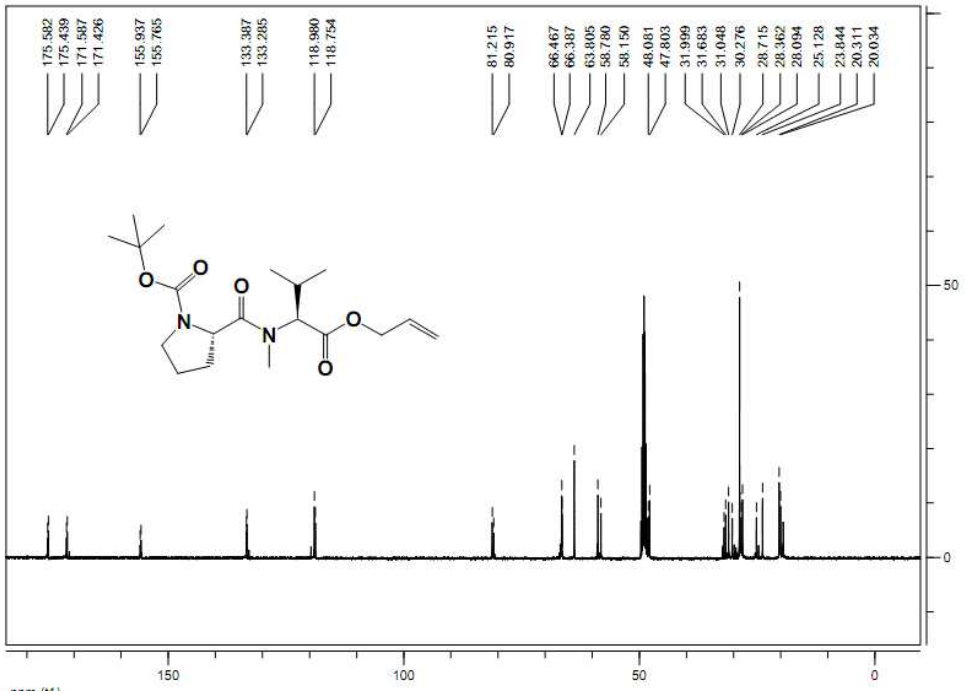
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **5**



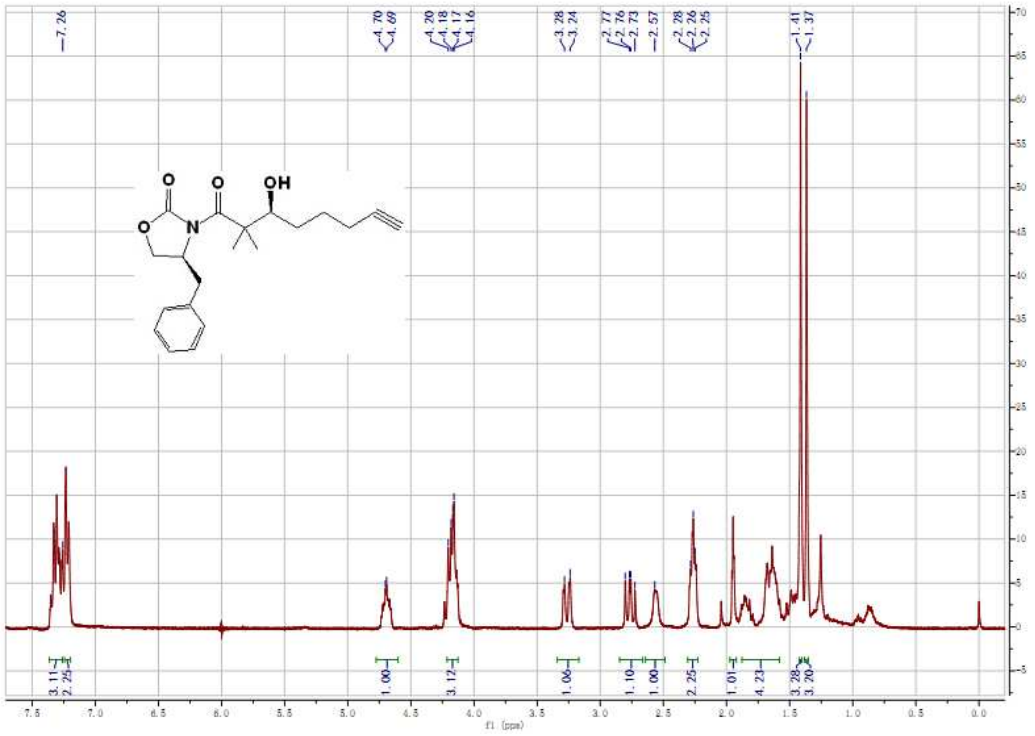
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **P2**



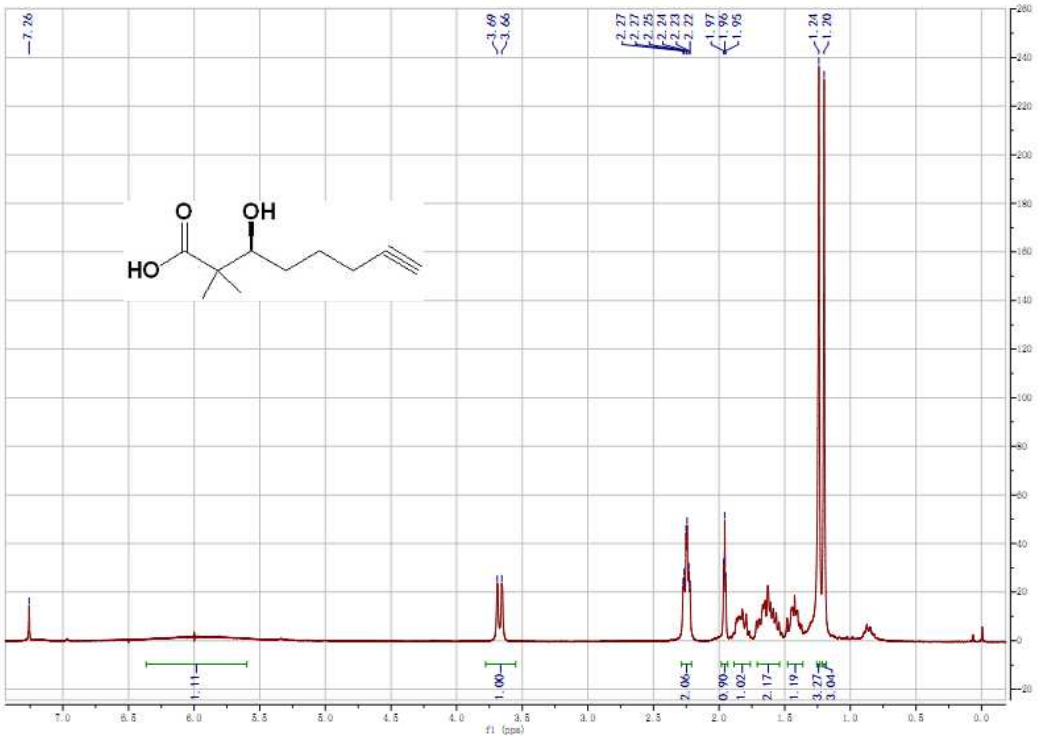
^{13}C NMR (100 MHz, CD_3OD) spectrum of compound **P2**



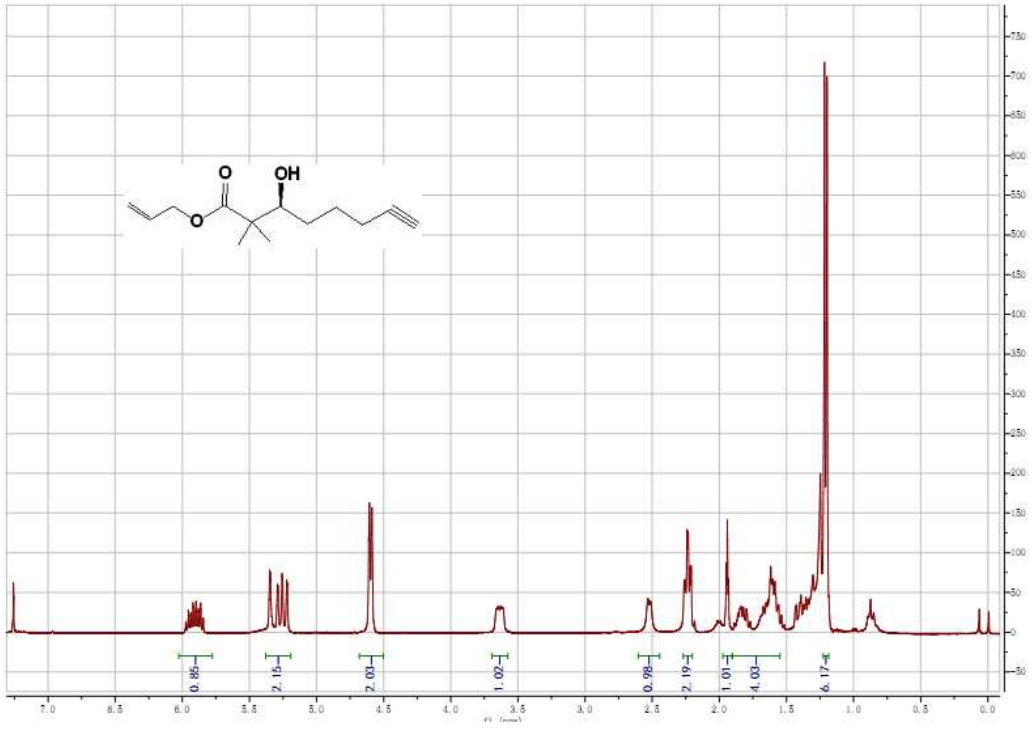
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **6**



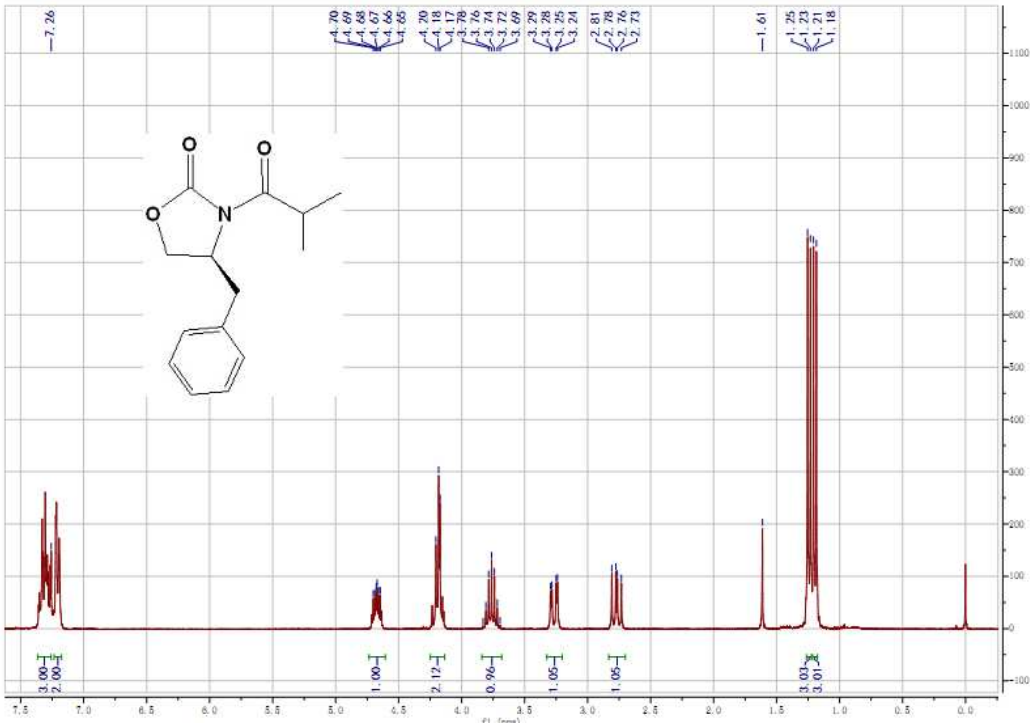
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **7**



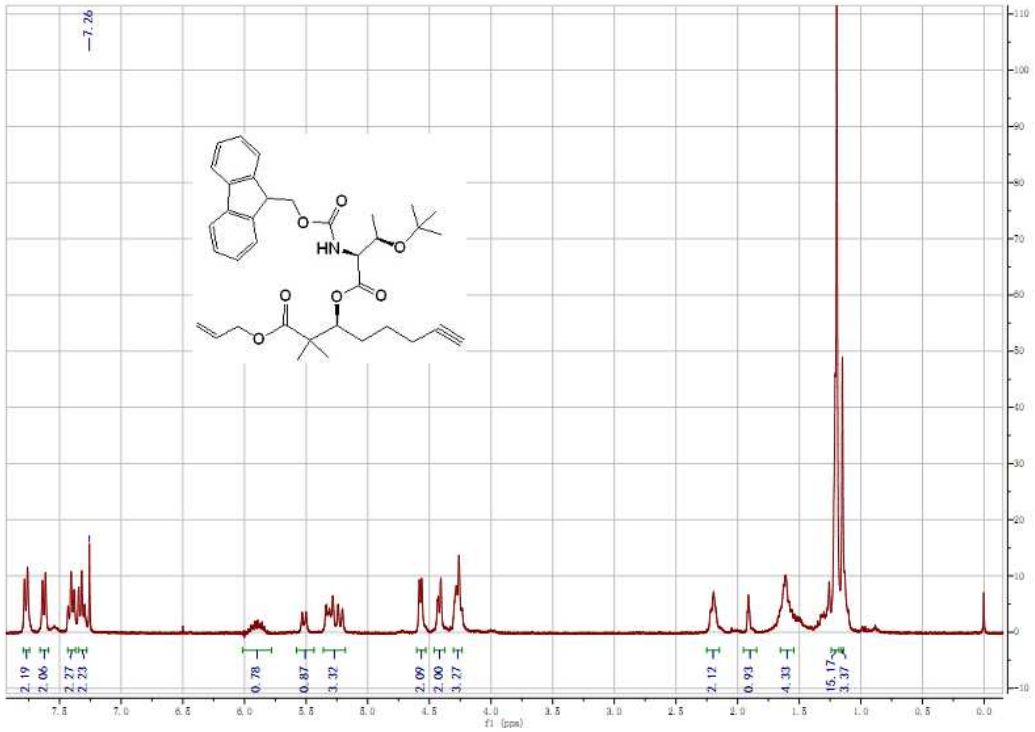
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **8**



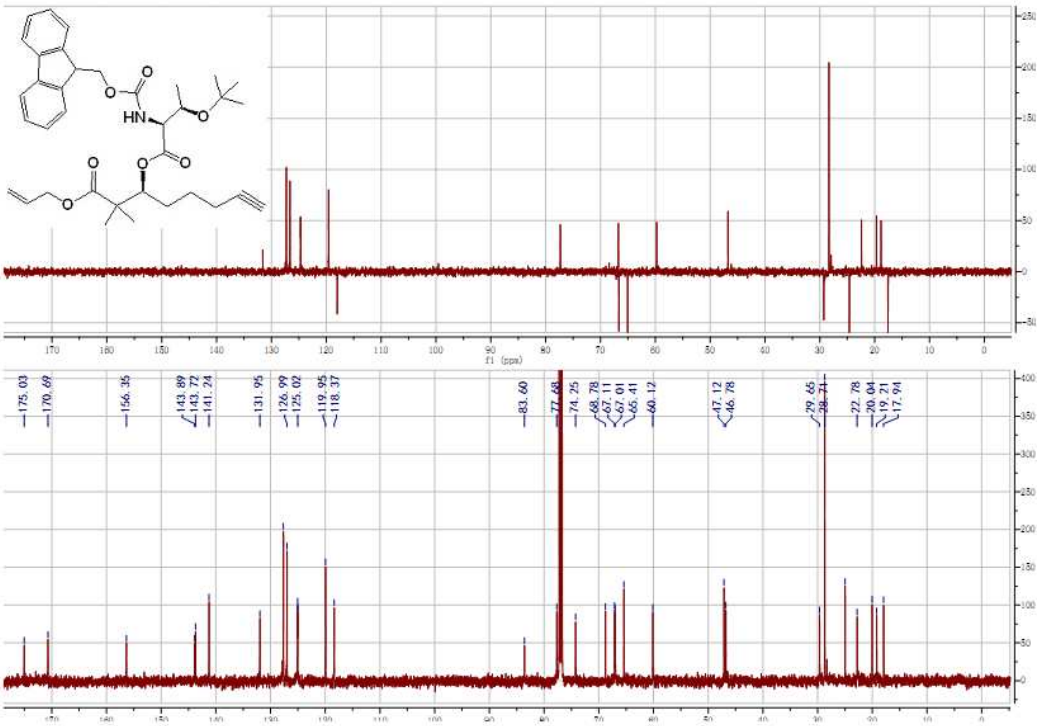
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **9**



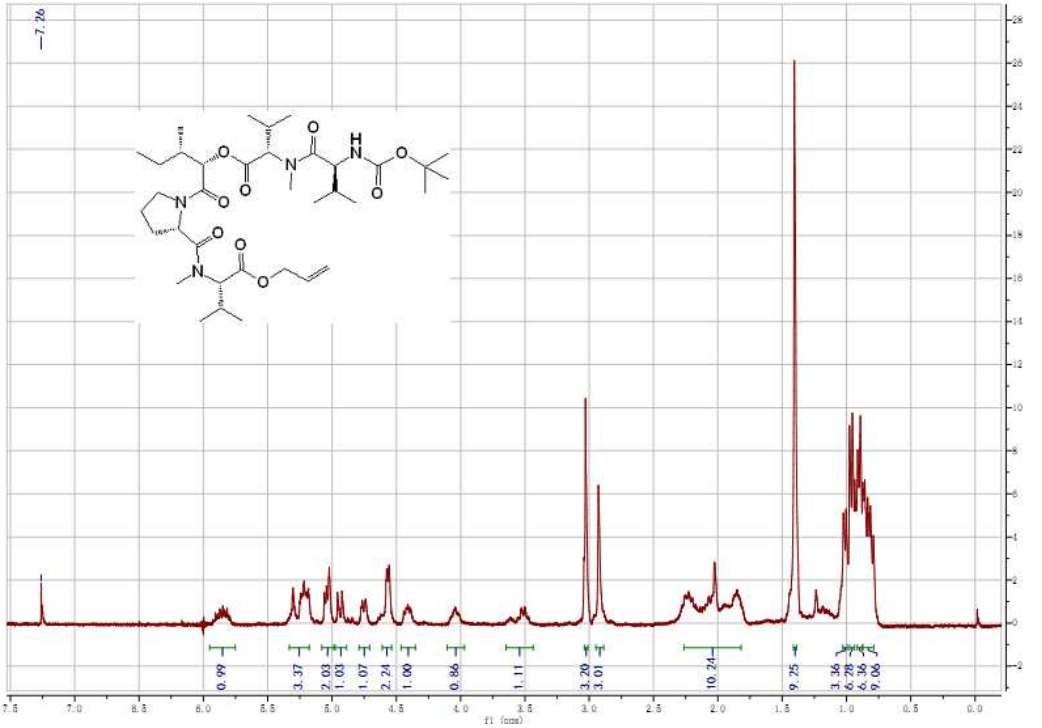
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **P3**



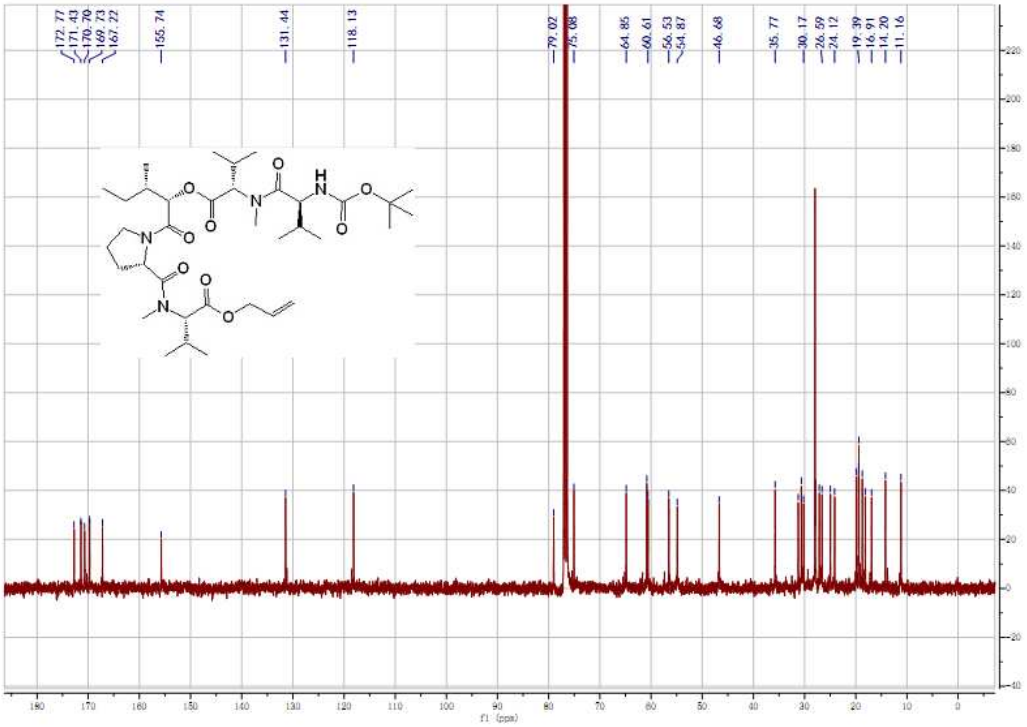
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **P3**



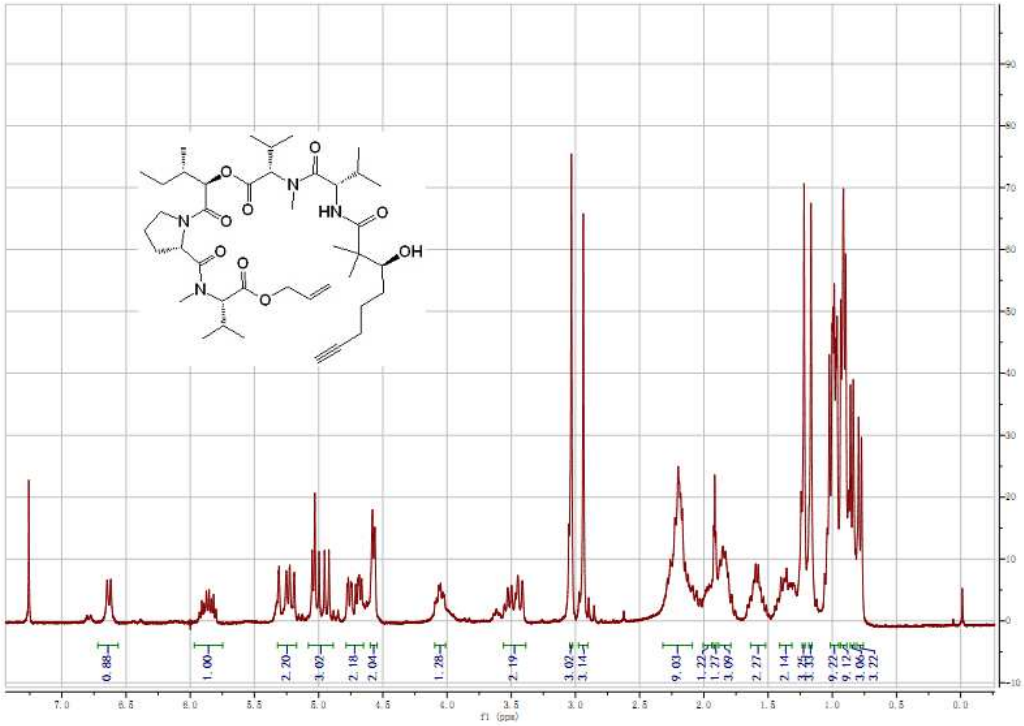
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **12**



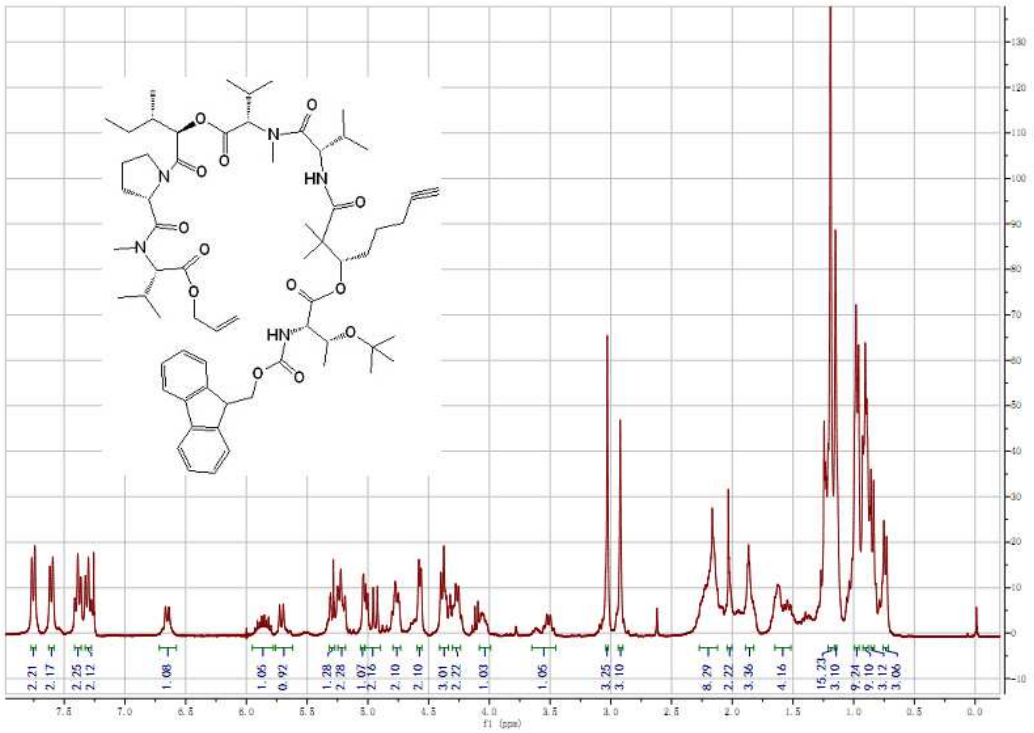
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **12**



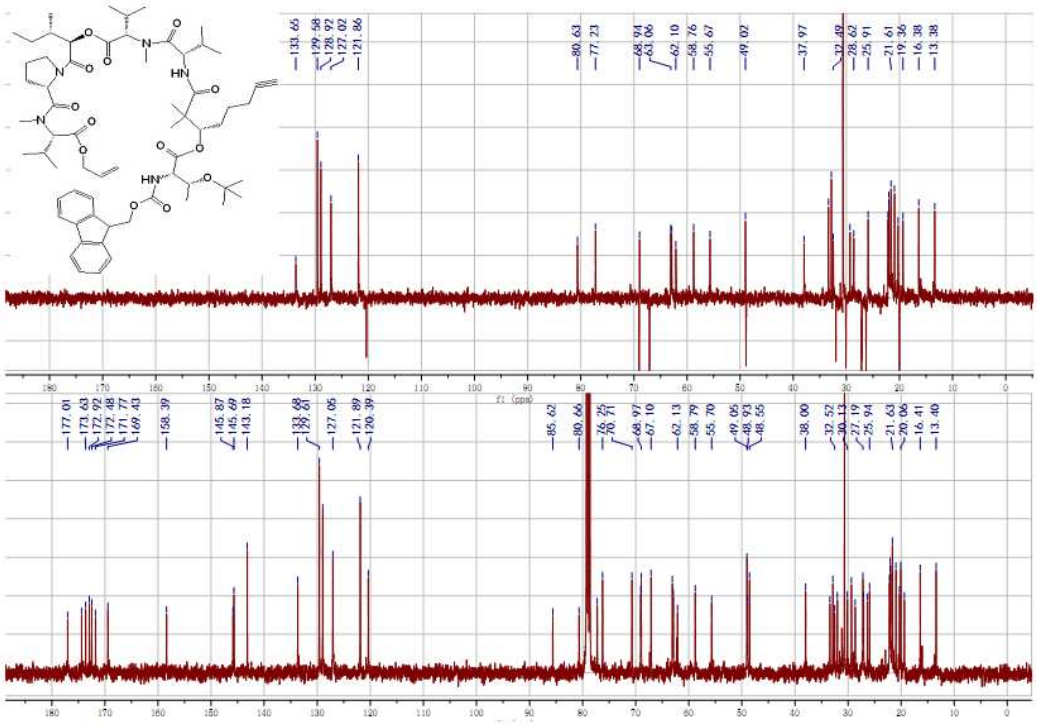
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **13**



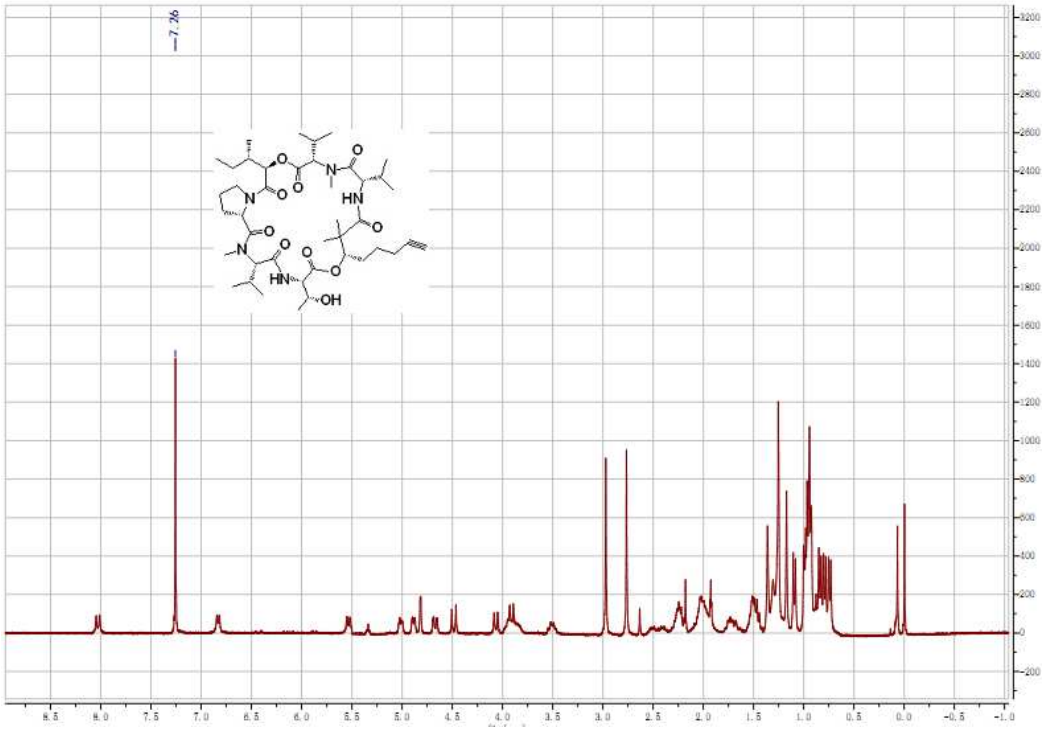
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **14**



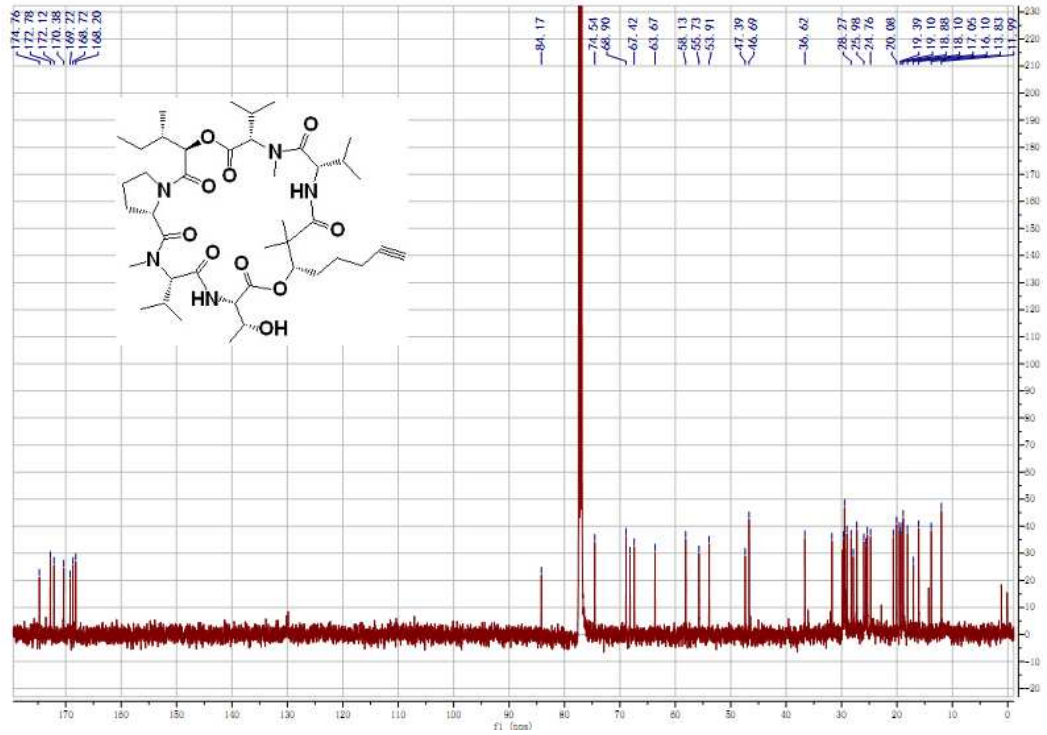
^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **14**



^{1}H NMR (300 MHz, $CDCl_3$) spectrum of compound **1**



^{13}C NMR (125 MHz, $CDCl_3$) spectrum of compound **1**

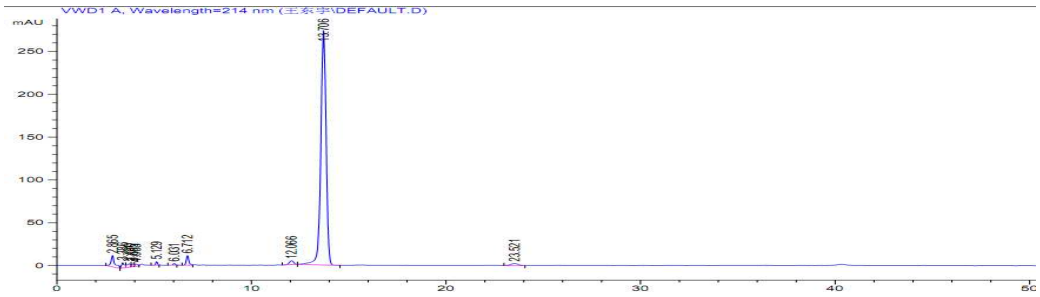


4. Comparison of HPLC for Synthetic **1** and Natural Viequeamide A

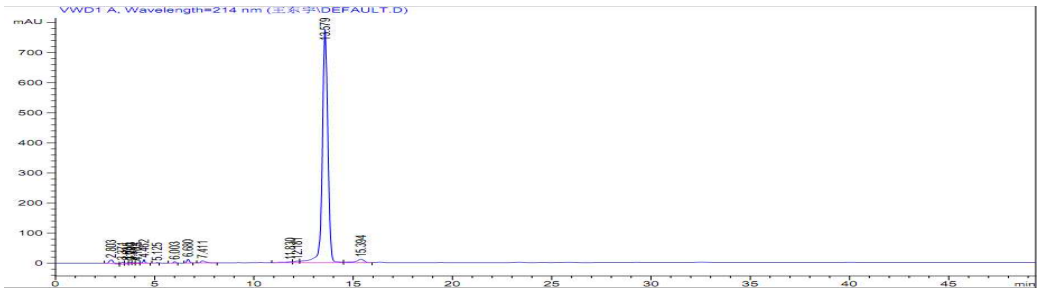
HPLC system: Agilent 1260 Infinity
Mass spectrometry: Waters Acquity UPLC/Synapt Q-TOF-MS
Flow rate: 0.6 ml/min
Wavelength monitoring: 214nm
Column temperature: 25 ˚C
Column: ZORBAX Eclipse XDB-C18 4.6×250mm, 5μm

Condition 1:

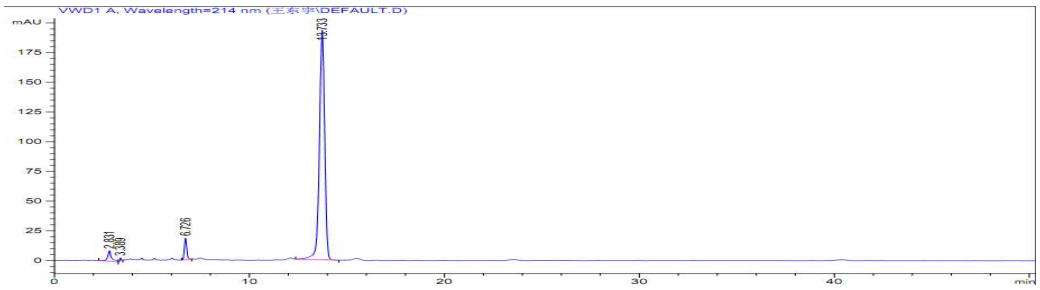
Synthetic **1** — $CH_3CN:H_2O$ = 80:20



Natural Viequeamide A — $CH_3CN:H_2O$ = 80:20

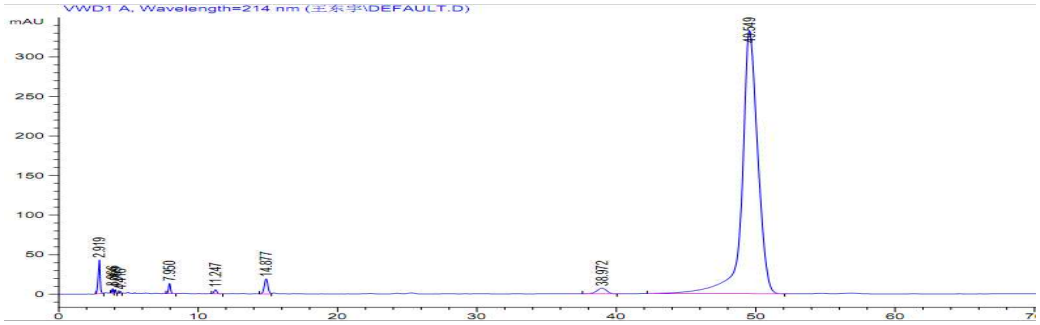


Synthetic **1**+ Natural Viequeamide A (mixture) — $CH_3CN:H_2O$ = 80:20

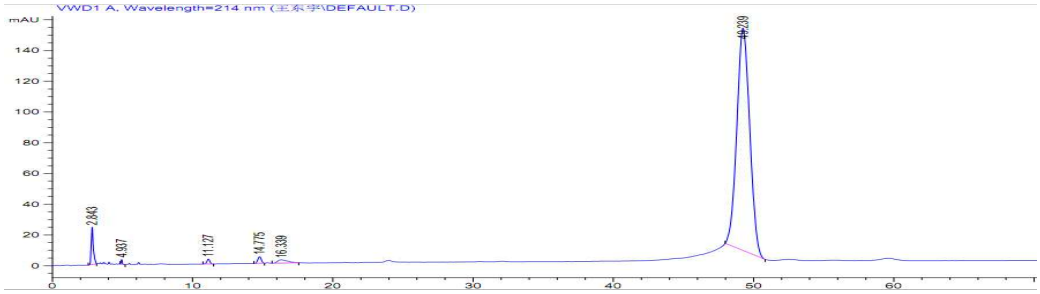


Condition 2:

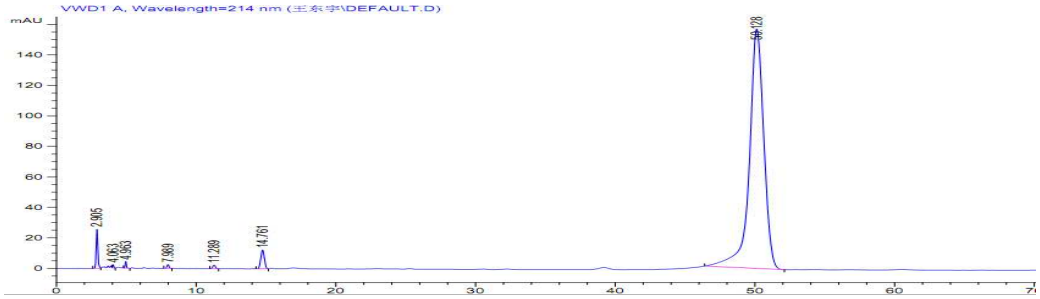
Synthetic **1** — $CH_3CN:H_2O$ = 60:40



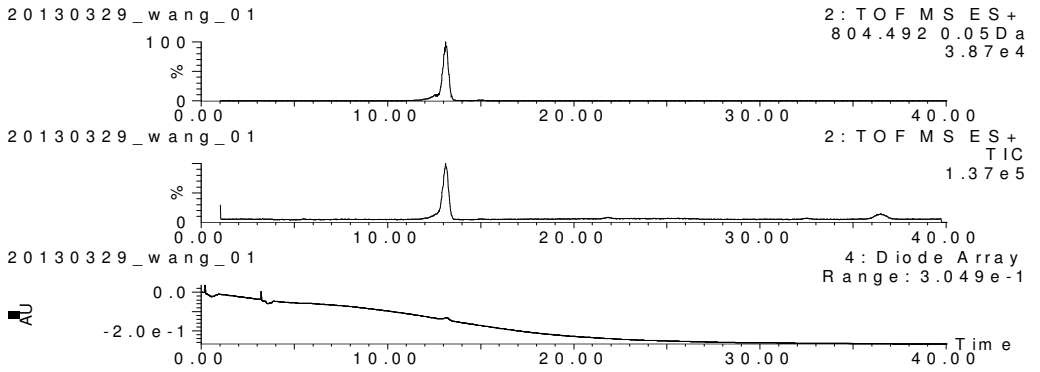
Natural Viequeamide A — $CH_3CN:H_2O$ = 60:40

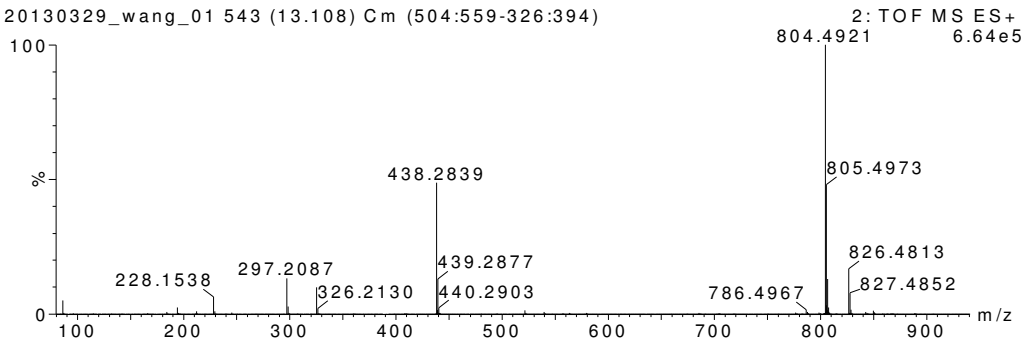


Synthetic 1+ Natural Viequeamide A (mixture) — $CH_3CN:H_2O$ = 60:40



LC/Q-TOF-MS for Synthetic **1**— $CH_3CN:H_2O$ = 80:20




20130329_wang_01 543 (13.108) Cm (504:559-326:394)
2: TOF MS ES+
804.4921
6.64e5
100
%
0
438.2839
805.4973
826.4813
827.4852
439.2877
440.2903
297.2087
326.2130
228.1538
786.4967
100
200
300
400
500
600
700
800
900
m/z