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Synthesis of Endolides A and B; Naturally Occurring *N*-Methylated Cyclic Tetrapeptides

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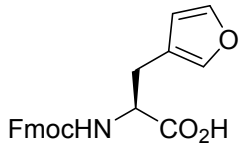
General Information

All solvents and reagents were used as supplied. L-3-(3-Furyl)alanine was recieved as a kind gift from Celso Almeida (Endobios, Portugal). All other Fmoc-amino acids and 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU) were purchased from GL Biochem (Shanghai, China). 2-Chlorotrityl chloride resin was purchased from ChemPep (Wellington, Florida, USA). 1-Propanephosphonic acid anhydride (T3P) solution (50% in ethyl acetate), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 2-nitrobenzenesulfonyl chloride (nosyl-Cl), 2,3,5-collidine (*sym*-collidine), 2-mercaptoethanol, dimethylsulfate, *N,N*-diisopropylethylamine (DIPEA), *N*-methylpyrrolidinone (NMP) and piperidine were purchased from Sigma Aldrich (St. Louis, MO, USA). Dimethylformamide (DMF, AR grade), acetonitrile (MeCN, HPLC grade), were purchased from Thermo Fisher (Hampshire, NH, USA). Trifluoroacetic acid (TFA) was obtained from Oakwood Chemicals (Estill, SC, USA). Dichloromethane (AR grade) was obtained from ECP Limited (Auckland, New Zealand). Optical rotations were determined at the sodium D line (589 nm) at 23 °C by using an Autopol IV instrument, with concentrations given in g/100 mL. High resolution mass spectra were obtained by electrospray ionisation (ESI) in positive ion mode at a nominal accelerating voltage of 70 eV on a microTOF mass spectrometer. Low-resolution mass spectra to confirm peptide identity employed a Waters Quattro Micro API mass spectrometer using ESI in positive mode. Analytical RP-HPLC chromatograms were recorded at 214 nm on Waters (Waltham, MA, USA) Alliance analytical HPLC employing a gradient of 20-80% Solvent B over 40 minutes and flow rate of 1.0 ml/min with a Phenomenex (Torrance, CA, USA) Luna C18 column (100 Å, 5µm, 4.6 mm x 250 mm) operated at room temperature. Solvent A = 100% H_2O + 0.1% TFA. Solvent B = 100% MeCN + 0.1% TFA. Preparative HPLC was performed on a Waters 1525 Binary HPLC pump equipped with a Waters 2489 UV/visible detector using a Waters Xterra Prep MS C18 OBD column (125 Å, 10 µm, 300 x 19 mm) operated at room temperature. Solvent A = 100% H_2O + 0.1% TFA. Solvent B = 100% MeCN + 0.1% TFA. Nuclear magnetic resonance experiments were performed with a Bruker (Billerica, MA, USA) AVANCE 400 (^{1}H 400 MHz; ^{13}C 100 MHz) spectrometer in acetone-d_6. Chemical shifts are recorded in parts per million (ppm) and were referenced to the residual solvent peak at δ = 2.05 ppm for ^{1}H spectra, and δ = 29.84 ppm for ^{13}C spectra. All experiments were conducted at 298 K. ^{1}H NMR spectroscopic data are reported as follows: chemical shift (δ_H), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; sex., sextet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets; td, triplet of doublets; br, broad; app., apparent), coupling constant (*J* in Hz) and assignment. Assignments were made with the aid of HSQC, COSY, NOESY and HMBC 2D NMR experiments.

Experimental Procedures

Fmoc-L-3-(3-furyl)alanine



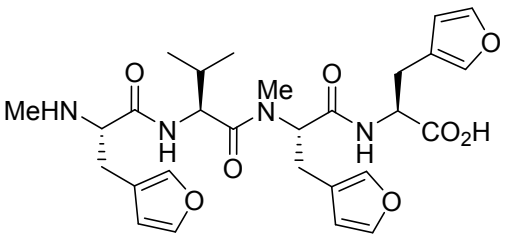
To a stirred solution of L-3-(3-furyl)alanine-OH (1.0 g, 5.23 mmol) and sodium bicarbonate (2.48 g, 29.6 mmol) in water (10 mL) was added a solution of Fmoc *N*-hydroxysuccinimide ester (2.99 g, 8.87 mmol) in 1,4-dioxane (40 mL) and the resulting solution was stirred at room temperature for 22 hours. Upon complete consumption of the starting material, the solution was concentrated *in vacuo*, and the resulting aqueous residue was washed with diethyl ether (2 x 100 mL), acidified to ~pH 3 with 5 M aqueous hydrochloric acid, then extracted with ethyl acetate (4 x 100 mL). The combined organic extracts were dried using $MgSO_4$, filtered, then concentrated *in vacuo*. The crude material was redissolved in 50% aqueous acetonitrile solution and lyophilised to yield the *title compound* (1.88 g, 4.99 mmol, 95%) as a light brown powder which was used without further purification. $[\alpha]_D^{23}$ = -4.8 (c 2.54, acetone); HRMS [ESI, $(M + H)^+$] found 378.1322, [$C_{22}H_{19}NO_5 + H^+$] requires 378.1336; δ_H (400 MHz, acetone-d_6) 7.85 (2 H, d, *J* 7.5, 2 x ArH), 7.68 (2 H, app.t, *J* 6.5, 2 x ArH), 7. 47 (1 H, t, *J* 1.5, ArH), 7.43 – 7.39 (3 H, m, 3 x ArH), 7.33 – 7.29 (2 H, m, 2 x ArH), 6.68 (1 H, brd, *J* 8.1, NH), 6.42 (1 H, s, ArH), 4.47 – 4.43 (1 H, m, CH), 4.32 (2 H, t, *J* 7.0, CH_2), 4.22 (1 H, t, *J* 7.0, CH), 3.06 (1 H, dd, *J* 14.5, 4.7, ½ x CH_2), 2.92 (1 H, dd, *J* 14.5, 8.6, ½ x CH_2); δ_C (100 MHz, acetone-d_6) 173.2 (C), 172.4 (C), 156.8 (C), 145.1 (C), 145.0 (C), 143.9 (CH), 142.1 (2 x C), 141.4 (CH), 128.5 (2 x CH), 127.9 (2 x CH), 126.1 (2 x CH), 120.8 (2 x CH), 112.2 (CH), 67.2 (CH_2), 55.2 (CH), 48.0 (CH), 27.8 (CH_2).

General procedure 1: Synthesis of linear peptides

All linear peptides were prepared on 2-chlorotrityl chloride resin on a 0.35 mmol, 0.5 mmol or 0.2 mmol scale using the Fmoc-SPPS strategy and custom made peptide reaction vessels with sintered glass filters. Briefly, a solution of Fmoc-L-3-(3-furyl)Ala-OH (46.9 mg, 0.124 mmol) and DIPEA (43.5 µL, 0.25 mmol) in dichloromethane (1 mL) was added to the pre-swelled 2-chlorotrityl chloride resin (loading 0.77 mmol/g, swelled in dichloromethane) and the resulting mixture was agitated for 1 hour at room temperature. Fmoc deprotection was achieved using 20% piperidine in DMF (2 mL, 2 x 5 minutes). Peptide couplings were performed using either Fmoc-3-(3-furyl)Ala-OH (46.9 mmol, 0.124 mmol), HATU (43.9 mg, 0.115 mmol) and DIPEA (43.5 µL, 0.25 mmol) in DMF (1 mL) at room temperature for 1 hour, or with Fmoc-Val-OH (67.9 mg, 0.20 mmol) or Fmoc-Leu-OH (70.7 mg, 0.20 mmol), HATU (72.5 mg, 0.19 mmol) and DIPEA (69.6 µL, 0.40 mmol) in DMF (1.5 mL) at room

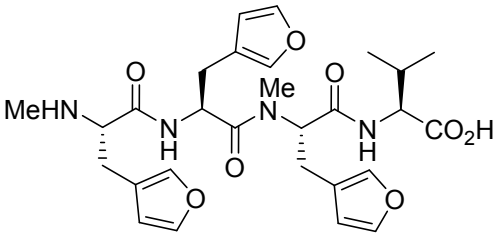
temperature for 1 hour. Site-selective on-resin *N*-methylation was performed in accordance with the procedure described by Kessler and co-workers.[1] Briefly, at the desired site of *N*-methylation, the peptide was Fmoc deprotected and the free amine was treated with 2-nitrobenzenesulfonyl chloride (44.3 mg, 0.20 mmol) and *sym*-collidine (66.0 µL, 0.5 mmol) in NMP (1.5 mL) with agitation at room temperature for 15 minutes, and the procedure repeated following washing with NMP (5 x 2 mL). The 2-NBS protected peptide was then treated with DBU (22.4 µL, 0.15 mmol) in NMP (1.5 mL) with agitation at room temperature for 3 minutes, followed by the addition of dimethylsulfate (47.4 µL, 0.5 mmol). Shaking was continued for 2 minutes at room temperature, before washing with NMP (5 x 2 mL) and repeating the DBU/dimethylsulfate procedure. The 2-NBS group was then removed using a solution of 2-mercaptoethanol (35.2 µL, 0.5 mmol) and DBU (37.3 µL, 0.25 mmol) in NMP (1.5 mL) with shaking for 10 minutes at room temperature, before washing with NMP (5 x 2 mL), and repeating for 15 minutes. Linear peptides were cleaved from the resin using a solution of 10% TFA in dichloromethane (5 mL, 10 minutes) and the solvent was evaporated to yield a crude gum. The crude linear peptide was redissolved in 50% aqueous acetonitrile solution, lyophilised and purified by reversed-phase high performance liquid chromatography (RP-HPLC) using a linear gradient of water and acetonitrile.

HNMe-3-(3-furyl)Ala-Val-NMe-3-(3-furyl)Ala-3-(3-furyl)Ala-OH (**5**)



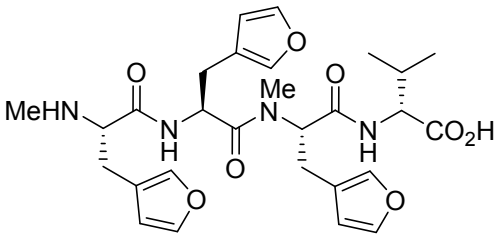
Peptide **5** (2.0 mg, 3.60 µmol, 10%) was prepared as a fluffy white solid according to general procedure **1**. MS (ESI+): *m/z* = 557.1 $[M + H]^+$. RP-HPLC (Luna C18, 100 Å, 5 µm, 4.6 × 250 mm, 20-80% B at 1.5% B per min, 1.0 mL min^{-1}): t_R = 13.31 min.

HNMe-3-(3-furyl)Ala-3-(3-furyl)Ala-NMe-3-(3-furyl)Ala-Val-OH (**6**)



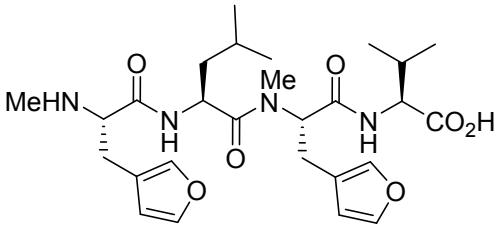
Peptide **6** (36.2 mg, 65.1 µmol, 33%) was prepared as a fluffy white solid according to general procedure **1**. HRMS [ESI, $(M + H)^+$] found 557.2596, [$C_{28}H_{36}N_4O_8 + H^+$] requires 557.2606; RP-HPLC (Luna C18, 100 Å, 5 µm, 4.6 × 250 mm, 20-80% B at 1.5% B per min, 1.0 mL min^{-1}): t_R = 13.90 min.

HNMe-3-(3-furyl)Ala-3-(3-furyl)Ala-NMe-3-(3-furyl)Ala-D-Val-OH (**6***)



Peptide **6*** (15.7 mg, 28.2 µmol, 56%) was prepared as a fluffy white solid according to general procedure **1**. MS (ESI+): *m/z* = 557.1 $[M + H]^+$. RP-HPLC (Luna C18, 100 Å, 5 µm, 4.6 × 250 mm, 20-80% B at 1.5% B per min, 1.0 mL min^{-1}): t_R = 14.51 min.

HNMe-3-(3-furyl)Ala-Leu-NMe-3-(3-furyl)Ala-Val-OH (**10**)

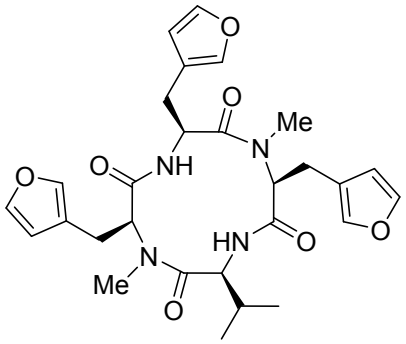


Peptide **10** (13.6 mg, 25.5 µmol, 51%) was prepared as a fluffy white solid according to general procedure **1**. HRMS [ESI, $(M + H)^+$] found 533.2958, [$C_{27}H_{40}N_4O_7 + H^+$] requires 533.2970; RP-HPLC (Luna C18, 100 Å, 5 µm, 4.6 × 250 mm, 20-80% B at 1.5% B per min, 1.0 mL min^{-1}): t_R = 14.28 min

General procedure 2: Cyclisation of linear tetrapeptides

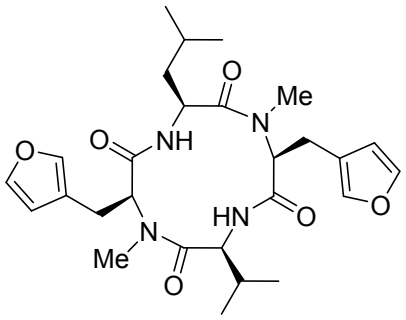
To a solution of the purified linear peptide in DMF (1 mM) was added DIPEA (6 eq.) and T3P (50% solution in ethyl acetate, 3 eq.) and the resulting solution was heated to 40 °C for 23 h. The reaction mixture was then cooled to room temperature and diluted with dichloromethane (~150 mL) before being washed with water (6 x ~100 mL), sodium bicarbonate (sat., ~100 mL), and brine (~100 mL). The organic layer was then dried using $MgSO_4$, filtered, then concentrated *in vacuo*. The crude linear peptide was redissolved in 50% aqueous acetonitrile solution, lyophilised and purified by reversed-phase high performance liquid chromatography (RP-HPLC) using a linear gradient of water and acetonitrile.

Endolide B (**2**)



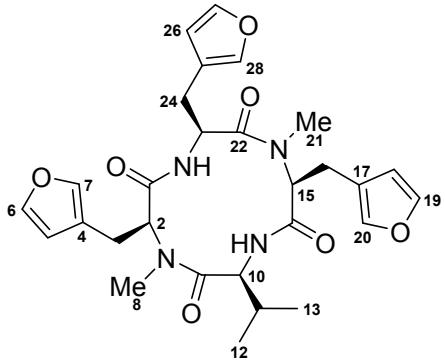
Endolide B (**2**) (6.9 mg, 12.8 µmol, 22%) was prepared as a fluffy white solid, according to general procedure **2** from linear precursor **6** (32 mg, 57.5 µmol). HRMS [ESI, $(M + Na)^+$] found 561.2321, [$C_{28}H_{34}N_4O_7 + Na^+$] requires 561.2320; RP-HPLC (Luna C18, 100 Å, 5 µm, 4.6 × 250 mm, 20-80% B at 1.5% B per min, 1.0 mL min^{-1}): t_R = 25.22 min; $[\alpha]_D^{23}$ = -143.5 (c 0.085, acetone) [lit.[2] -95 (c 0.033, acetone)]; ^1H and ^{13}C NMR data see Tables S1 and S2.

Endolide A (**1**)

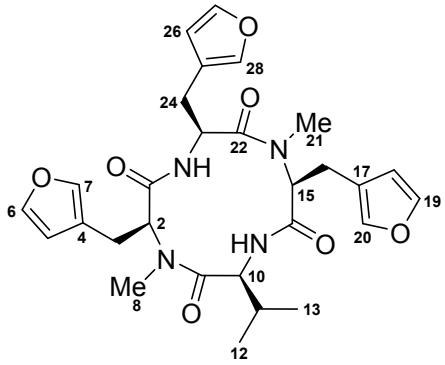


Endolide A (**1**) (2.7 mg, 5.25 µmol, 28%) was prepared as a fluffy white solid according to general procedure **2**, using linear precursor **10** (10.1 mg, 19.0 µmol). HRMS [ESI, $(M + Na)^+$] found 537.2664, [$C_{27}H_{38}N_4O_6 + Na^+$] requires 537.2684; RP-HPLC (Luna C18, 100 Å, 5 µm, 4.6 × 250 mm, 20-80% B at 1.5% B per min, 1.0 mL min^{-1}): t_R = 27.50 min; $[\alpha]_D^{23}$ = -128.2 (c 0.845, acetone) [lit.[2] -69 (c 0.033, acetone)]; ^1H and ^{13}C NMR data see Tables S3 and S4.

Table S1. ^{1}H NMR comparison of natural endolide B (**2**)[2] with synthetic endolide B (**2**).



Amino acid	H	Natural endolide B[2] δ_H (acetone-d_6, 300 MHz)	Synthetic endolide B δ_H (acetone-d_6, 400 MHz)	Δδ
***N*-Me-L-3(3-Furyl)Ala (a)**	2	4.29 (dd, *J* 11.3, 3.3)	4.30 (dd, *J* 11.6, 3.2)	+0.01
	3a	3.31 (dd, *J* 15.3, 3.3)	3.31 (dd, *J* 15.5, 2.6)	0
	3b	2.83 (dd, *J* 15.3, 11.3)	2.84 (dd, *J* 15.4, 11.6)	+0.01
	5	6.34 (br s)	6.35 (dd, *J* 1.9, 1.0)	+0.01
	6	7.51 (t, *J* 1.6)	7.52 (t, *J* 1.7)	+0.01
	7	7.41 (br s)	7.41 (br s)	0
	NMe-8	2.72 (s)	2.73 (s)	+0.01
L-Val	10	4.36 (br t, *J* 9.2)	4.37 (app. t, *J* 9.3)	+0.01
	11	2.11 (m)	2.12 (app. sex, *J* 6.8)	+0.01
	12	0.82 (d, *J* 6.6)	0.84 (d, *J* 6.8)	+0.02
	13	0.85 (d, *J* 6.6)	0.86 (d, *J* 6.8)	+0.01
	NH-10	7.83 (d, 9.5)	7.79 (d *J* 9.4)	-0.04
***N*-Me-L-3(3-Furyl)Ala (b)**	15	4.37 (dd, *J* 11.3, 3.3)	4.37 (dd, *J* 11.4, 3.3)	0
	16a	3.37 (dd, *J* 15.3, 3.3)	3.39 (dd, *J* 15.5, 2.5)	+0.02
	16b	2.95 (dd, *J* 15.3, 11.3)	2.96 (dd, *J* 15.1, 12.6)	+0.01
	18	6.33 (br s)	6.34 (br s)	+0.01
	19	7.46 (t, *J* 1.6)	7.47 (t, *J* 1.7)	+0.01
	20	7.41 (br s)	7.41 (br s)	0
	NMe-21	2.80 (s)	2.81 (s)	+0.01
L-3(3-Furyl)Ala	23	4.85 (dt, *J* 9.5, 6.9)	4.86 (dt, *J* 9.5, 6.8)	+0.01
	24a	2.95 (dd, *J* 14.9, 6.9)	2.97 (dd, *J* 15.0, 6.6)	+0.02
	24b	2.59 (dd, *J* 14.9, 6.9)	2.61 (dd, *J* 14.7, 6.7)	+0.02
	26	6.29 (br s)	6.30 (br m)	+0.01
	27	7.40 (t, *J* 1.6)	7.40 (t, *J* 1.7)	0
	28	7.27 (br s)	7.28 (br m)	+0.01
	NH-23	7.96 (d, *J* 9.5)	7.92 (d, *J* 9.4)	-0.04

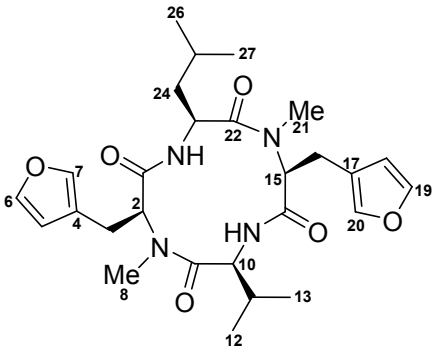


Amino acid	C	Natural endolide B[2] δ_H (acetone-d_6, 75 MHz)	Synthetic endolide B δ_H (acetone-d_6, 100 MHz)	Δδ
***N*-Me-L-3(3-Furyl)Ala (a)**	1	170.1	170.2	+0.1
	2	62.6	62.6	0
	3	24.4	24.5	+0.1
	4	122.0	122.1 or 122.0[a]	+0.05
	5	111.0	111.0	0
	6	144.5	144.49 or 144.48[b]	0
	7	141.1	141.1	0
	NMe-8	30.3	30.4	+0.1
L-Val	9	172.1	172.1	0
	10	56.2	56.3	+0.1
	11	30.1	30.2	+0.1
	12	20.8	20.8	0
	13	18.4	18.5	+0.1
***N*-Me-L-3(3-Furyl)Ala (b)**	14	170.7	170.8	+0.1
	15	62.8	62.8	0
	16	24.7	24.8	+0.1
	17	122.0	122.1 or 122.0[a]	+0.05
	18	111.0	111.0	0
	19	144.5	144.49 or 144.48[b]	0
	20	141.0	141.0	0
	NMe-21	30.6	30.7	+0.1
L-3(3-Furyl)Ala	22	172.5	172.6	+0.1
	23	51.3	51.4	+0.1
	24	28.0	28.1	+0.1
	25	121.7	121.8	+0.1
	26	112.8	112.9	+0.1
	27	143.2	143.3	+0.1
	28	141.3	141.4	+0.1

Table S2. ^{13}C NMR comparison of natural endolide B (**2**)[2] with synthetic endolide B (**2**).

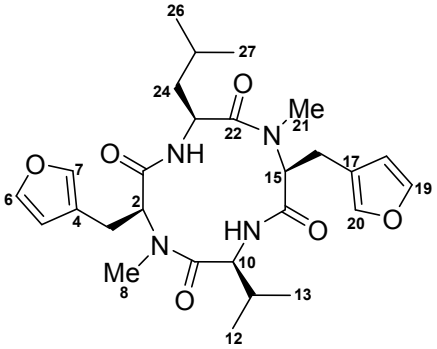
[a,b] Signals could not be assigned using 2D NMR spectroscopy

Table S3. ^{1}H NMR comparison of natural endolide A (**1**)[2] with synthetic endolide A (**1**).



Amino acid	H	Natural endolide A[2] δ_H (acetone-d_6, 300 MHz)	Synthetic endolide A δ_H (acetone-d_6, 400 MHz)	Δδ
***N*-Me-L-3(3-Furyl)Ala (a)**	2	4.29 (dd, *J* 11.7, 3.3)	4.31 (dd, *J* 11.7, 3.2)	+0.02
	3a	3.36 (dd, *J* 15.0, 3.3)	3.37 (dd, *J* 15.4, 3.3)	+0.01
	3b	2.91 (dd, *J* 15.0, 11.7)	2.92 (m)	+0.01
	5	6.37 (br s)	6.38 (dm, *J* 4.9)	+0.01
	6	7.53 (t, *J* 1.6)	7.53 (t, *J* 1.6)	0
	7	7.43 (br s)	7.43 (br d, *J* 4.0)	0
	NMe-8	2.74 (s)	2.75 (s)	+0.01
L-Val	10	4.35 (br t, *J* 9.2)	4.37 (t, *J* 8.3)	+0.02
	11	2.12 (m)	2.14 (app. sex, *J* 6.8)	+0.02
	12	0.83 (d, *J* 6.6)	0.85 (d, *J* 6.7)	+0.02
	13	0.85 (d, *J* 6.6)	0.87 (d, *J* 6.7)	+0.02
	NH-10	7.81 (d, 9.2)	7.79 (d, *J* 8.9)	-0.02
***N*-Me-L-3(3-Furyl)Ala (b)**	15	4.37 (dd, *J* 11.7, 3.3)	4.39 (dd, *J* 11.6, 3.3)	+0.02
	16a	3.38 (dd, *J* 15.0, 3.3)	3.40 (dd, *J* 15.4, 3.3)	+0.02
	16b	2.94 (dd, *J* 15.0, 11.7)	2.95 (m)	+0.01
	18	6.37 (br s)	6.38 (d m, *J* 4.9)	+0.01
	19	7.53 (t, *J* 1.6)	7.53 (t, *J* 1.6)	0
	20	7.43 (br s)	7.43 (br d, *J* 4.0)	0
	NMe-21	2.78 (s)	2.79 (s)	+0.01
L-Leu	23	4.67 (td, *J* 9.2, 5.9)	4.69 (dt, *J* 8.9, 6.0)	+0.02
	24a	1.30 (m)	1.30 (m)	0
	24b	1.65 (m)	1.69 (m)	+0.04
	25	1.54 (m)	1.55 (m)	+0.01
	26	0.87 (d, *J* 6.6)	0.89 (d, *J* 6.7)	
	27	0.83 (d, *J* 6.6)	0.85 (d, *J* 6.7)	+0.02

	NH-23	7.91 (d, *J* 9.2)	7.89 (d, *J* 9.7)	-0.02



Amino acid	C	Natural endolide A[2] δ_H (acetone-d_6, 75 MHz)	Synthetic endolide A δ_H (acetone-d_6, 100 MHz)	Δδ
***N*-Me-L-3(3-Furyl)Ala (a)**	1	170.3	170.4	+0.1
	2	62.7	62.8	+0.1
	3	24.5	24.5	0
	4	122.1	122.1	0
	5	111.0	111.1	+0.1
	6	144.5	144.5	0
	7	141.0	141.1	+0.1
	NMe-8	30.3	30.4	+0.01
L-Val	9	172.1	172.2	+0.1
	10	56.2	56.3	0
	11	30.2	30.2	0
	12	20.8	20.8	0
	13	18.5	18.5	0
***N*-Me-L-3(3-Furyl)Ala (b)**	14	170.7	170.8	+0.1
	15	62.9	63.0	+0.1
	16	24.5	24.5	0
	17	122.0	122.1	+0.1
	18	110.9	111.0	+0.1
	19	144.4	144.5	+0.1
	20	141.1	141.1	0
	NMe-21	30.6	30.6	0
L-Leu	22	172.9	173.0	+0.1
	23	49.2	49.3	+0.1
	24	42.0	42.1	+0.1
	25	25.1	25.1	0
	26	22.5	22.6	+0.1
	27	23.3	23.3	0

Table S4. ^{13}C NMR comparison of natural endolide A (**1**)[2] with synthetic endolide A (**1**).

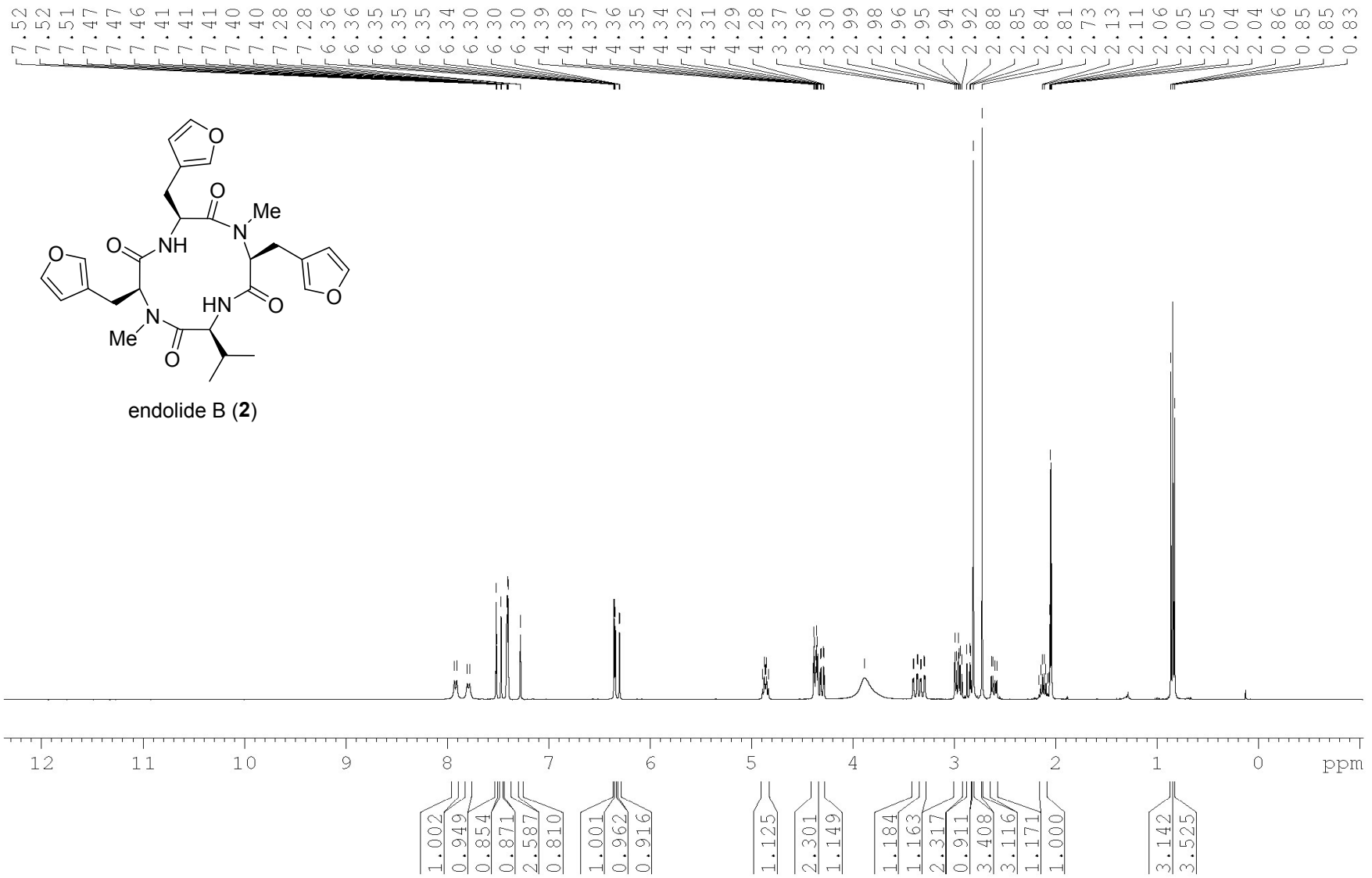


Figure S1. ^{1}H NMR spectrum of endolide B (**2**) (acetone-d_6, 400 MHz).

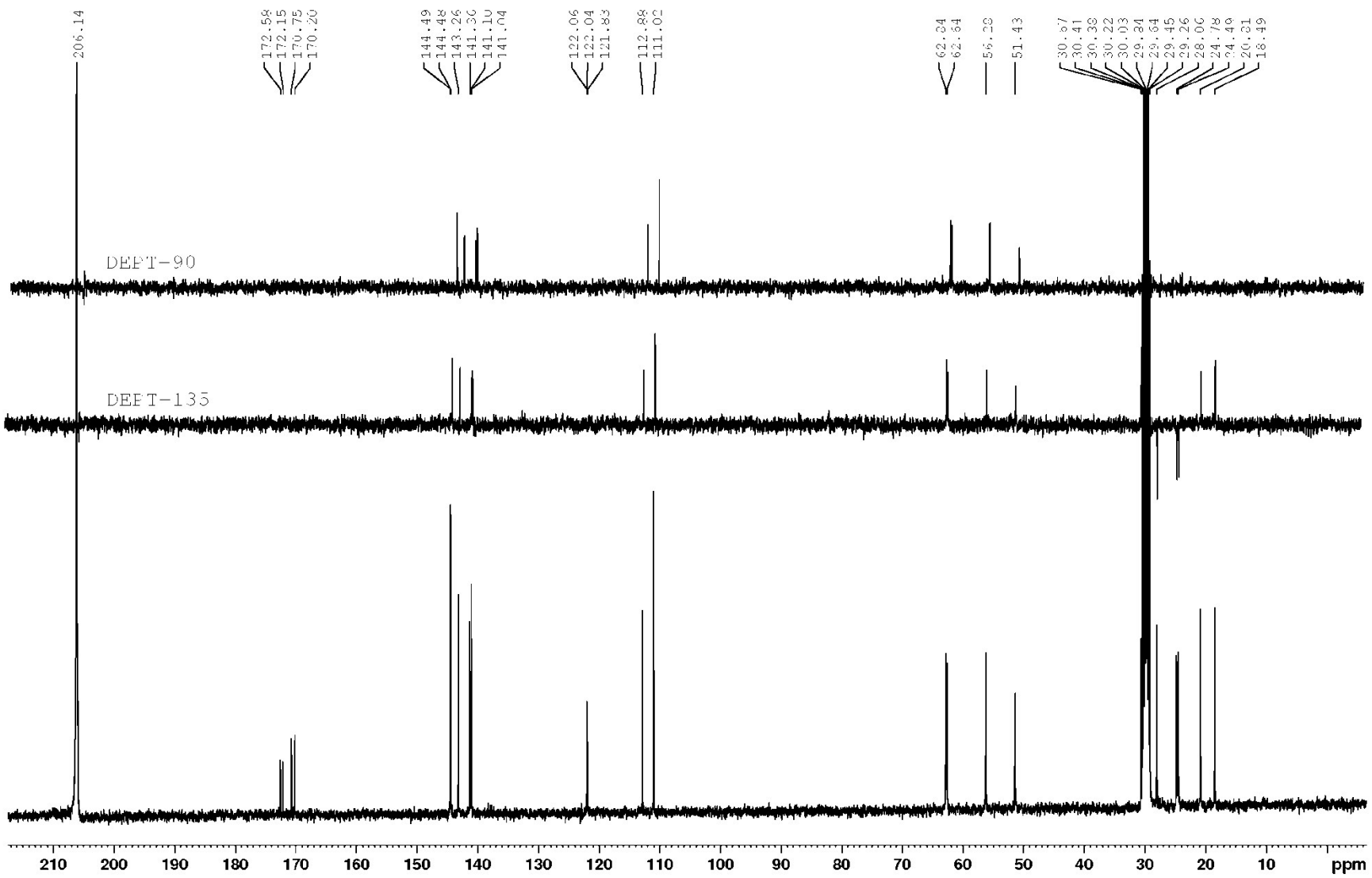


Figure S2. ^{13}C NMR spectrum of endolide B (**2**) (acetone-d_6, 100 MHz).

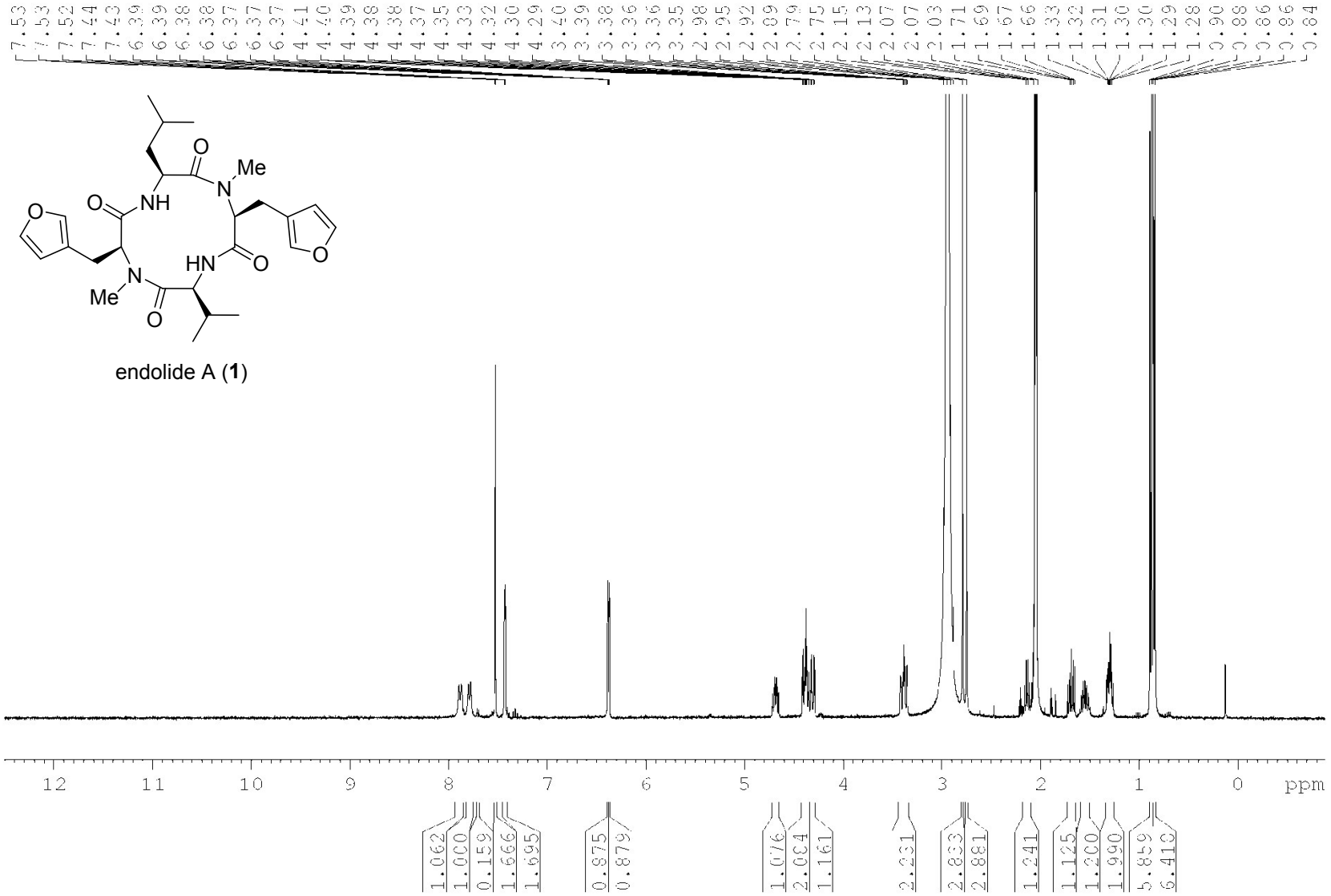


Figure S3. ^{1}H NMR spectrum of endolide A (**1**) (acetone-d_6, 400 MHz).

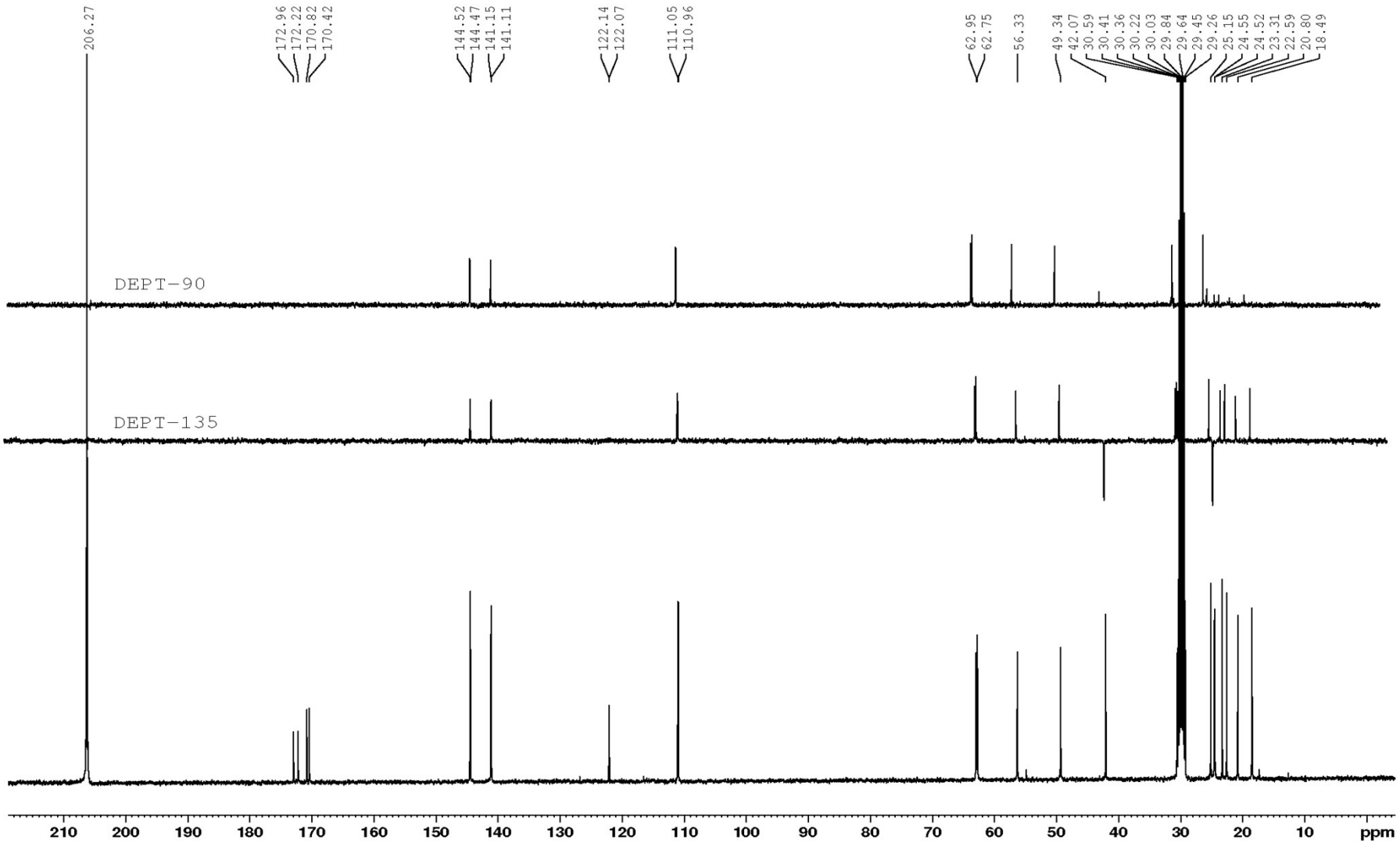


Figure S4. ^{13}C NMR spectrum of endolide A (**1**) (acetone-d_6, 100 MHz).

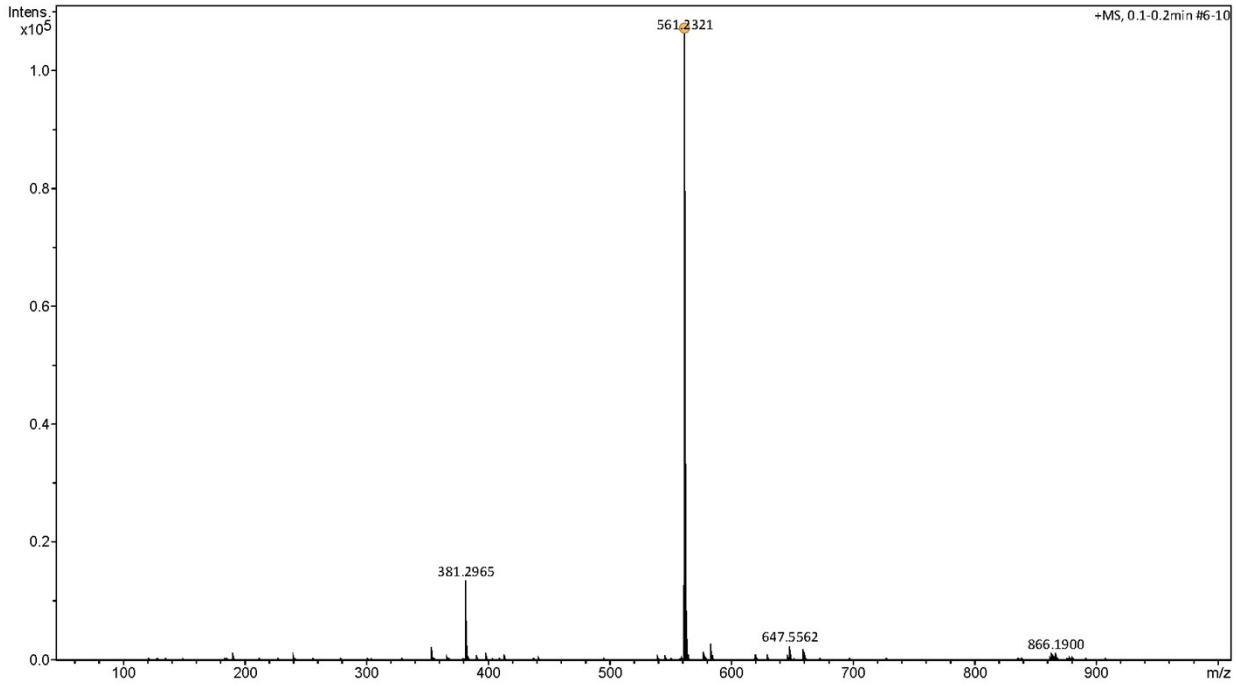


Figure S5: HRMS spectrum of endolide B (**2**).

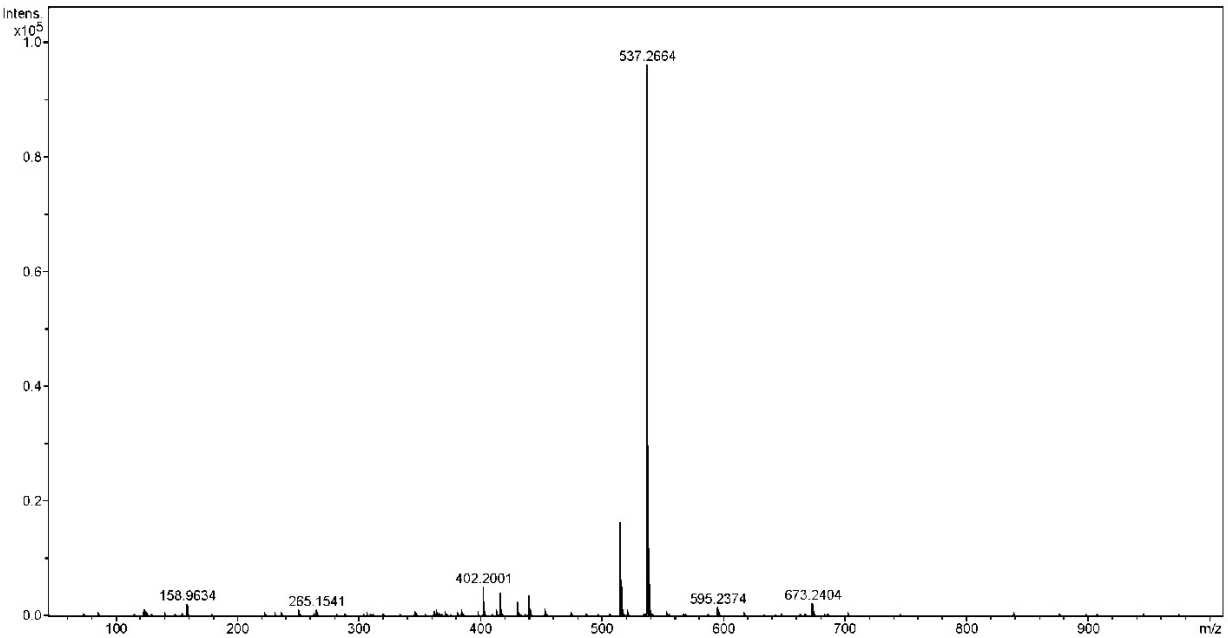


Figure S6: HRMS spectrum of endolide A (**1**).

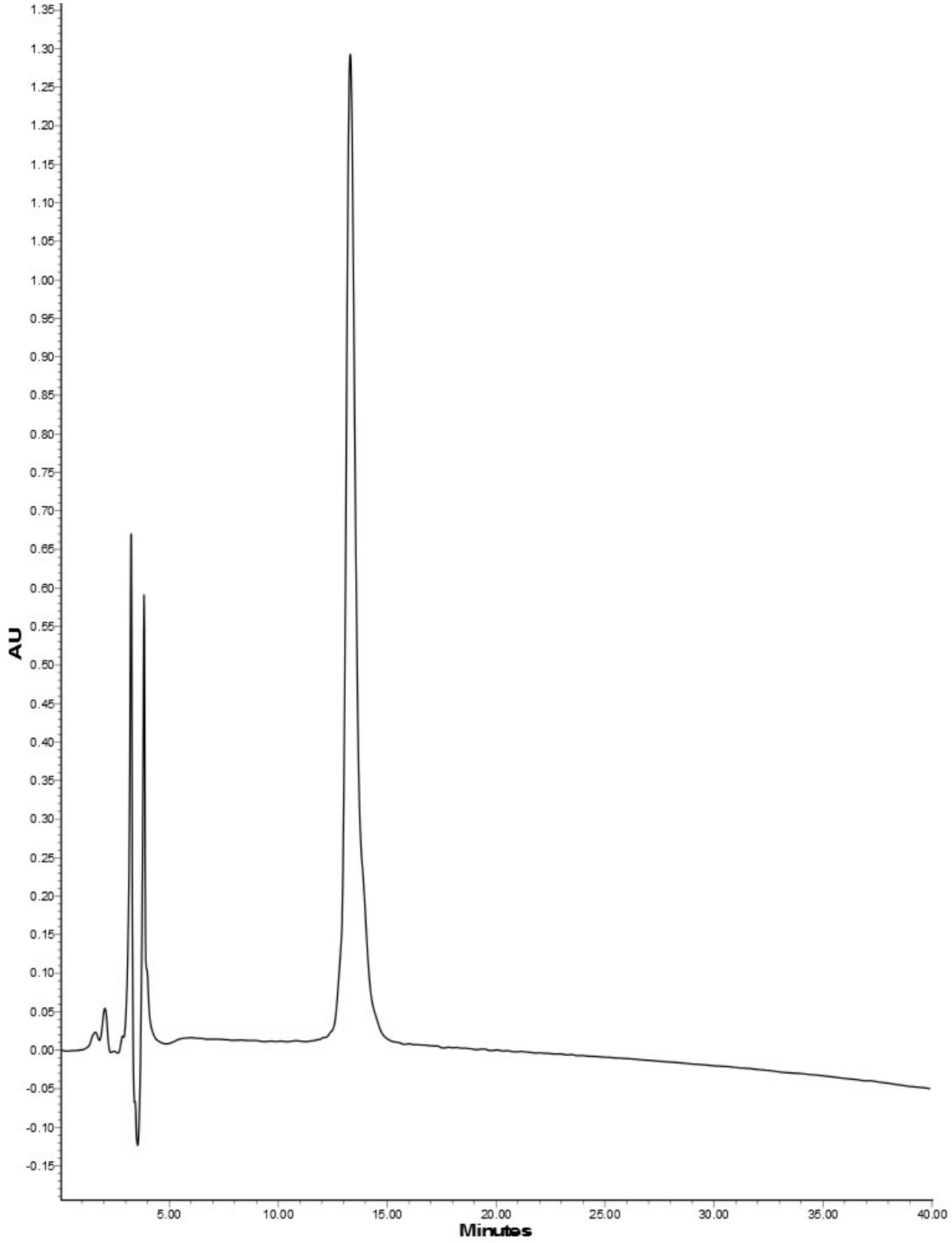


Figure S7: Analytical RP-HPLC chromatogram of purified **5**, 95% purity (214 nm, peaks with t_R <4 min result from solvent spikes during injection.)

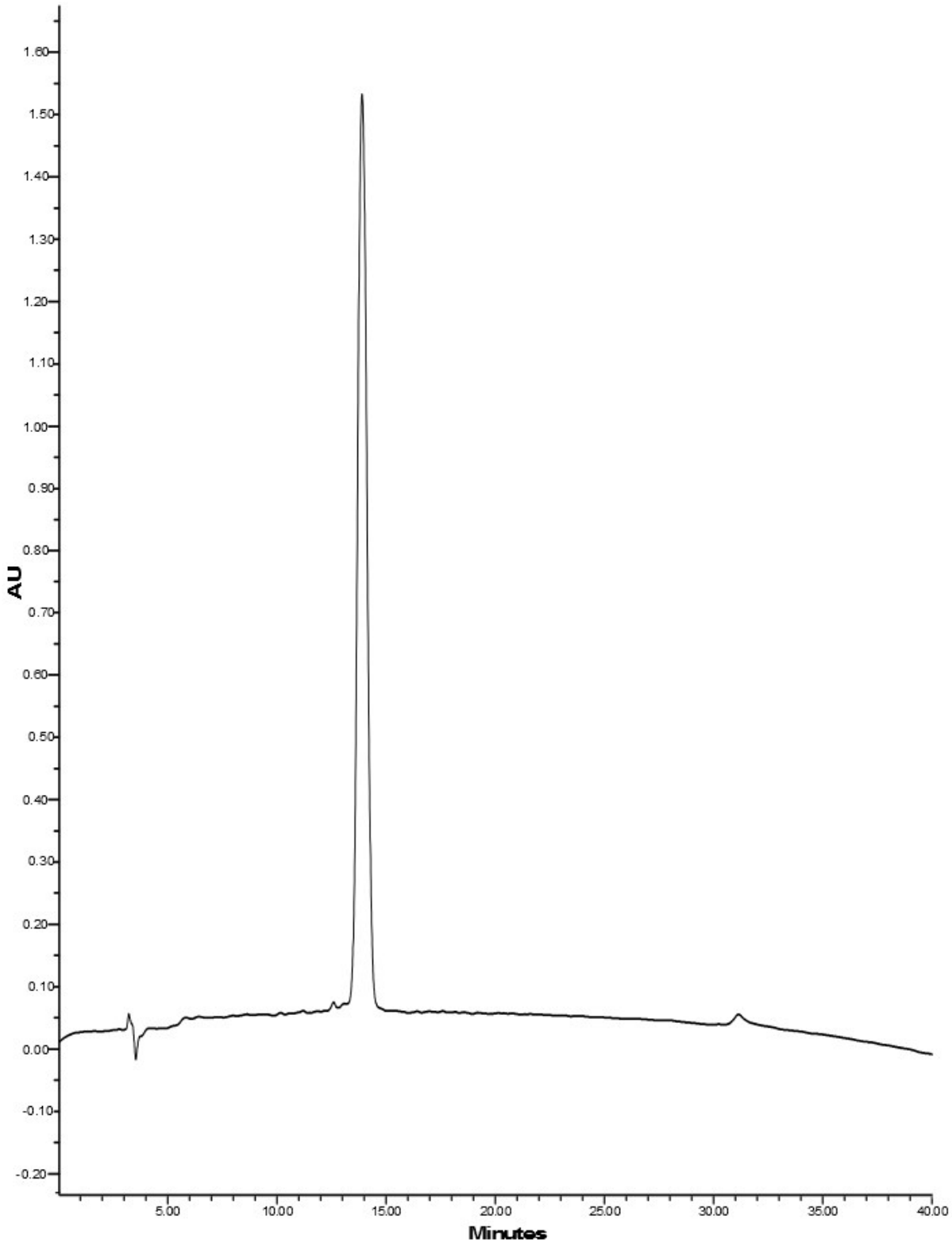


Figure S8: Analytical RP-HPLC chromatogram of purified **6**, 99% purity (214 nm, peaks with t_R <4 min result from solvent spikes during injection.)

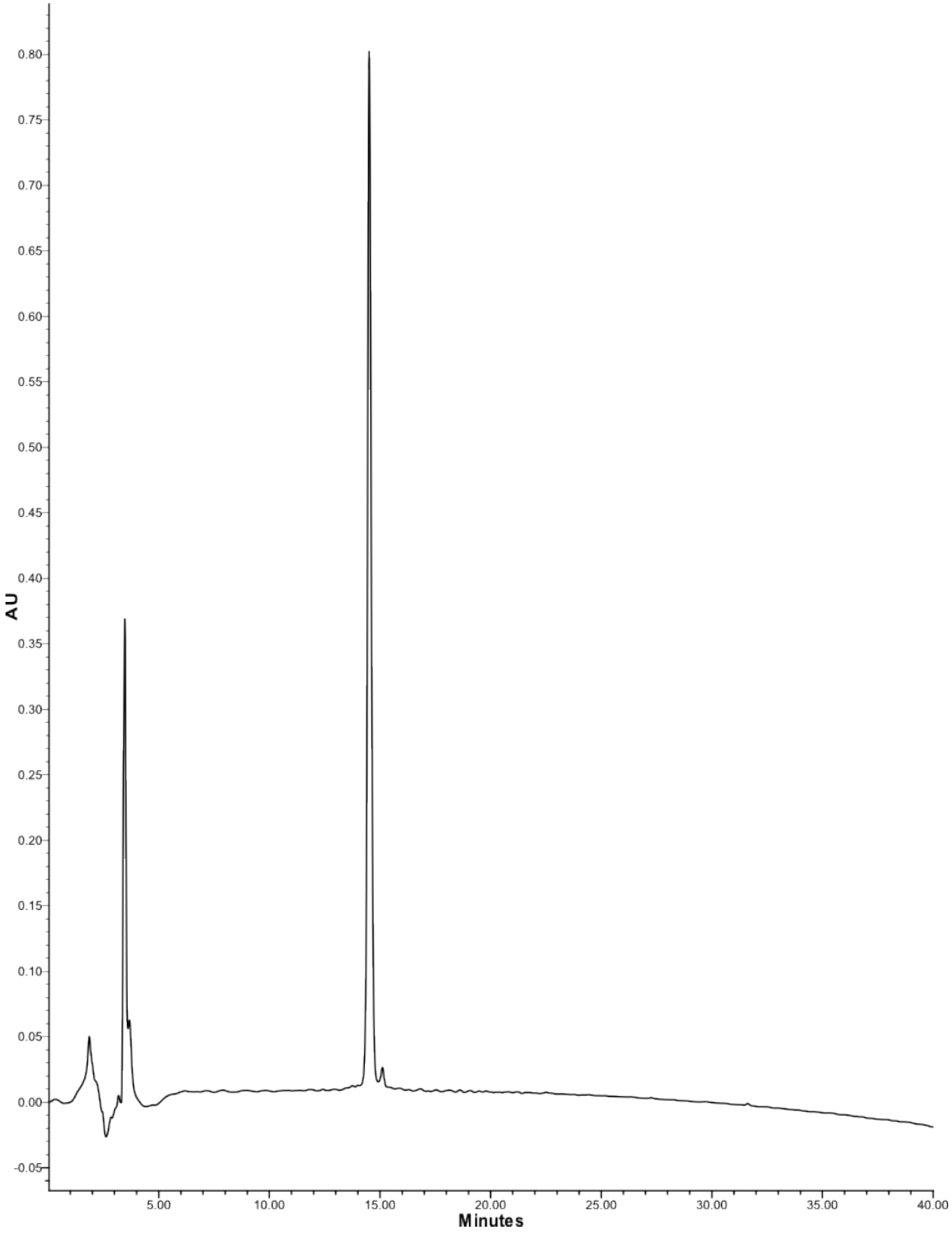


Figure S9: Analytical RP-HPLC chromatogram of purified **6***, 98% purity (214 nm, peaks with t_R <4 min result from solvent spikes during injection.)

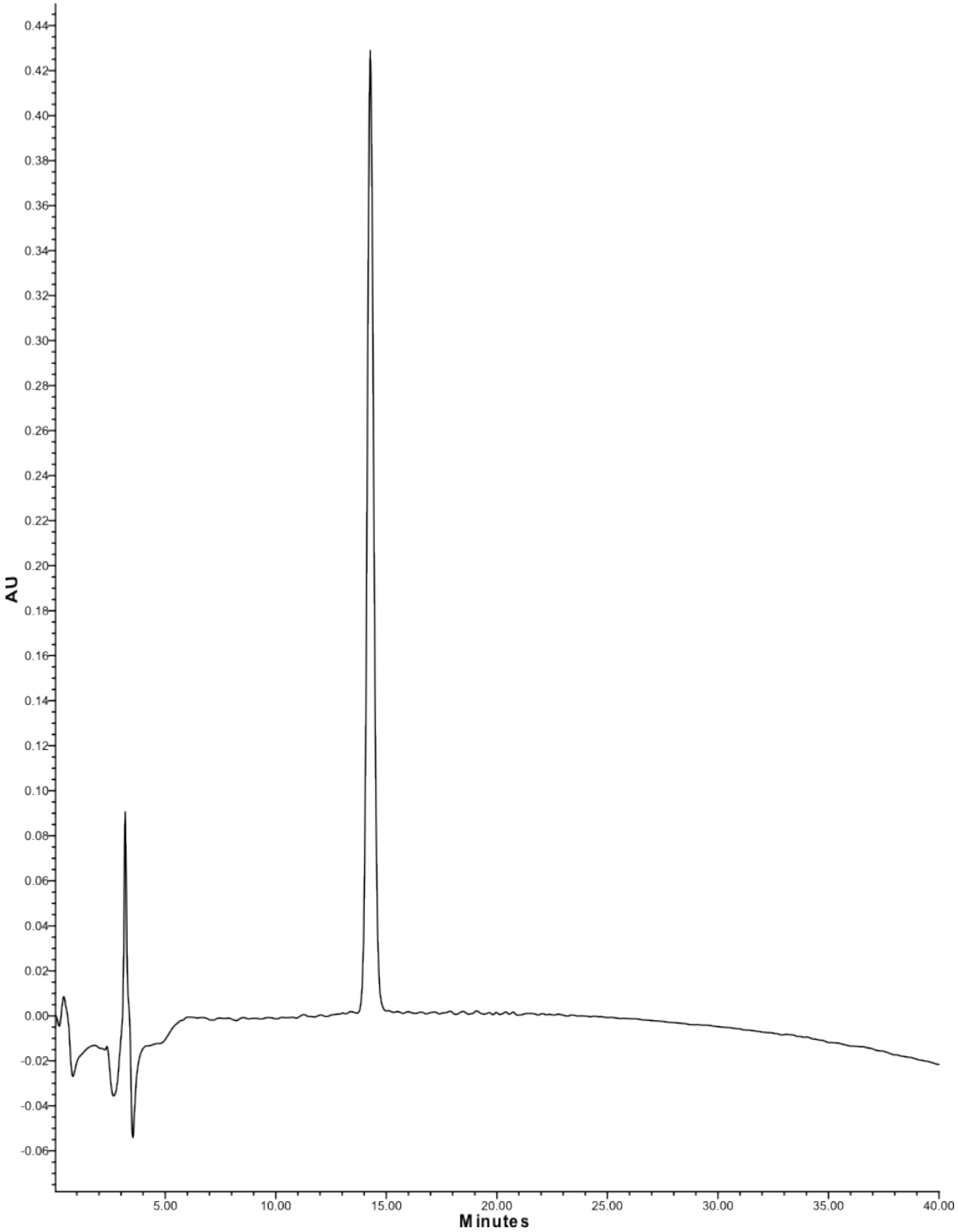


Figure S10: Analytical RP-HPLC chromatogram of purified **10**, >99% purity (214 nm, peaks with t_R <4 min result from solvent spikes during injection.)

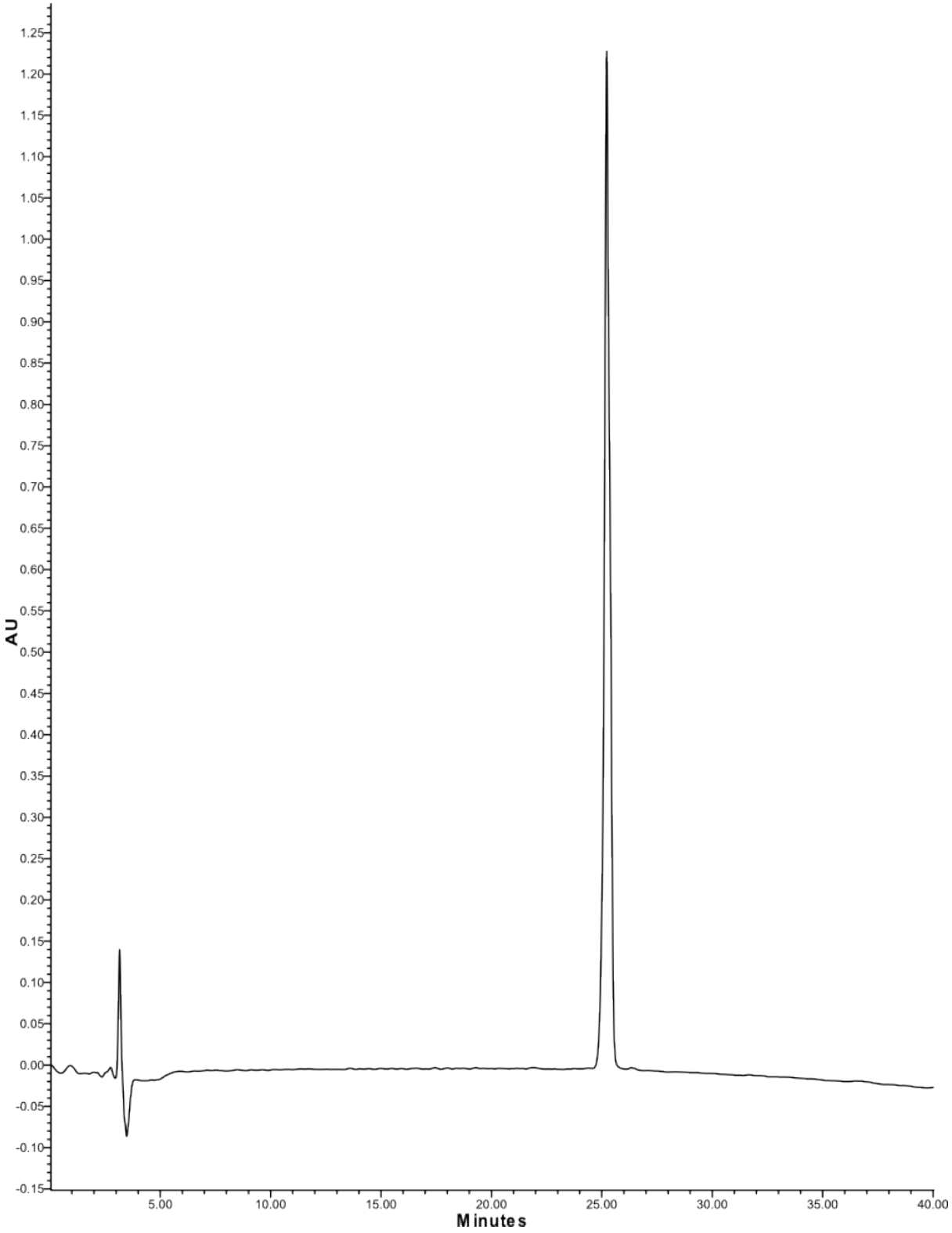


Figure S11: Analytical RP-HPLC chromatogram of purified endolide B (**2**), >99% purity (214 nm, peaks with t_R <4 min result from solvent spikes during injection.)

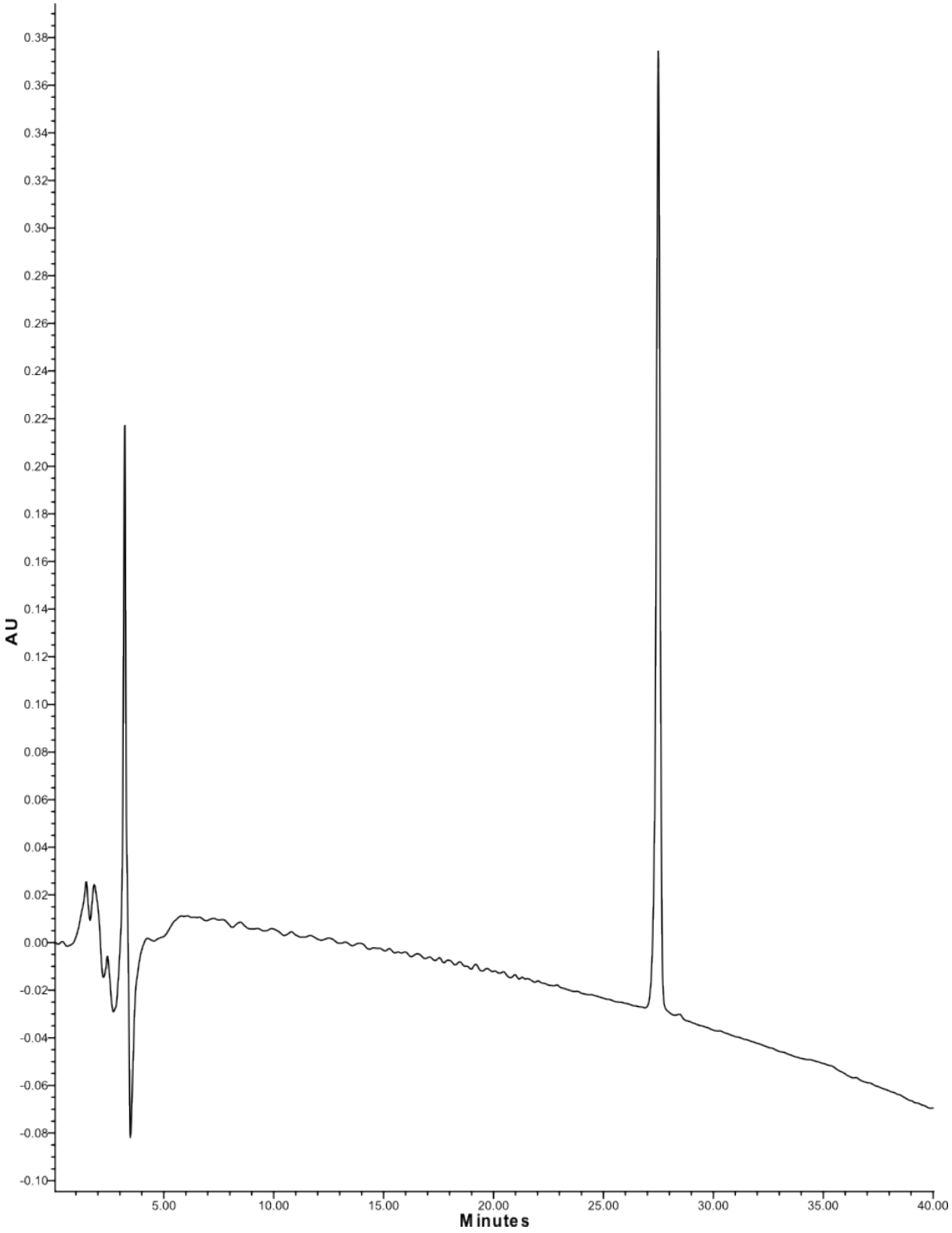


Figure S12: Analytical RP-HPLC chromatogram of purified endolide A (**1**), >99 % purity (214 nm, peaks with t_R <4 min result from solvent spikes during injection.)

References

1. J. Chatterjee, B. Laufer and H. Kessler, *Nat. Protoc.*, 2012, **7**, 432.
2. C. Almeida, F. El Maddah, S. Kehraus, G. Schnakenburg and G. M. König, *Org. Lett.*, 2016, **18**, 528.