Supporting Information

Bifunctional Doscadenamides Activate Quorum Sensing in Gram-Negative Bacteria and Synergize with TRAIL to Induce Apoptosis in Cancer Cells

Xiao Liang,[†,‡] Qi-Yin Chen,[†,‡] Gustavo M. Seabra,[†,‡] Susan Matthew,[†] Jason C. Kwan,[†] Chenglong Li,[†,‡] Valerie J. Paul[§] and Hendrik Luesch[†,‡]*

[†]Department of Medicinal Chemistry, University of Florida, Gainesville, Florida 32610, United States

[‡]Center for Natural Products, Drug Discovery and Development (CNPD3), University of Florida, Gainesville, Florida 32610, United States

[§]Smithsonian Marine Station, Fort Pierce, Florida 34949, United States

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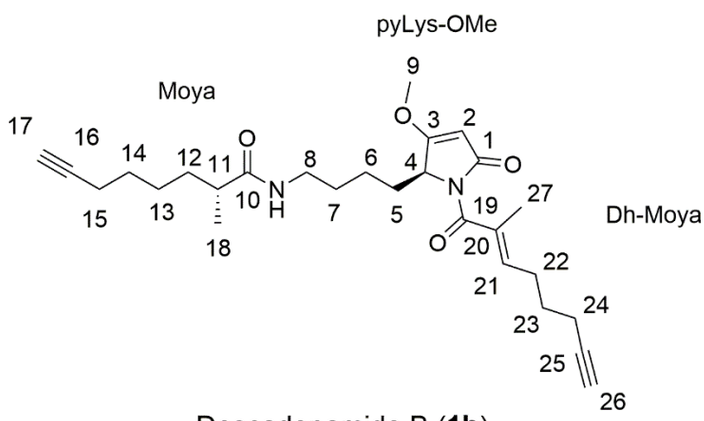
Table S1. ^{1}H and ^{13}C NMR spectral data of doscadenamide B (**1b**) at 600 MHz and 150 MHz in $CDCl_3$ at 27 °C (δ in ppm, J in Hz)

Unit	C/H no.	δH	δC[a]	^{1}H-^{1}H COSY	HMBC[b]
*py*Lys-OMe	1		168.7		
	2	5.01, s	93.6		1, 4, 9
	3		177.2		
	4	4.78, dd (4.3, 4.3)	58.5	5	3, 5, 6
	5a	2.02, ddt (16.1, 10.9, 5.3)	28.7	4, 5b, 6	4, 6
	5b	1.81, m		4, 5a, 6	4, 6
	6a	1.27, m	20.6	5, 6b, 7	7, 10
	6b	1.19, m		5, 6a, 7	7, 10
	7a	1.52 m	29.3	6, 8	5, 6, 8
	7b	1.50 m	29.3	6, 8	5, 6, 8
	8a	3.23, m	39.1	NH, 7	
	8b	3.17, m		NH, 7	
	9	3.85, s	58.7		3
	NH	5.47, br t (6.8)		8	
Moya	10		175.9		
	11	2.13, m	41.5	12, 18	18
	12a	1.62, m	33.7	11, 12b, 13	11, 14, 18
	12b	1.37, m		11, 12a, 13,	11, 14, 18
	13a	1.37, m	26.6	11, 12, 14	11, 14
	13b	1.40, m		12, 13a, 14	11, 14
	14a	1.52, m	28.3	13, 14b, 15	12, 13, 15, 16
	14b	1.50, m		13, 14a, 15	12, 13, 15, 16
	15	2.17, m	18.2	14, 17	13, 14, 16
	16		84.0		
	17	1.92, t (2.7)	68.4	15	
	18	1.12, d (6.7)	17.9	11	10, 11, 12
Dh-Moya	19		170.7		
	20		132.8		
	21	5.94, t (7.6)	136.4	21, 22	19, 22, 27
	22	2.30, m	27.1	21, 23, 27	20, 21, 23, 24
	23	1.69, m	27.3	22, 24	21, 22, 24, 25
	24	2.26, td (7.0, 2.6)	17.9	23, 26	20, 21, 22, 23, 25, 26
	25		83.9		
	26	1.95, t (2.7)	68.7	24	
	27	1.90, s	13.8	21	19, 20, 21, 22

[a]The chemicals shifts of ^{13}C were derived based on HMBC; [b]HMBC correlations are from proton stated to the indicated carbons.

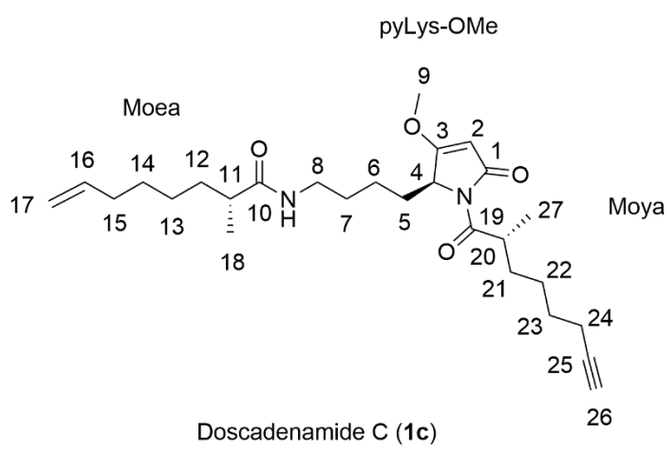


Doscadenamide B (**1b**)

Table S2. ^{1}H and ^{13}C NMR spectral data of doscadenamide C (**1c**) at 600 MHz and 150 MHz in $CDCl_3$ at 27 °C (δ in ppm, J in Hz)

Unit	C/H no.	δH	δC[a]	^{1}H-^{1}H COSY	HMBC[b]
*py*Lys-OMe	1		169.9		
	2	5.04, s	94.0		1, 9
	3		179.0		
	4	4.65, dd (6.0, 3.1)	59.0	5a, 5b	3, 5, 6
	5a	2.07, m	28.9	4, 5b, 6	3, 4, 6
	5b	1.85, tdd (11.6, 5.7, 3.0)		4, 5a, 6	3, 4, 6
	6a	1.17, m	20.3	5, 6b, 7	8, 10
	6b	1.14, m		5, 6a, 7	8, 10
	7	1.48, m	29.8	6, 8	5, 6, 8
	8a	3.24, m	39.1	NH, 7	6, 7, 10
	8b	3.16, m		NH, 7	6, 7, 10
	9	3.85, s	58.8		3
	NH	5.44, m		8	
Moea	10		176.4		
	11	2.11, m	41.6	12, 18	10, 12, 13, 18
	12a	1.64, m	33.8	12b, 11, 13	10, 11, 14, 18
	12b	1.35, m		12a, 11, 13	10, 11, 14, 18
	13	1.28, m	27.0	12, 13b, 14	12
	14	1.38, m	28.8	13, 15	12, 13, 15, 16
	15	2.04, m	33.8	14, 16, 17	13, 14, 16, 17
	16	5.78, dddd (16.9, 13.5, 6.5, 3.2)	138.9	15, 17	
	17	4.96, m	114.5	15, 16	
	18	1.12, d (6.9)	17.9	11	10, 11, 12
Moya	19		177.1		
	20	3.76, m	39.2	21, 27	19, 21, 22, 27
	21a	1.75, dddd (13.4, 10.0, 6.1, 2.7)	33.7	20, 21b	20, 22, 27
	21b	1.44, m		20, 21a	21, 22, 27
	22a	1.44, m	26.4	21, 22b, 23	21
	22b	1.39, m		21, 22a, 23	21
	23	1.54	28.4	22, 24	21, 22, 25
	24	2.19, m	18.3	23, 26	22, 23, 26
	25		84.5		
	26	1.93, td (2.7, 1.2)	68.6	24	
	27	1.13, d (6.9)	16.2	20	19, 20, 21

[a]The chemicals shifts of ^{13}C were derived based on HMBC; [b]HMBC correlations are from proton stated to the indicated carbons.

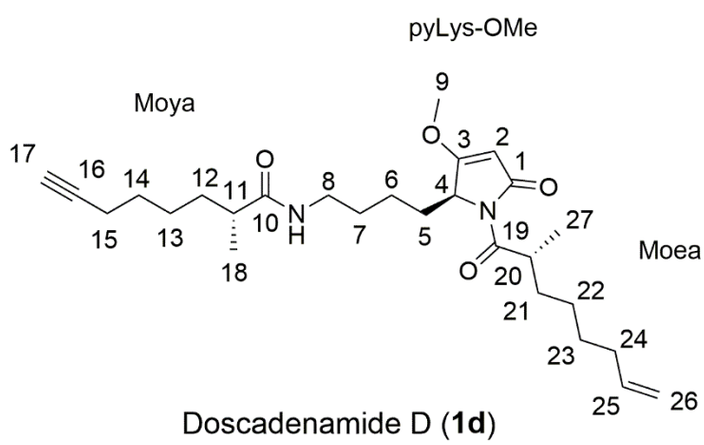


Doscadenamide C (**1c**)

Table S3. ^{1}H and ^{13}C NMR spectral data of doscadenamide D (**1d**) at 600 MHz and 150 MHz in $CDCl_3$ at 27 °C (δ in ppm, J in Hz)

Unit	C/H no.	δH	δC[a]	^{1}H-^{1}H COSY	HMBC[b]
*py*Lys-OMe	1		169.5		
	2	5.05, s	94.2		1, 9
	3		178.5		
	4	4.64, dd (5.8, 3.0)	58.5	5a, 5b	1, 2, 3, 5, 6
	5a	2.13, ddt (13.8, 11.4, 5.4)	28.1	4, 5b, 6	4, 6, 7
	5b	1.85, tdd (14.1, 5.4, 3.1)		4, 5a, 6	4, 6, 7
	6a	1.19, m	19.4	5, 6b, 7	8, 10
	6b	1.14, m		5, 6a, 7	8, 10
	7	1.48, m	28.7	6, 8	5, 6, 8
	8a	3.22, m	38.4	NH, 7	6, 7, 10
	8b	3.17, m		NH, 7	6, 7, 10
	9	3.85, s	58.0		3
	NH	5.43, br t (5.3)		8	
Moya	10		175.8		
	11	2.12, m	40.9	12, 18	10, 12, 13, 18
	12a	1.64, m	33.1	12b, 11	10, 11, 14, 18
	12b	1.38, m		12a, 11	10, 11, 14, 18
	13a	1.38, m	26.3	12, 13b, 14	12, 14, 15
	13b	1.31, m		12, 13a, 14	12, 14, 15
	14	1.52, m	27.7	13, 14b, 15	12, 15, 16
	15	2.18, tt (7.2, 2.4)	17.7	14, 17	14, 16, 17
	16		83.7		
	17	1.93, t (2.7)	68.2	15	
	18	1.12, d (6.9)	17.4	11	10, 11, 12
Moea	19		176.3		
	20	3.75, ddq (7.0, 7.0, 7.0)	38.6	21, 27	19, 21, 22, 27
	21a	1.74, m	32.0	20, 21b, 22	19, 20, 22, 27
	21b	1.35, m		20, 21a, 22	19, 20, 22, 27
	22a	1.38, m	25.9	21, 22b, 23	20, 21, 23, 24
	22b	1.31, m		21, 22a, 23	20, 21, 23, 24
	23a	1.47	28.4	22, 23b, 24	22, 24, 25
	23b	1.39		22, 23a, 24	22, 24, 25
	24	2.03, qt (7.3, 1.4)	32.9	23, 25	22, 23, 25, 26
	25	5.79, ddt (16.9, 10.1, 6.7)	138.5	26, 24	23, 24
	26	4.94, m	113.7	25	24
	27	1.17, d (6.9)	17.4	20	19, 20, 21

[a]The chemicals shifts of ^{13}C were derived based on HMBC; [b]HMBC correlations are from proton stated to the indicated carbons.



Doscadenamide D (**1d**)

Table S4. ^{1}H and ^{13}C NMR spectral data of doscadenamide E (**1e**) at 600 MHz and 150 MHz in $CDCl_3$ at 27 °C (δ in ppm, J in Hz)

Unit	C/H no.	δH	δC[a]	^{1}H-^{1}H COSY	HMBC[b]
*py*Lys-OMe	1		169.6		
	2	5.05, s	93.4		1, 4
	3		178.6		
	4	4.63, dd (5.8, 3.0)	58.3	5a, 5b	
	5a	2.12, m	28.1	4, 5b, 6	
	5b	1.86, dddd (13.2, 11.3, 5.4, 3.1)		4, 5a, 6	
	6a	1.19, m	19.5	5, 6b, 7	
	6b	1.14, m		5, 6a, 7	
	7	1.47, m	27.6	6, 8	
	8a	3.22, m	38.5	NH, 7	10
	8b	3.17, m		NH, 7	10
	9	3.85, s	58.1		3
	NH	5.44, t (5.2)		8	
Moea	10		176.3		
	11	2.12, m	41.2	12, 18	10, 18
	12a	1.64, m	24.1	12b, 11, 13	13
	12b	1.38, m		12a, 11, 13	13
	13	1.35, m	28.4	12, 13b, 14	10, 16, 15
	14	1.39, m	28.2	13, 15	16
	15	2.03, q (7.1)	33.0	14, 16, 17	14, 16, 17
	16	5.79, ddt (16.9, 10.2, 6.6)	138.2	15, 17	
	17	4.96, m	113.8	16, 15	
	18	1.12, d (6.9)	17.3	11	10, 11
Oya	19		172.8		
	20	2.94, m	36.4	21	19, 21, 22
	21	1.67, m	23.3	20, 22	19, 20, 22
	22	1.50, m	27.7	21, 23	
	23	1.56, m	27.6	22, 24	24, 25
	24	2.20, td (7.0, 2.7)	17.7	23, 26	22, 23, 25, 26
	25		83.7		
	26	1.93, t (2.6)	67.9	24	

[a]The chemicals shifts of ^{13}C were derived based on HMBC; [b]HMBC correlations are from proton stated to the indicated carbons.

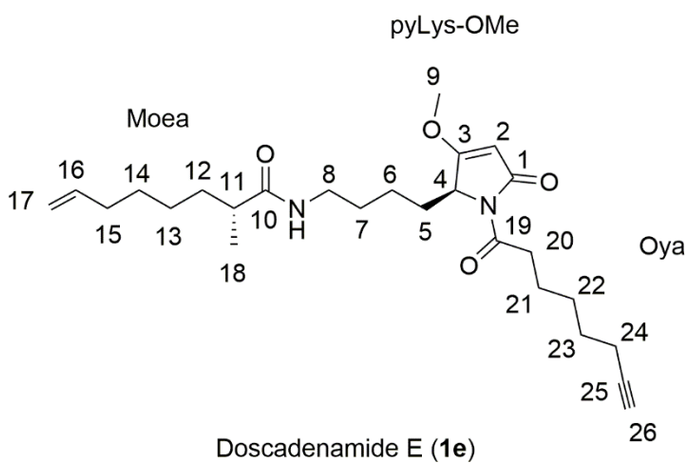
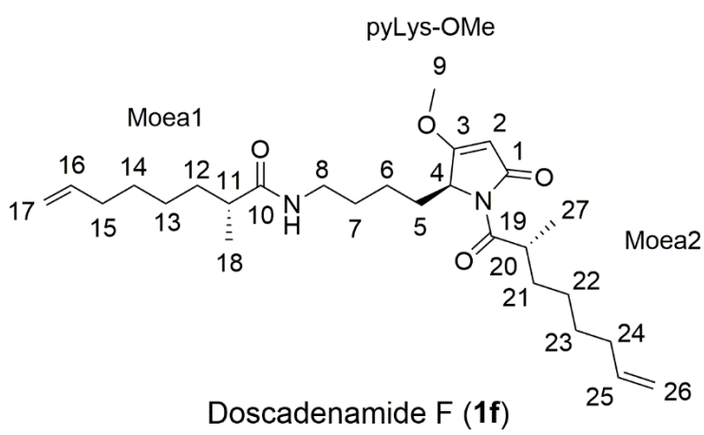


Table S5. ^{1}H and ^{13}C NMR spectral data of doscadenamide F (**1f**) at 600 MHz and 150 MHz in $CDCl_3$ at 27 °C (δ in ppm, J in Hz)

Unit	C/H no.	δH	δC[a]	^{1}H-^{1}H COSY	HMBC[b]
*py*Lys-OMe	1		169.2		
	2	5.04, s	94.0		1, 9
	3		179.0		
	4	4.65, dd (5.8, 3.1)	59.0	5a, 5b	3, 5, 6
	5a	2.06, m	28.9	4, 5b, 6	3, 4, 6
	5b	1.85, dddd (14.2, 11.1, 5.6, 3.2)		4, 5a, 6	3, 4, 6
	6a	1.20, m	20.2	5, 6b, 7	4, 7
	6b	1.13, m		5, 6a, 7	4, 7
	7	1.48, m	29.4	6, 8	5
	8a	3.24, m	39.1	NH, 7	6, 7, 10
	8b	3.15, m		NH, 7	6, 7, 10
	9	3.85, s	58.6		3
	NH	5.40, br t (5.3)		8	
Moea1	10		176.3		
	11	2.11, m	41.7	12, 18	10, 12, 13, 18
	12a	1.62, m	34.0	12b, 11	11, 13, 18
	12b	1.35, m		12a, 11	11, 13, 18
	13	1.28, m	27.0	12, 13b, 14	14, 15
	14	1.39, m	28.8	13, 14b, 15	13, 15, 16
	15	2.04, m	33.6	14, 16, 17	13, 14, 16, 17
	16	5.78, m	138.8	7, 15	14, 15
	17	4.95, m	114.3	16	15
	18	1.11, d (6.6)	17.9	11	10, 11, 12
Moea2	19		176.5		
	20	3.76, ddq (6.4, 6.4, 6.4)	39.0	21a,b, 27	19, 21, 22, 27
	21a	1.74, m	34.0	20, 21b, 22a	20, 22, 27
	21b	1.41, m		20, 21a, 22b	20, 22, 27
	22	1.34, m	26.6	21, 23	21
	23	1.39	28.8	22, 24	22, 24, 25
	24	2.04, m	33.6	23, 25, 26	22, 23, 25, 26
	25	5.78, m	138.8	24, 26	23, 24
	26	4.97, m	114.3	25	24
	27	1.12, d (6.6)	16.1	20	19, 20, 21

[a]The chemicals shifts of ^{13}C were derived based on HMBC; [b]HMBC correlations are from proton stated to the indicated carbons.

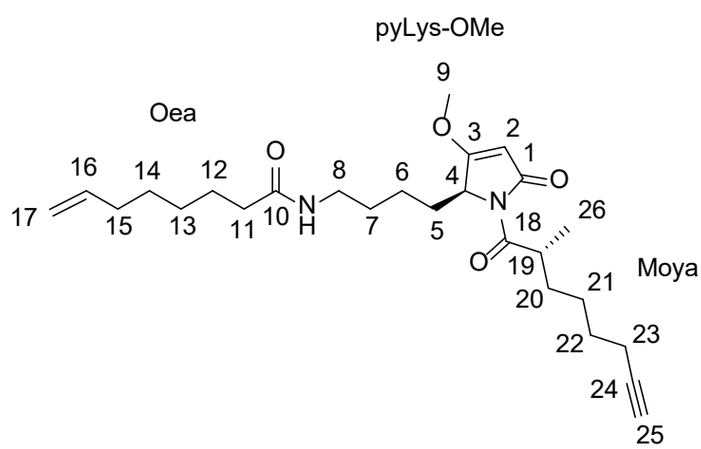


Doscadenamide F (**1f**)

Table S6. ^{1}H and ^{13}C NMR spectral data of doscadenamide G (**1g**) at 600 MHz and 150 MHz in $CDCl_3$ at 27 °C (δ in ppm, J in Hz)

Unit	C/H no.	δH	δC[a]	^{1}H-^{1}H COSY	HMBC[b]
*Py*Lys-OMe	1		169.4		
	2	5.05, s	93.4	4	1, 4
	3		178.6		
	4	4.65, dd (6.0, 3.0)	58.3	5a, b	2, 3, 5, 6
	5a	2.09,m	28.2	4, 5b, 6	3, 4, 6
	5b	1.85, m		4, 5a, 6	
	6a	1.19, m	19.6	5, 6b, 7	5, 8
	6b	1.12, m		5, 6a, 7	4, 5, 8
	7	1.50, m	25.7	6a, b, 8	6
	8a	3.23, m	38.6	NH, 7	5, 6, 10
	8b	3.16, m		NH, 7	5, 6, 10
	9	3.85, s	58.1		3
	NH	5.44, m		8a, b	
Oea	10		172.4		
	11	2.14, t (7.8)	36.1	12	10, 13, 14, 15
	12	1.64, m	23.6	11, 13	10, 11, 13
	13	1.45, m	28.7	12, 14	16
	14	1.42, m	25.8	13, 15	16
	15	2.05, m	33.0	14, 16, 17	13, 16, 17
	16	5.79, m	138.2	15, 17	15
	17	4.97, m	113.9	16, 15	15, 16
Moya	18		176.5		
	19	3.76, q (6.6)	38.3	20, 27	4, 18, 20
	20a	1.75, m	33.1	19, 20b, 21	19
	20b	1.44, m		19, 20a, 21	18, 19, 21, 26
	21	1.55, m	27.7	20, 22	20, 23, 24, 26
	22	1.56, m	27.6	21, 23	20, 23, 24
	23	2.19, td (7.2, 3.1)	17.6	22, 25	22, 24, 25
	24		83.9		
	25	1.93, t (2.6)	67.8	23	23
	26	1.13, d (6.6)	19.5	19	18,19,20

[a]The chemicals shifts of ^{13}C were derived based on HMBC; [b]HMBC correlations are from proton stated to the indicated carbons.

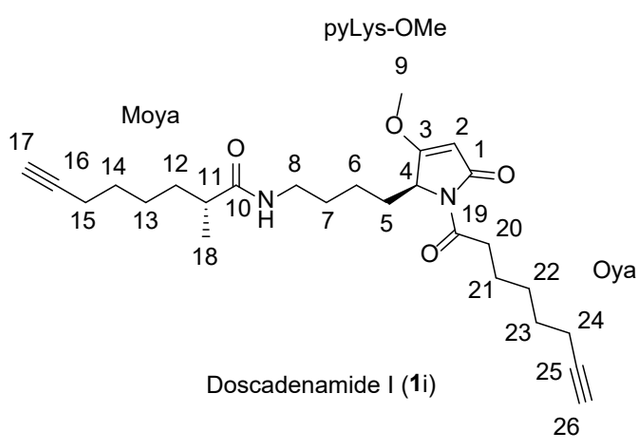


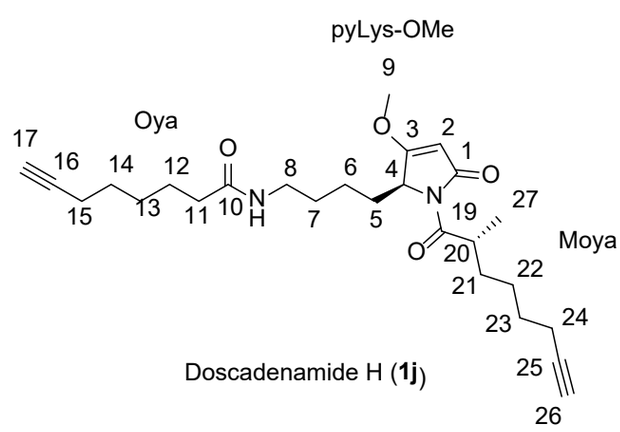
Note: The structure was proposed from 1D NMR of pure doscadenamide G (**1g**) and 2D NMR (not shown) of the mixture with doscadenamide G (**1g**) and doscadenamide H (**1h**).

Table S7. ^{1}H and ^{13}C NMR spectral data of doscadenamide I/J (**1i**/**j**) at 600 MHz and 150 MHz in $CDCl_3$ at 27 °C (δ in ppm, J in Hz)

Unit	C/H no.	δH	δC[a]	^{1}H-^{1}H COSY	HMBC[b]
*py*Lys-OMe	1		169.5		
(**1i**, **1j**)	2(j/i)	5.05/5.05, s	93.3		1, 4, 9
	3		178.5		
	4(j/i)	4.65/4.63, dd (5.8, 3.0)	58.3	5	3, 5, 6
	5a(j/i)	2.07/2.11, m	28.1	4, 5b, 6	4, 6
	5b(j/i)	1.83/1.87, m		4, 5a, 6	4, 6
	6a(j/i)	1.20, m	19.6	5, 6b, 7	7, 10
	6b(j/i)	1.12, m		5, 6a, 7	7, 10
	7a(j/i)	1.51 m	27.7	6, 8	5, 6, 8
	7b(j/i)	1.49 m		6, 8	
	8a (j/i)	3.23, m	38.4	NJ, 7	
	8b (j/i)	3.16, m		NJ, 7	
	9(j/i)	3.85, s	58.1		3
	NJ (j/i)	5.50/5.46, br t (5.7)		8	
Oya (**1j**)	10		172.3		
Moya (**1i**)	11(j/i)	2.14/2.16, m	41.5	12, 18(i)	12, 18(i)
	12a(i)	1.67, m	23.3(i)	11, 12b, 13	11, 13
	12b(i)/12(j)	1.40/1.38, m	23.3	11, 12a(i), 13	11, 13
	13(j/i)	1.41/1.50, m	28.2/28.8	12, 14	12, 14
	14(j/i)	1.52, m	28.8	13, 15	13, 15
	15(j/i)	2.21, m	17.6	14, 17	13, 14, 16
	16		83.8		
	17(j/i)	1.94, m	67.8	15	
	18(i)	1.12, d (6.8)	17.3	11(i)	11(i)
Moya (**1j**)	19		172.4		
Oya (**1i**)	20(j/i)	3.77, j (6.5)/2.93, m	39.0(j)/36.3(i)	21, 27(j)	21, 27(j)
	21a(j)/21(i)	1.75/1.65, m	24.0(i)	20, 22	20, 22
	21b(j)	1.40, m		20(j), 22(j)	
	22(j/i)	1.45/1.50, m	27.1/28.8	21, 23	21, 23
	23(j/i)	1.60/1.58, m	27.5	22, 24	22, 24
	24(j/i)	2.21, m	17.6	23, 26	23, 25, 26
	25		83.4		
	26(j/i)	1.94, m	67.8	24	24, 25
	27(j)	1.12, s	17.3	20(j)	20

[a]The chemicals shifts of ^{13}C were derived based on HMBC; [b]HMBC correlations are from proton stated to the indicated carbons.





Note: The structures of doscadenamides I and J (1**i**/**j**) were proposed from NMR spectra and total synthesis of these two analogs.

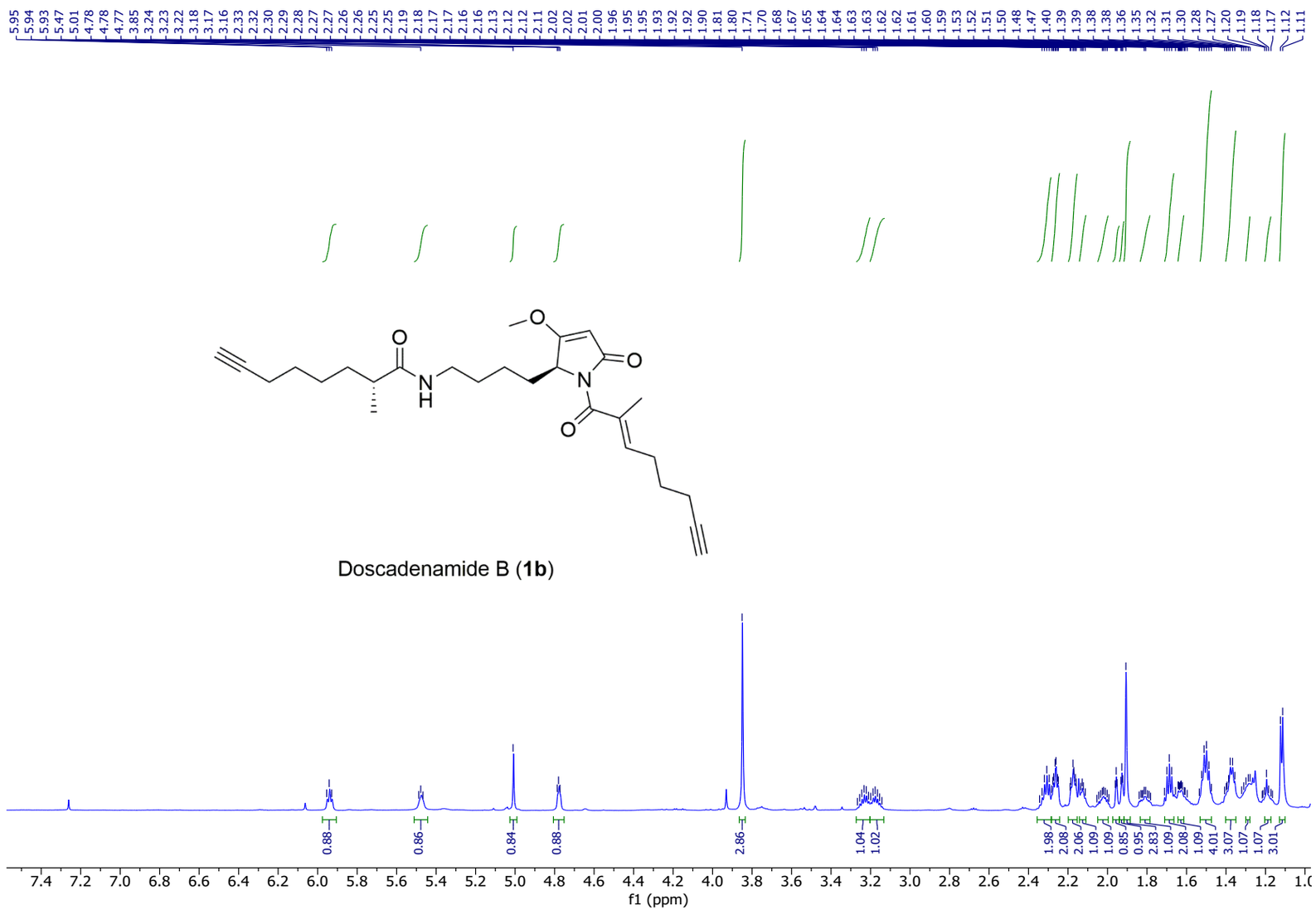


Figure S1. ^{1}H NMR spectrum of natural product doscadenamide B (**1b**) in $CDCl_3$ (600 MHz) at 27 °C.

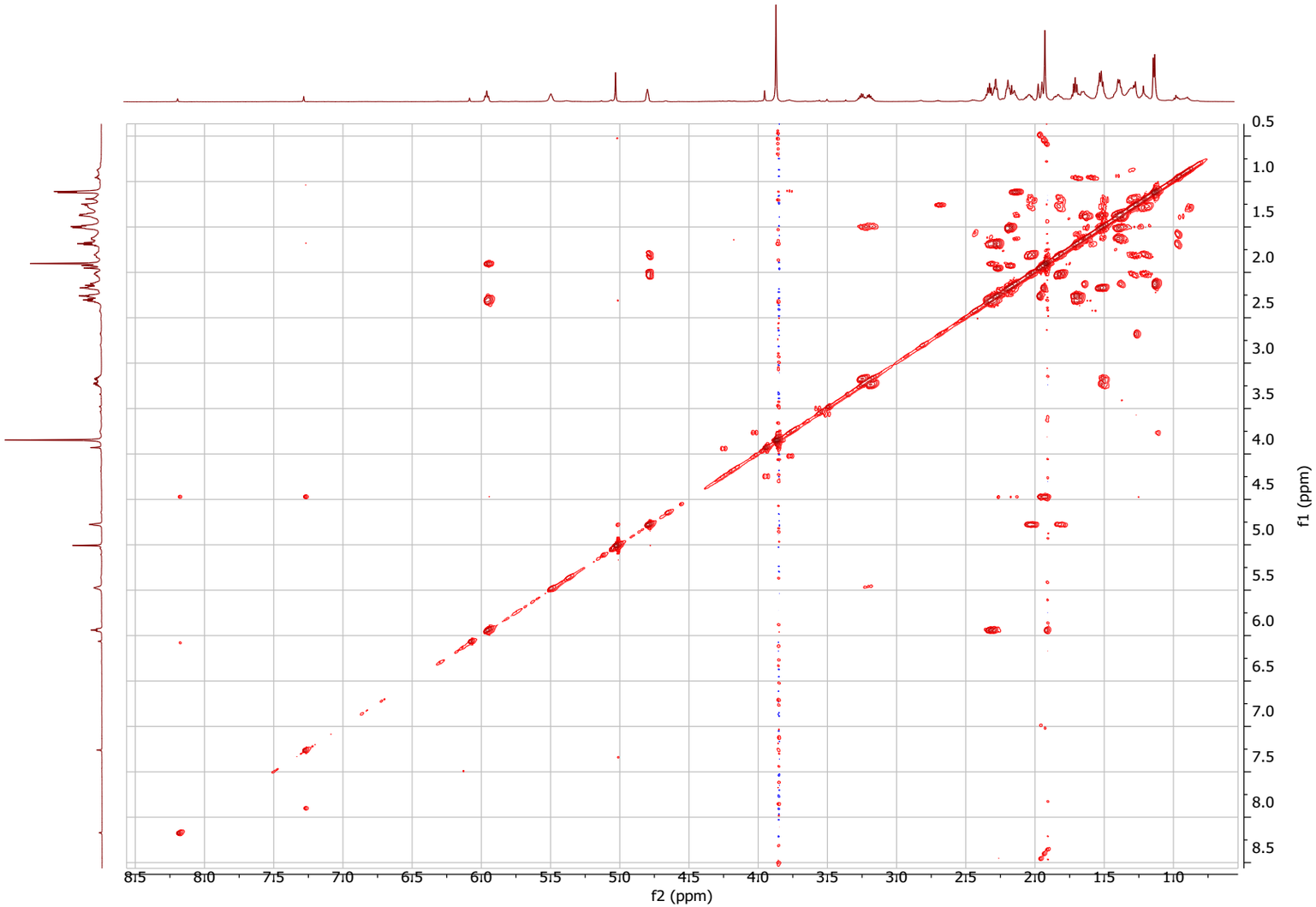


Figure S2. COSY spectrum of natural product doscadenamide B (**1b**) in $CDCl_3$ (600 MHz) at 27 °C.

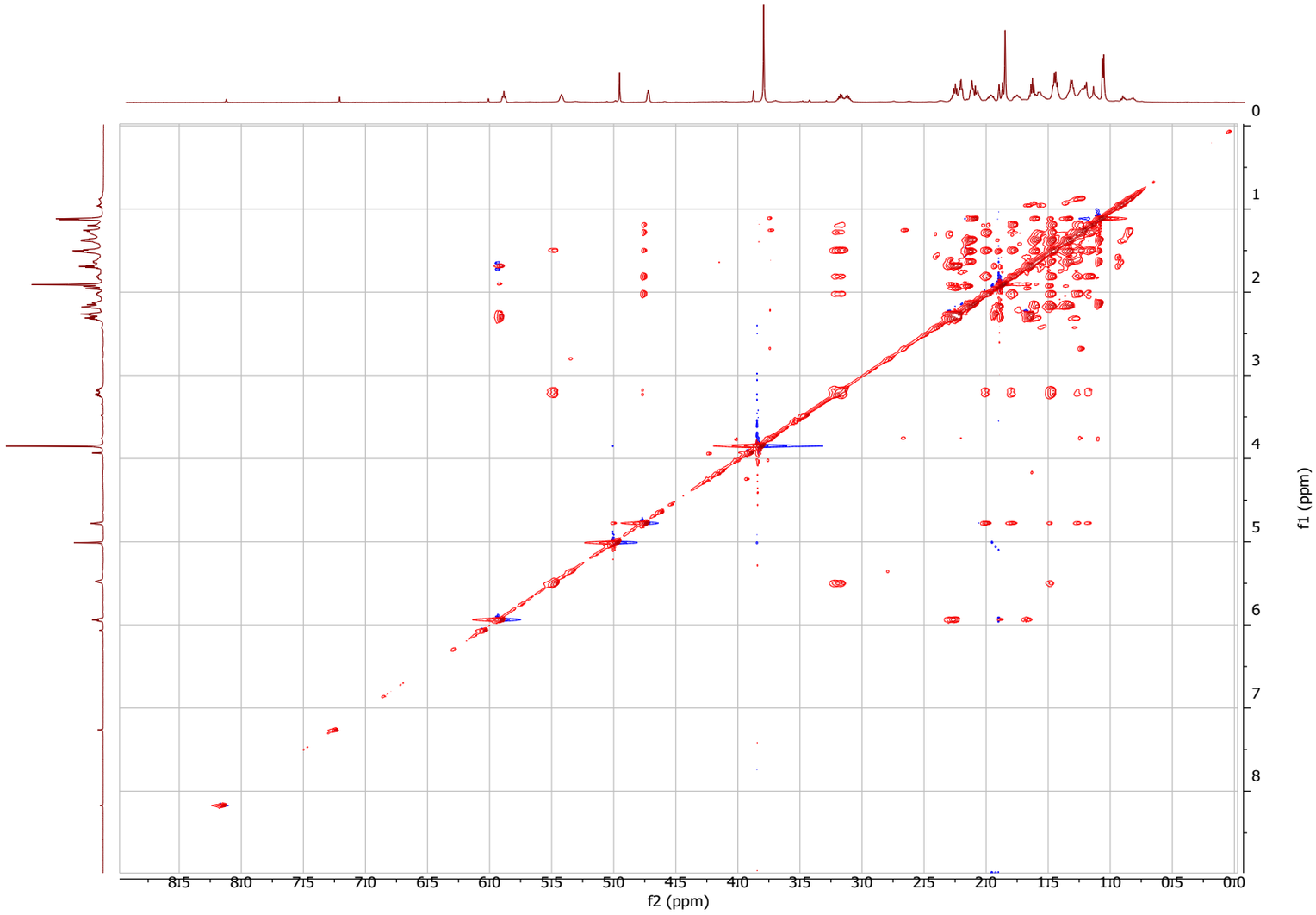


Figure S3. TOCSY spectrum of natural product doscadenamide B (**1b**) in $CDCl_3$ (600 MHz) at 27 °C.

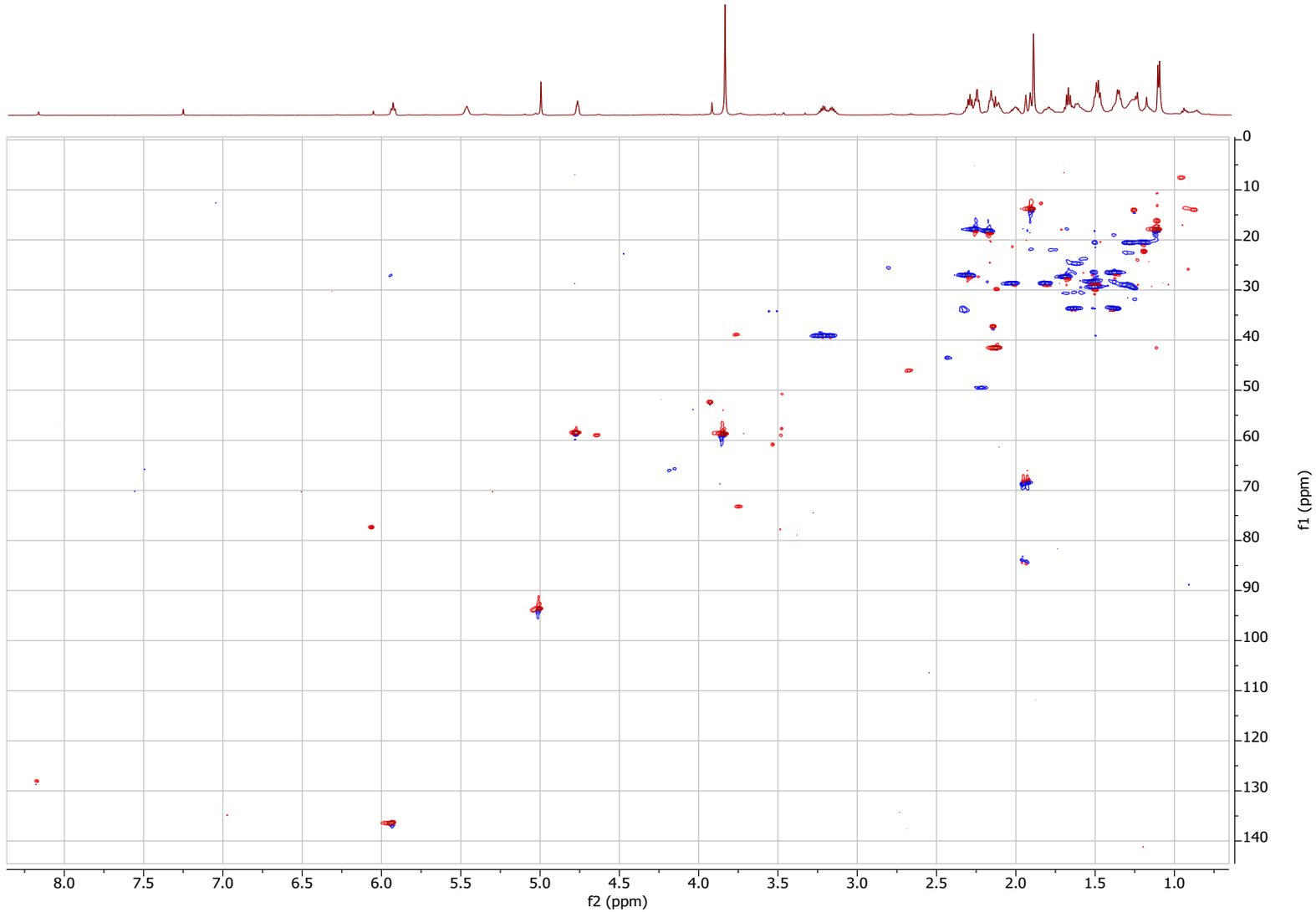


Figure S4. HSQC spectrum of natural product doscadenamide B (**1b**) in $CDCl_3$ (600 MHz) at 27 °C.

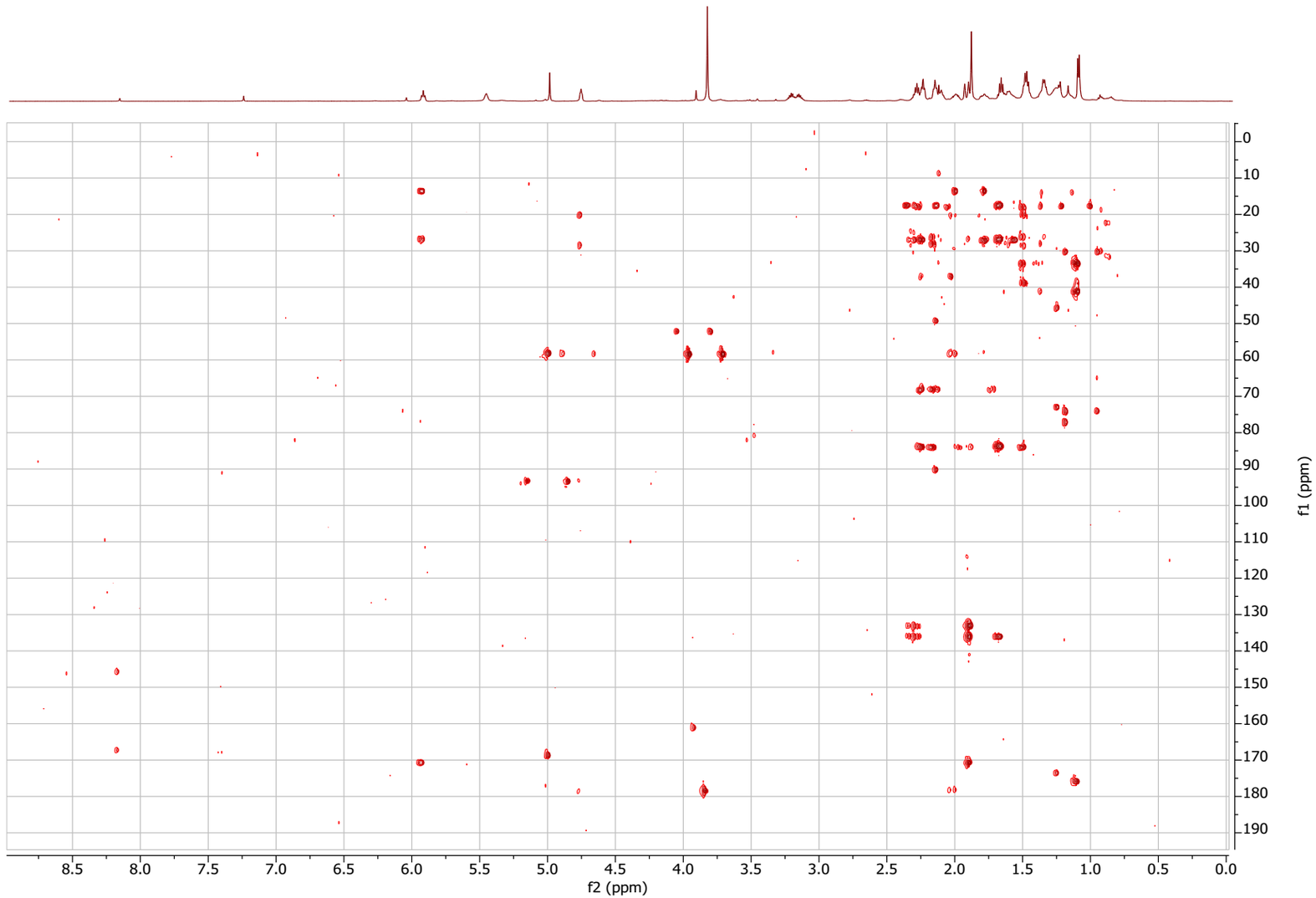


Figure S5. HMBC spectrum of natural product doscadenamide B (**1b**) in $CDCl_3$ (600 MHz) at 27 °C.

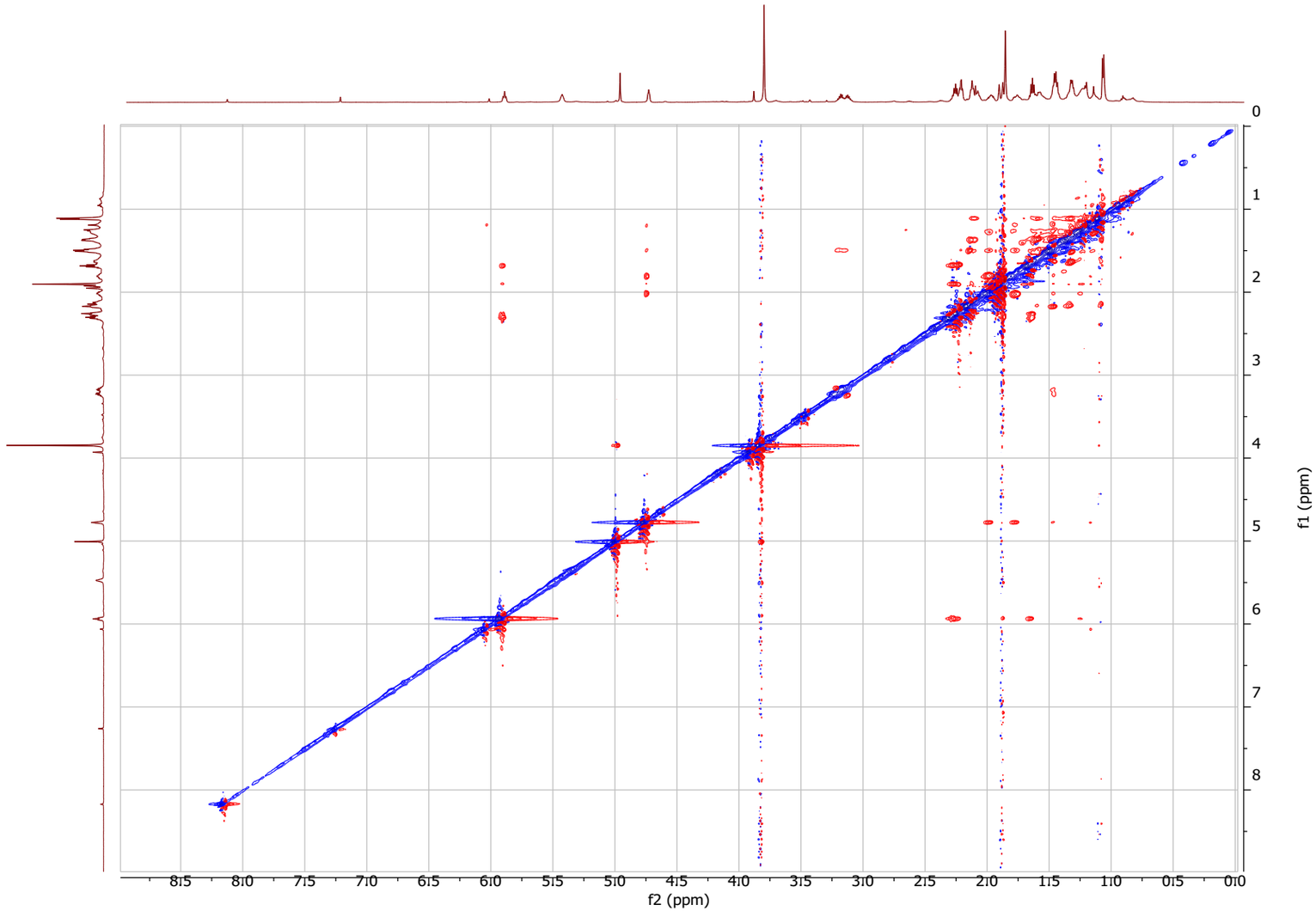


Figure S6. NOESY spectrum of natural product doscadenamide B (**1b**) in $CDCl_3$ (600 MHz) at 27 °C.

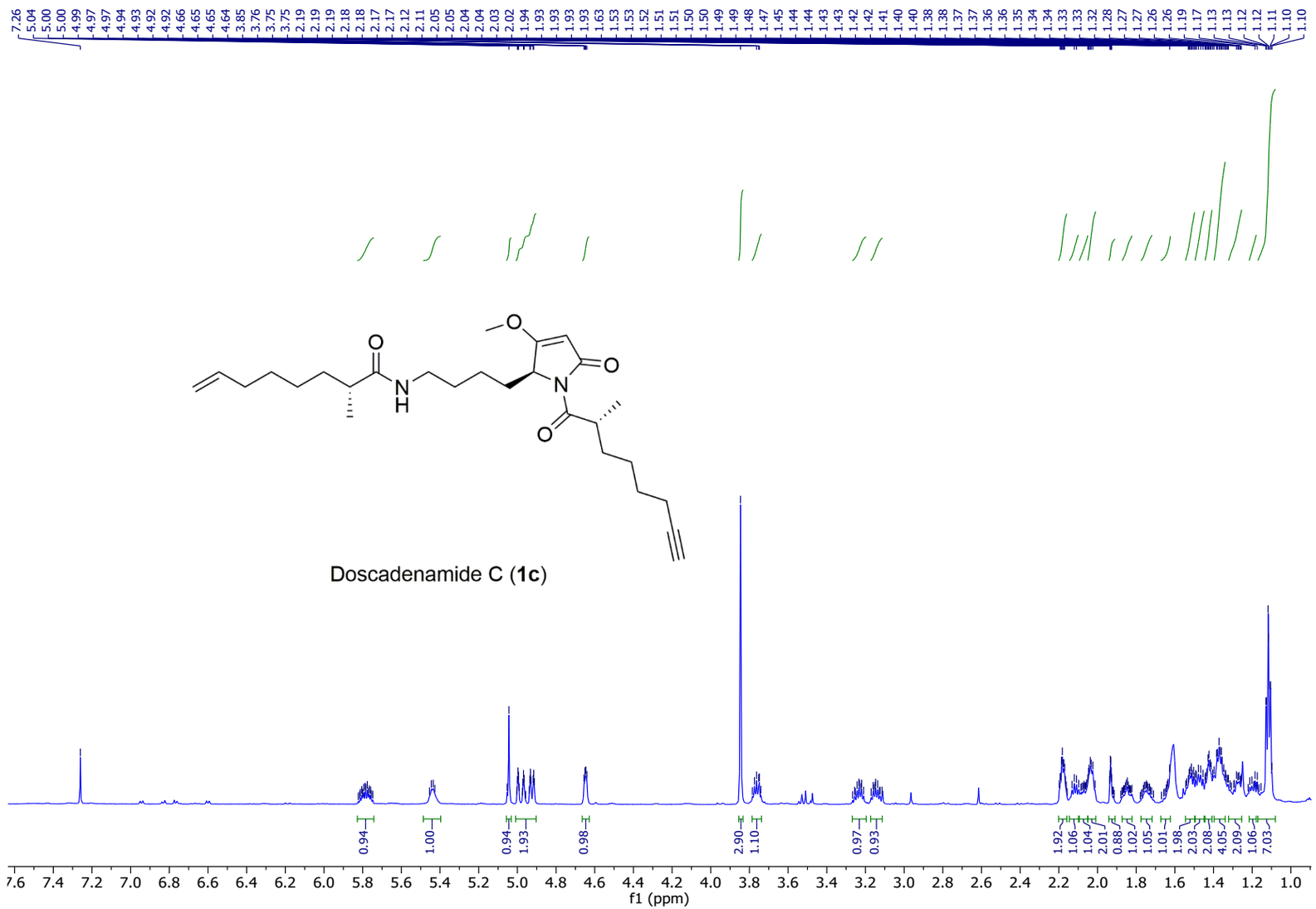


Figure S7. ^{1}H NMR spectrum of natural product doscadenamide C (**1c**) in $CDCl_3$ (600 MHz) at 27 °C.

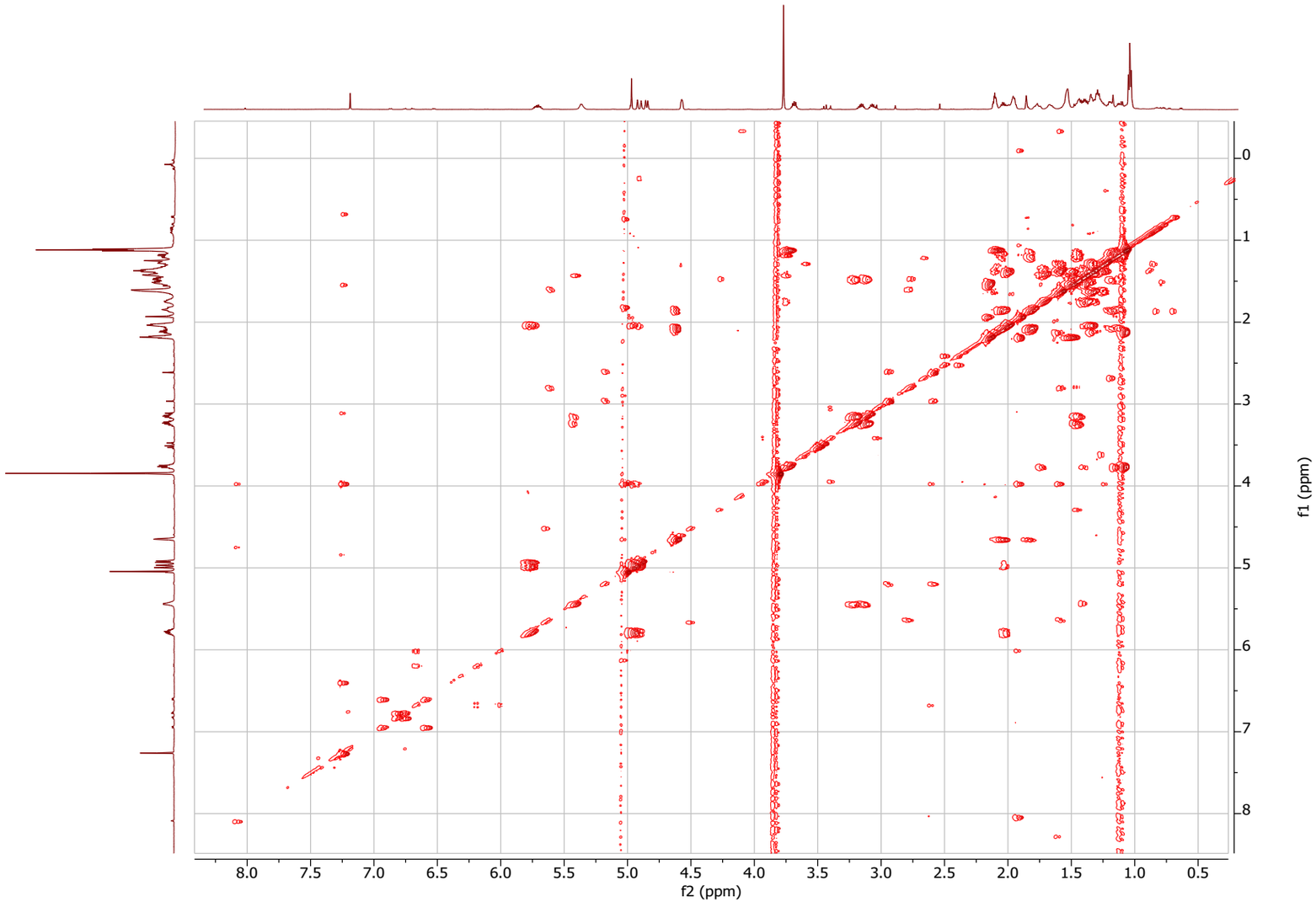


Figure S8. COSY spectrum of natural product doscadenamide C (**1c**) in $CDCl_3$ (600 MHz) at 27 °C.

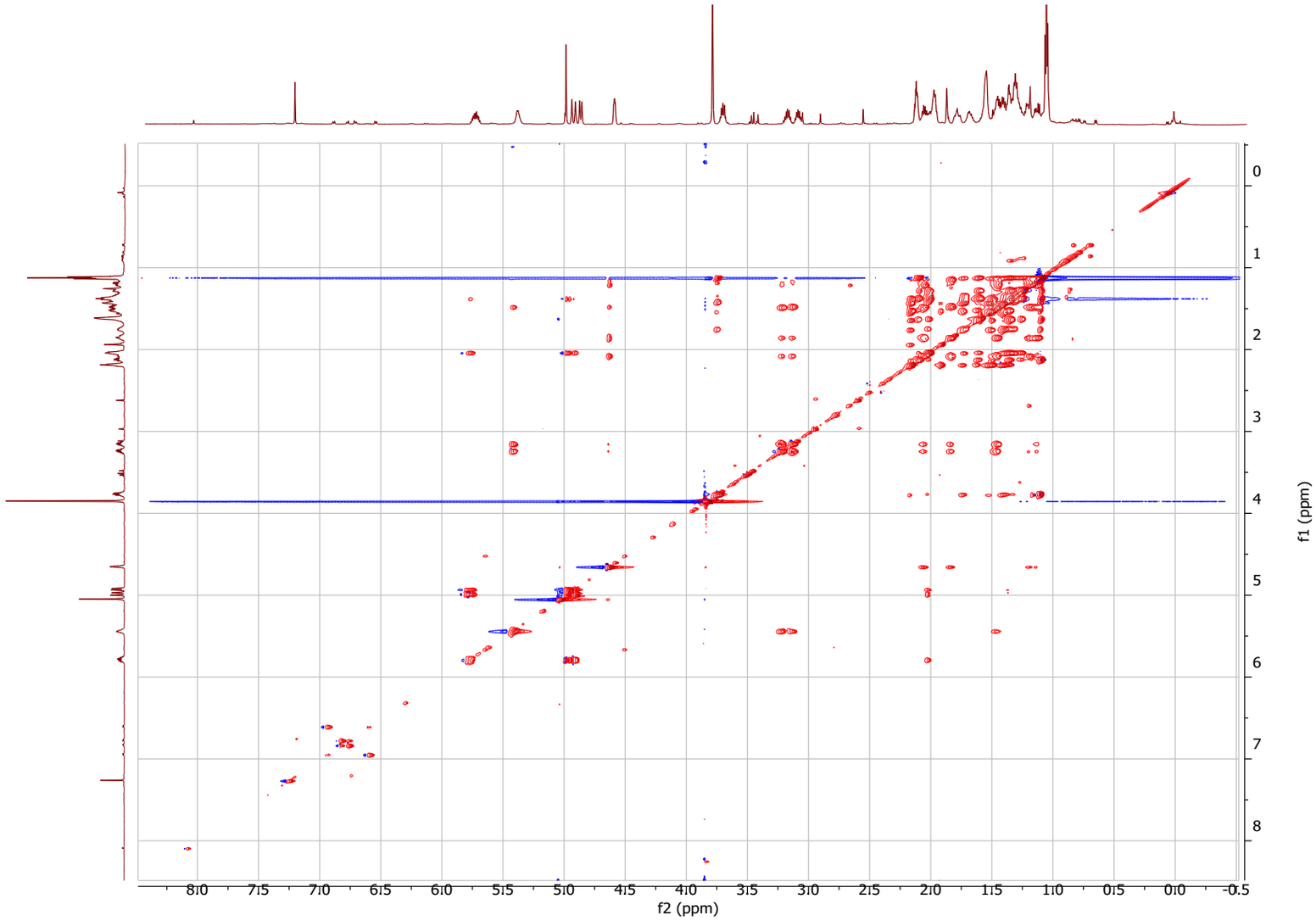


Figure S9. TOCSY spectrum of natural product doscadenamide C (**1c**) in $CDCl_3$ (600 MHz) at 27 °C.

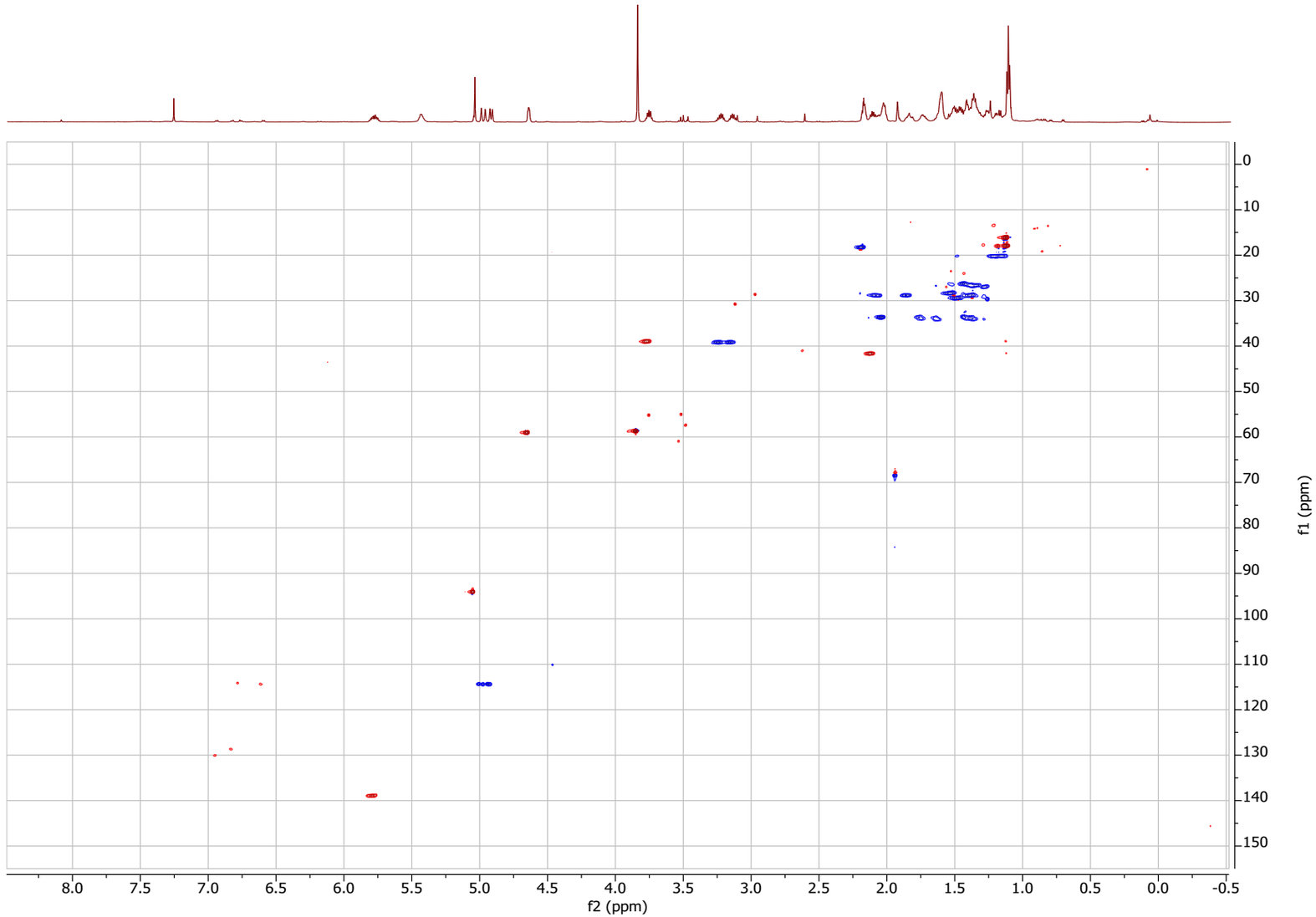


Figure S10. HSQC spectrum of natural product doscadenamide C (**1c**) in $CDCl_3$ (600 MHz) at 27 °C.

Figure S11. HMBC spectrum of natural product doscadenamide C (**1c**) in $CDCl_3$ (600 MHz) at 27 °C.

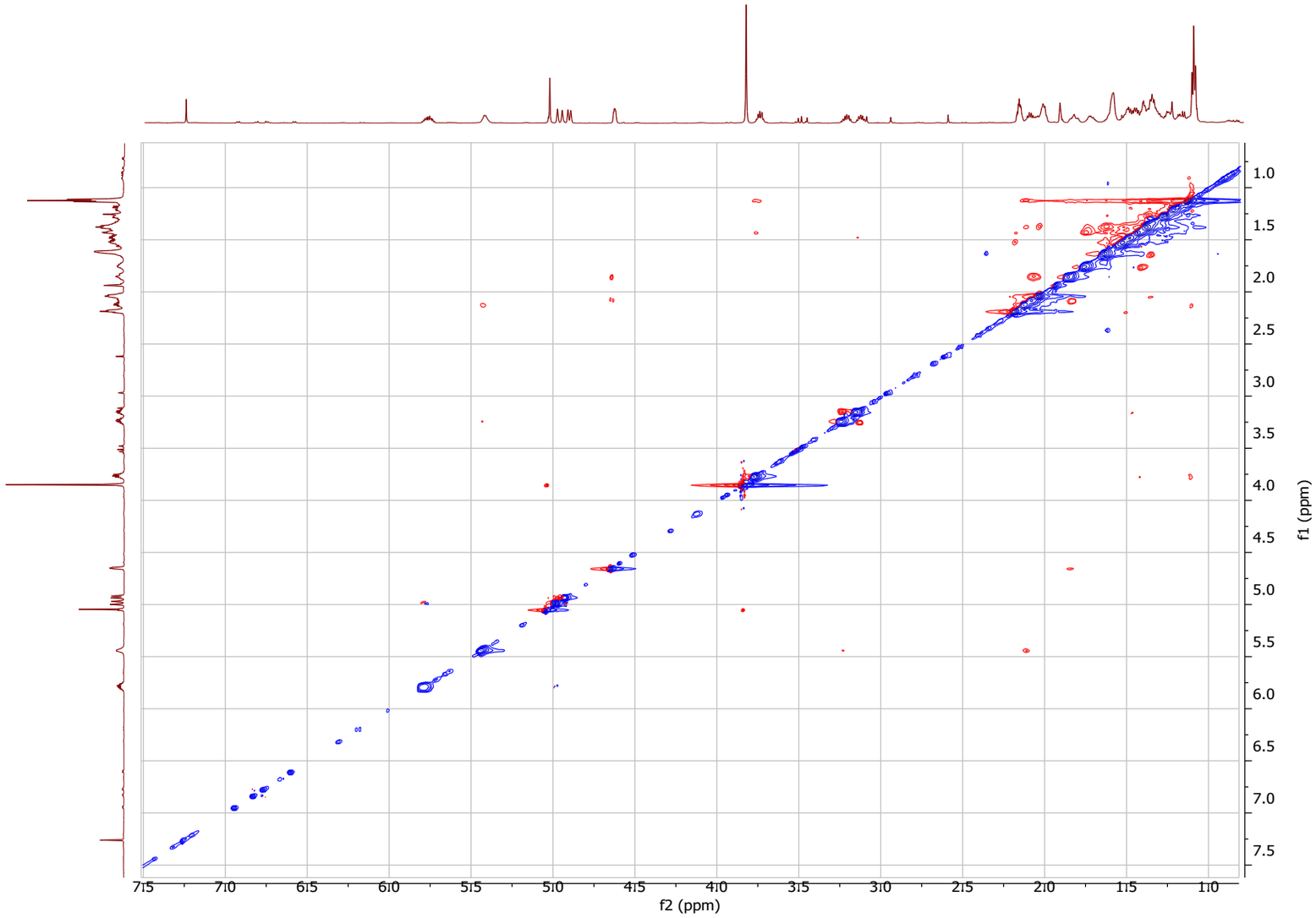


Figure S12. NOESY spectrum of natural product doscadenamide C (**1c**) in $CDCl_3$ (600 MHz) at 27 °C.

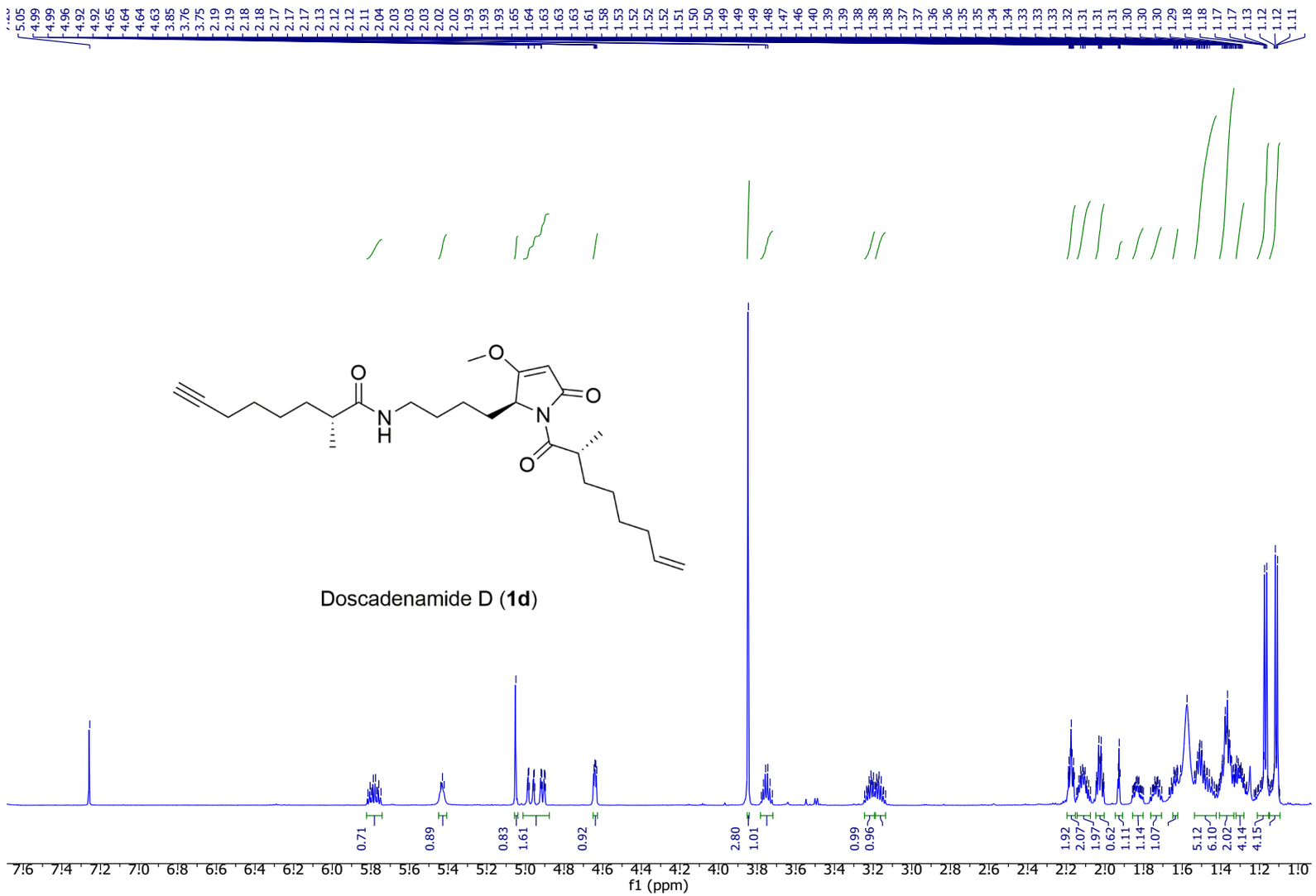


Figure S13. ^{1}H NMR spectrum of natural product doscadenamide D (**1d**) in $CDCl_3$ (600 MHz) at 27 °C.

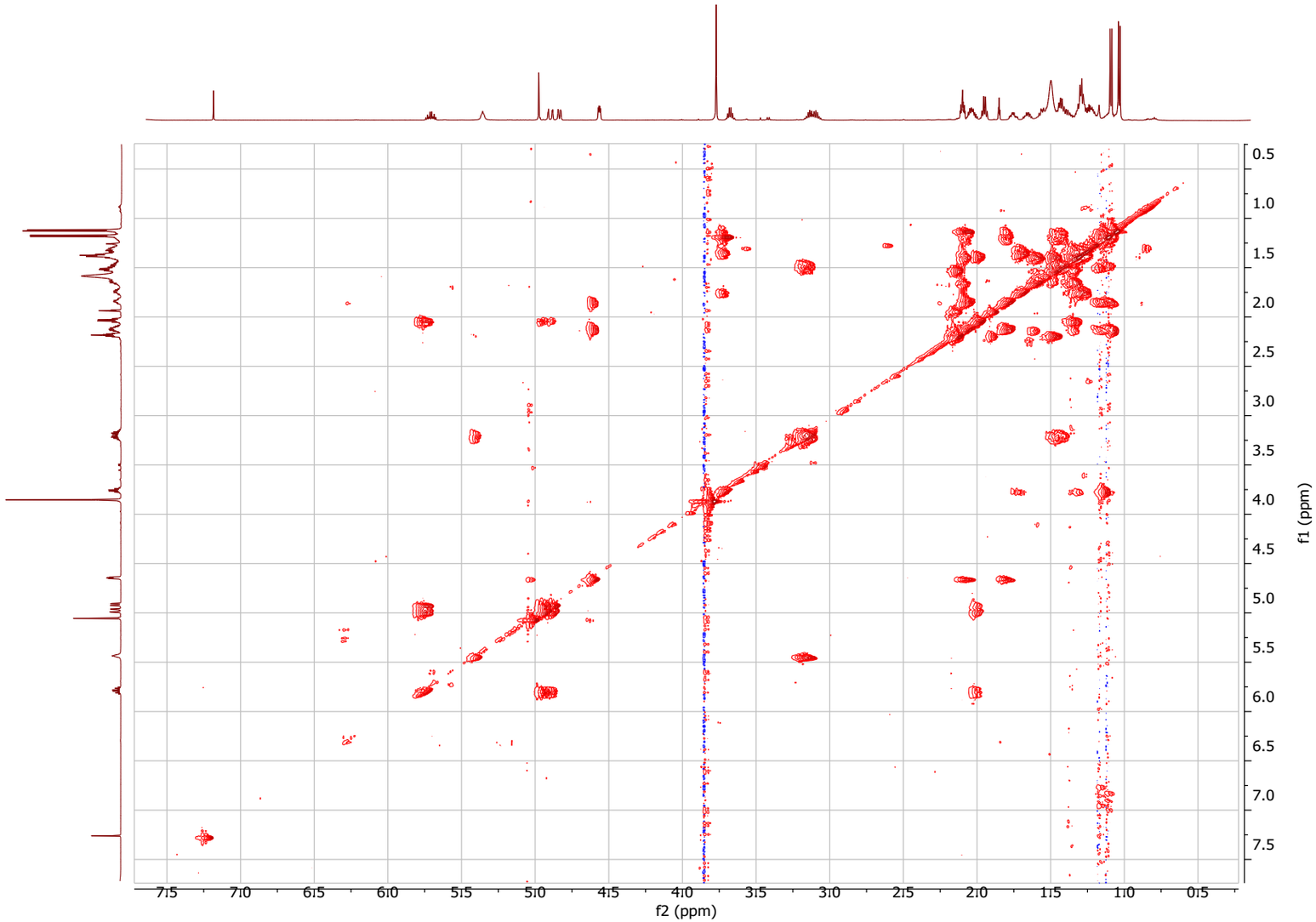


Figure S14. COSY spectrum of natural product doscadenamide D (**1d**) in $CDCl_3$ (600 MHz) at 27 °C.

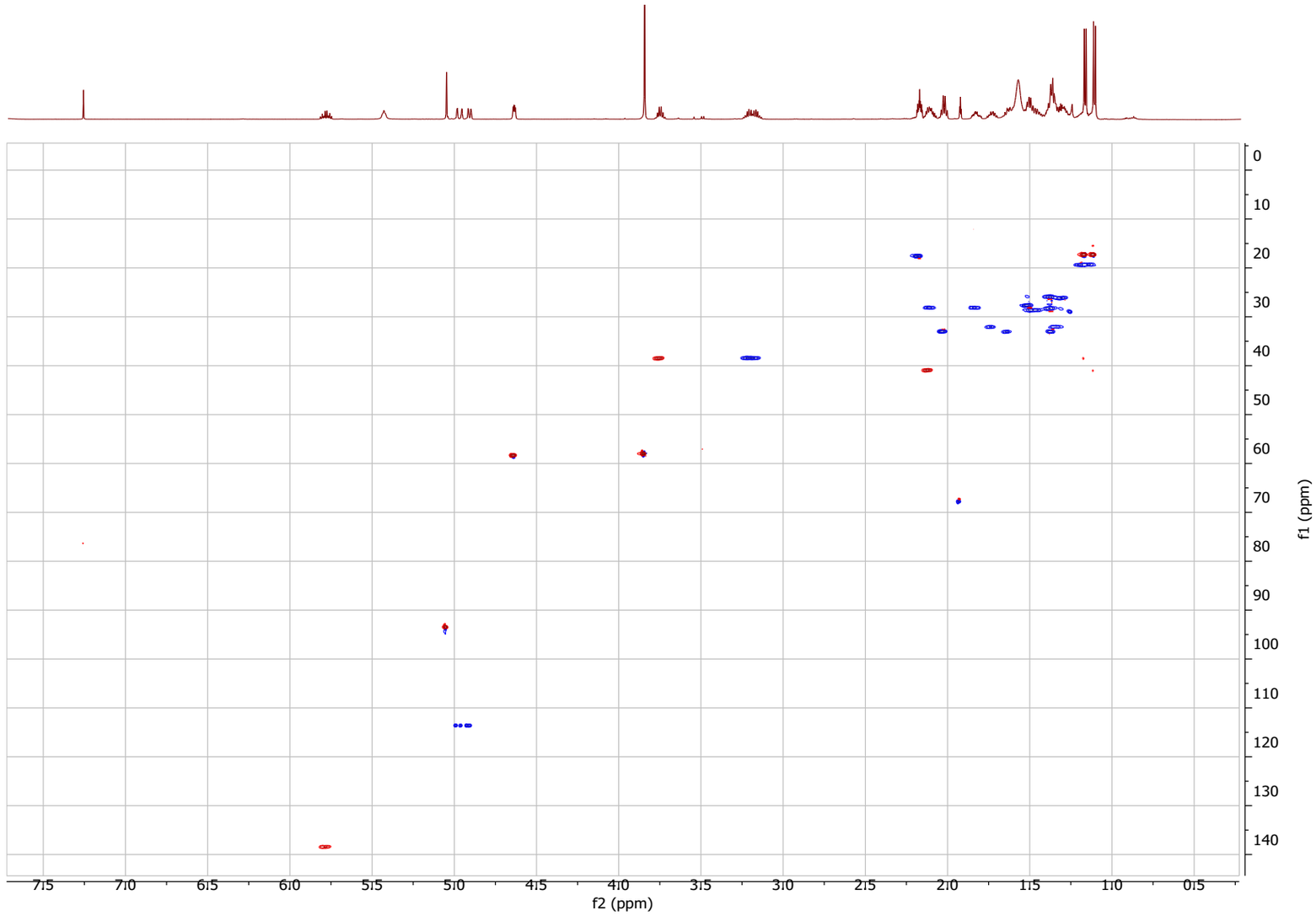


Figure S15. HSQC spectrum of natural product doscadenamide D (**1d**) in $CDCl_3$ (600 MHz) at 27 °C.

Figure S16. HMBC spectrum of natural product doscadenamide D (**1d**) in $CDCl_3$ (600 MHz) at 27 °C.

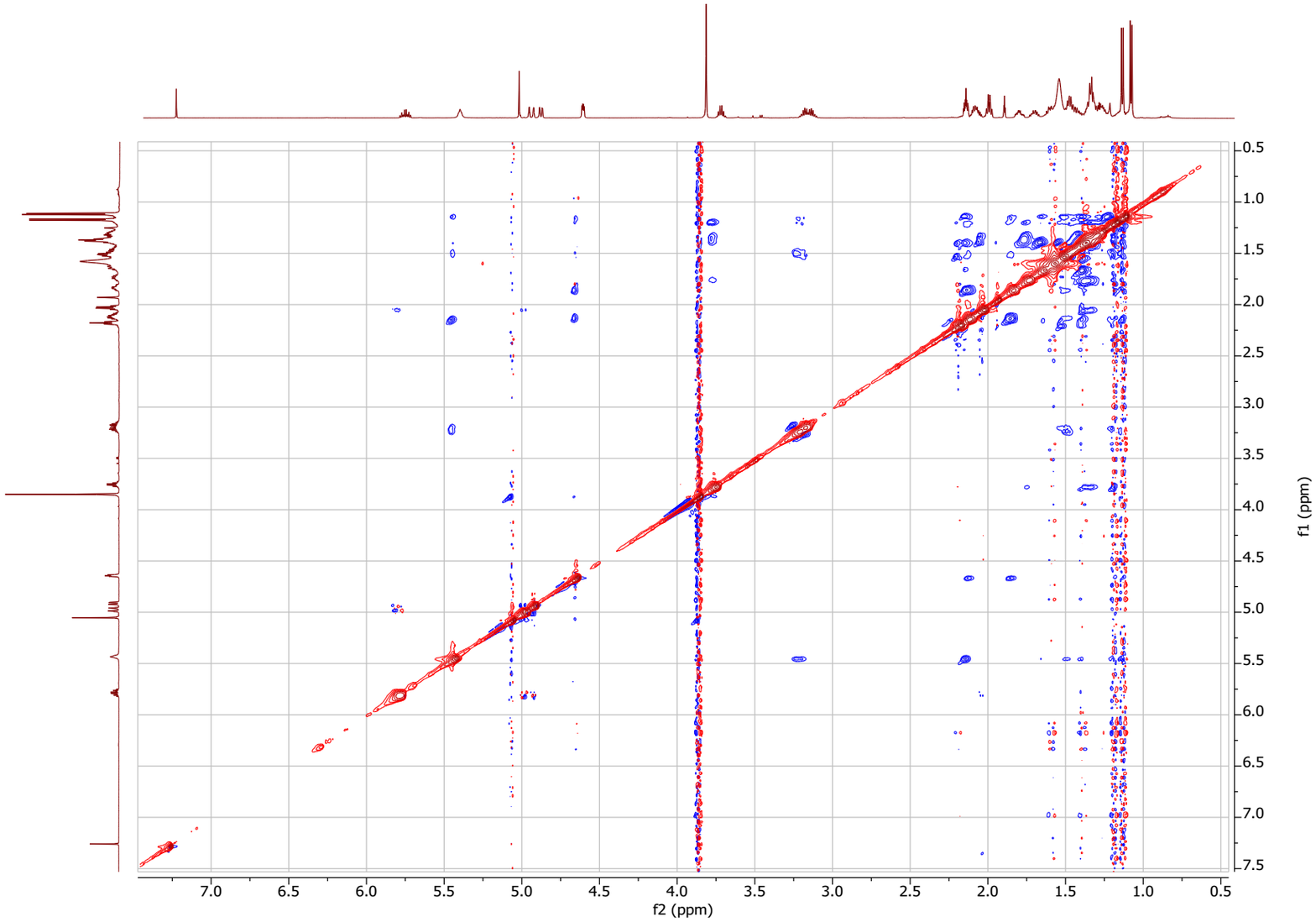


Figure S17. NOESY spectrum of natural product doscadenamide D (**1d**) in $CDCl_3$ (600 MHz) at 27 °C.

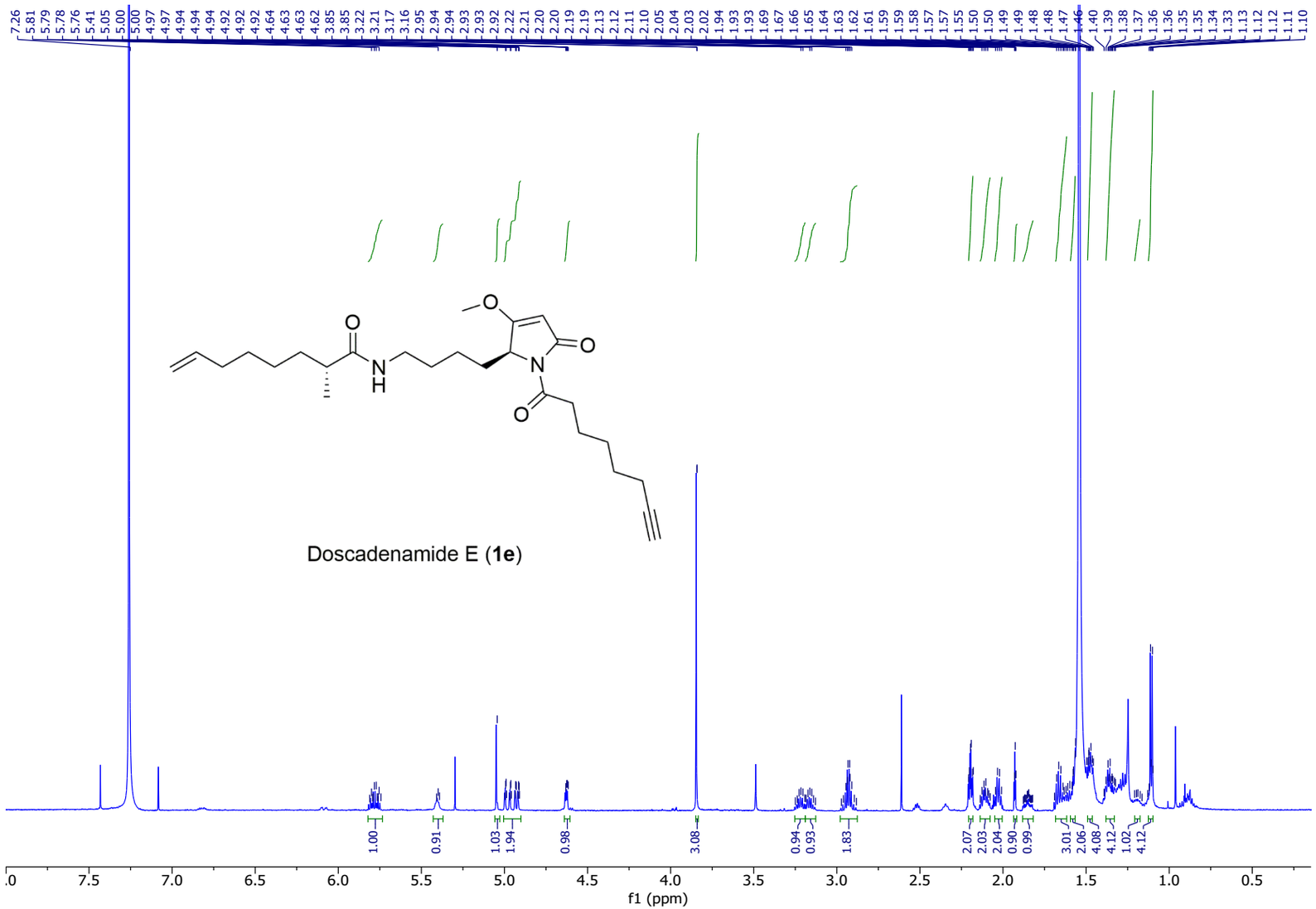


Figure S18. ^{1}H NMR spectrum of natural product doscadenamide E (**1e**) in $CDCl_3$ (600 MHz) at 27 °C.

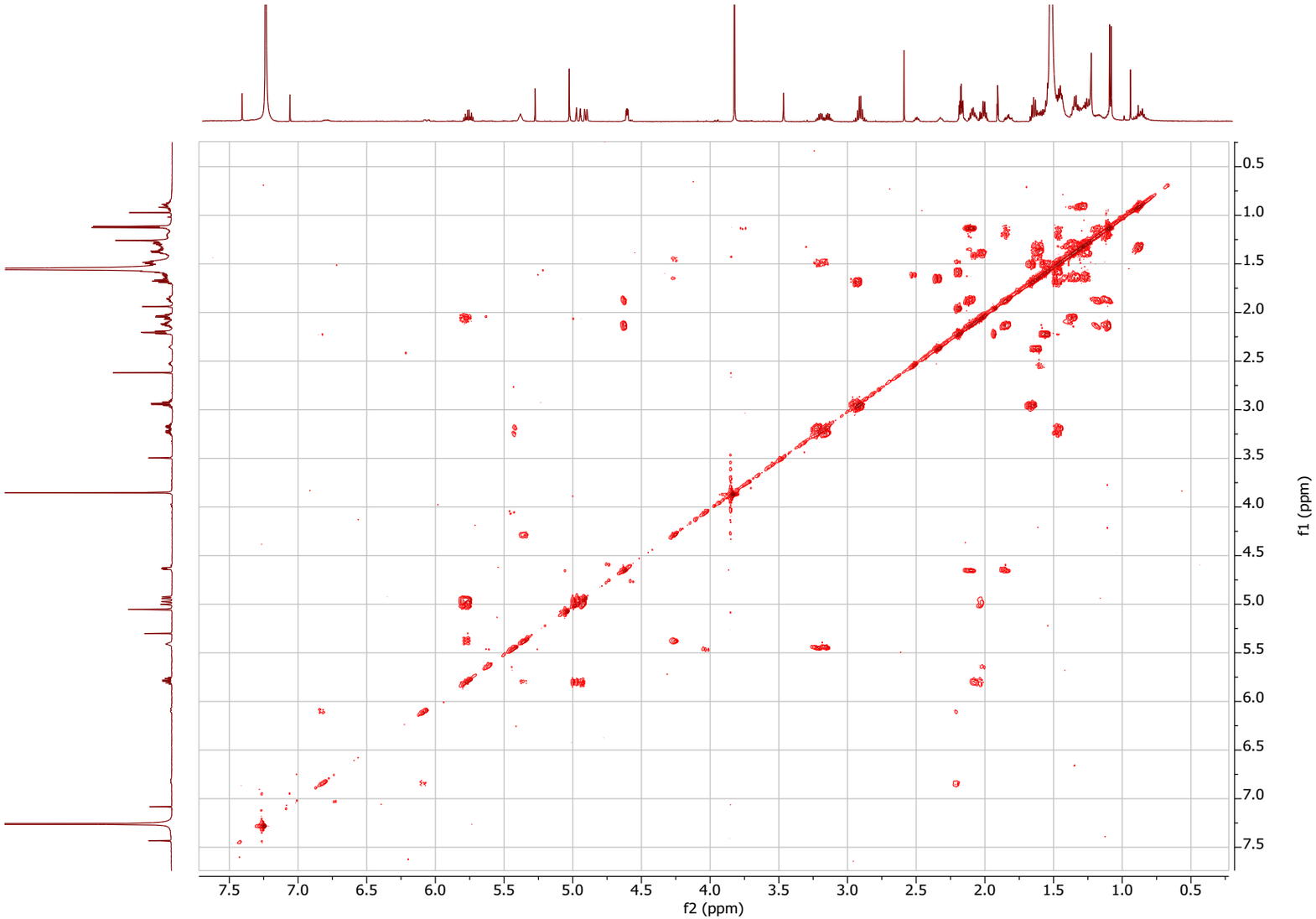


Figure S19. COSY spectrum of natural product doscadenamide E (**1e**) in $CDCl_3$ (600 MHz) at 27 °C.

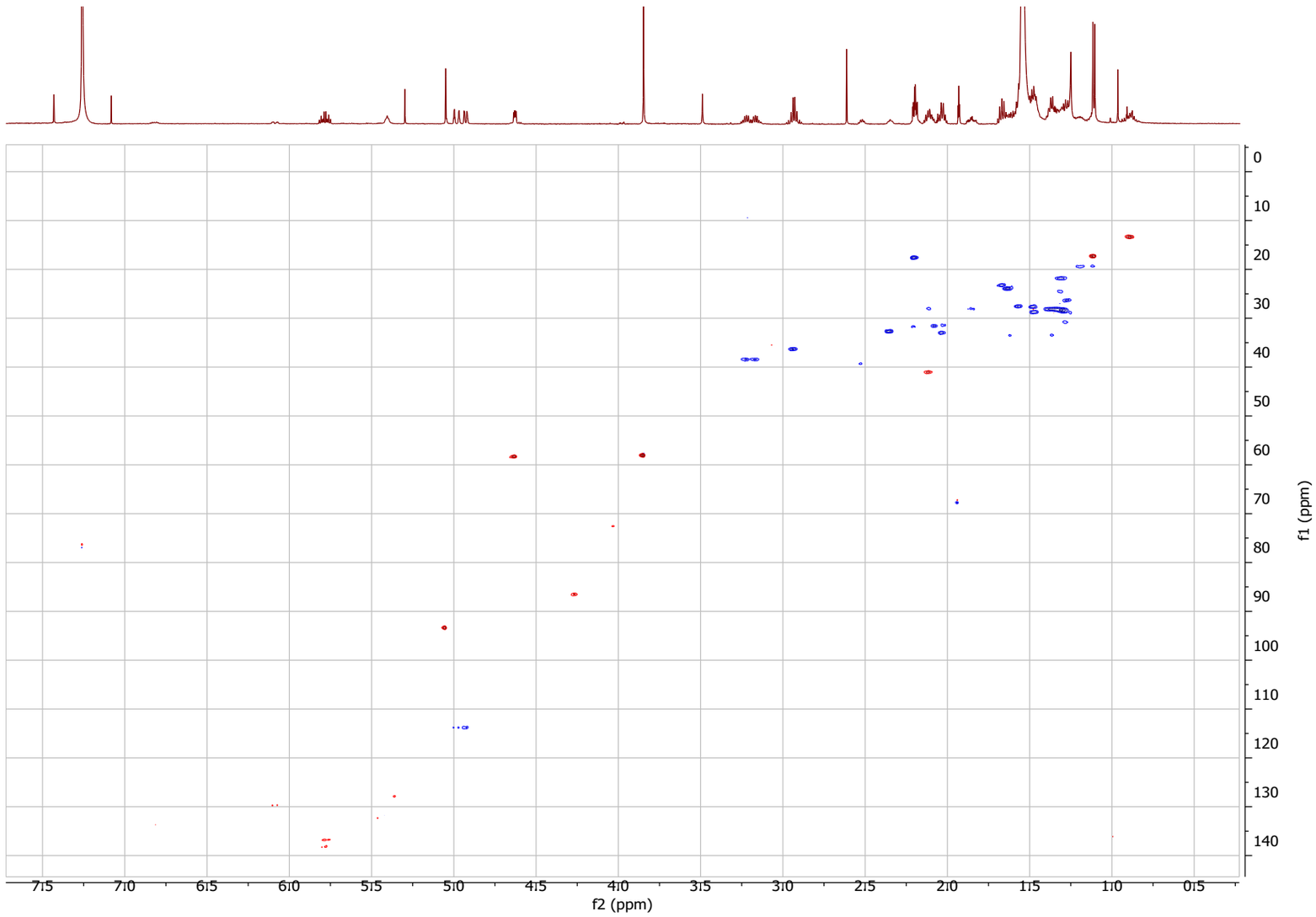


Figure S20. HSQC spectrum of natural product doscadenamide E (**1e**) in $CDCl_3$ (600 MHz) at 27 °C.

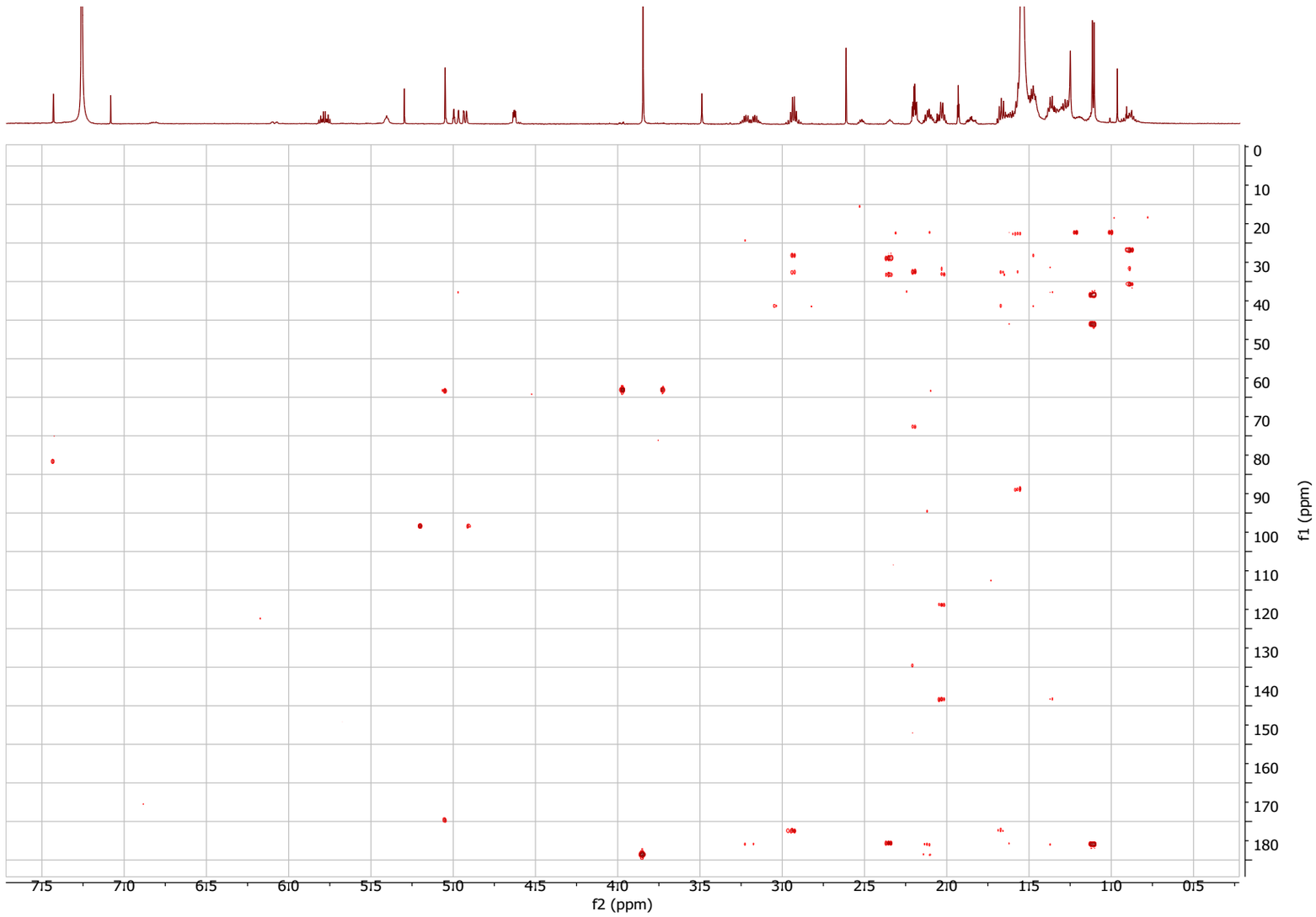


Figure S21. HMBC spectrum of natural product doscadenamide E (**1e**) in $CDCl_3$ (600 MHz) at 27 °C.

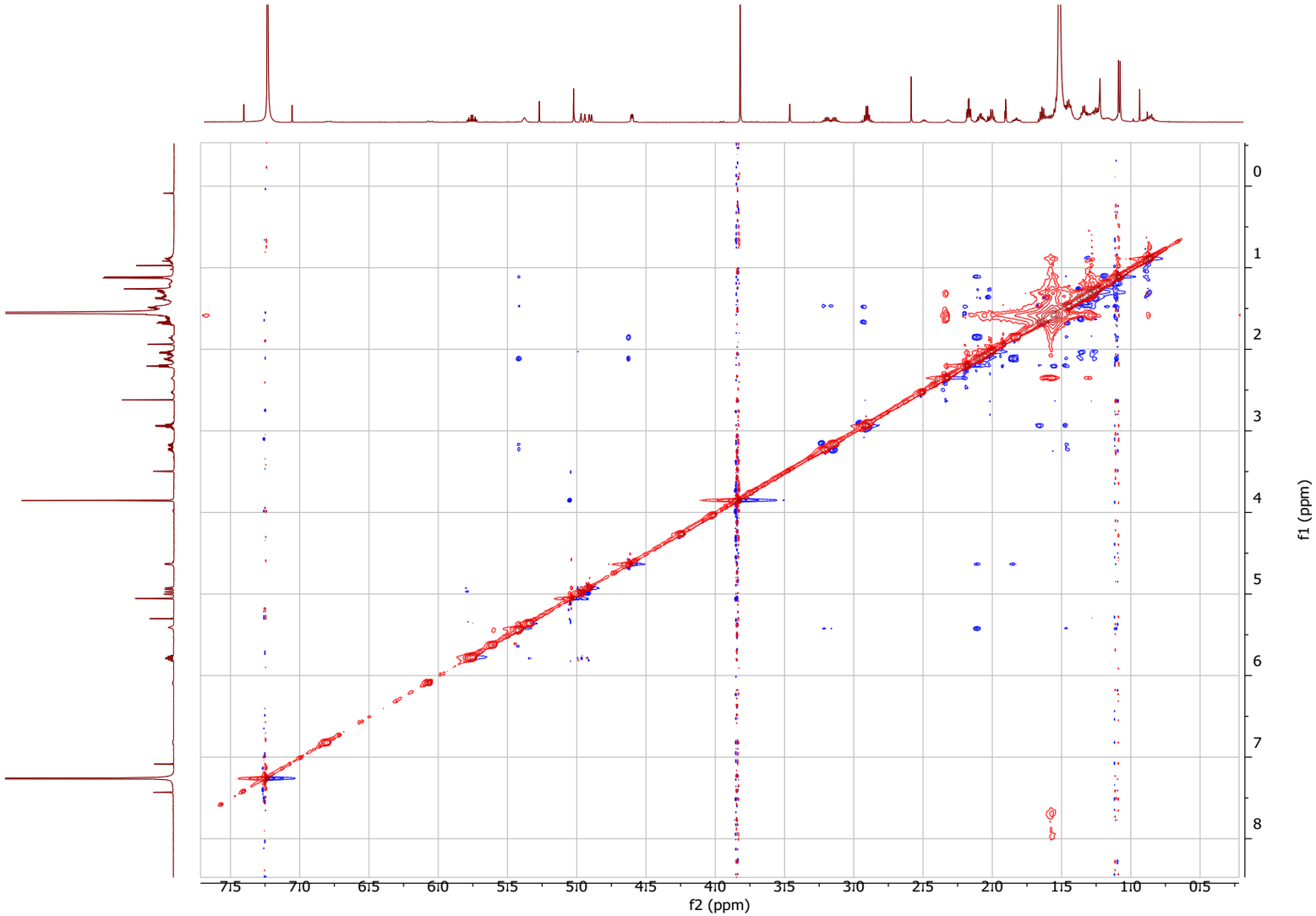


Figure S22. ROESY spectrum of natural product doscadenamide E (**1e**) in $CDCl_3$ (600 MHz) at 27 °C.

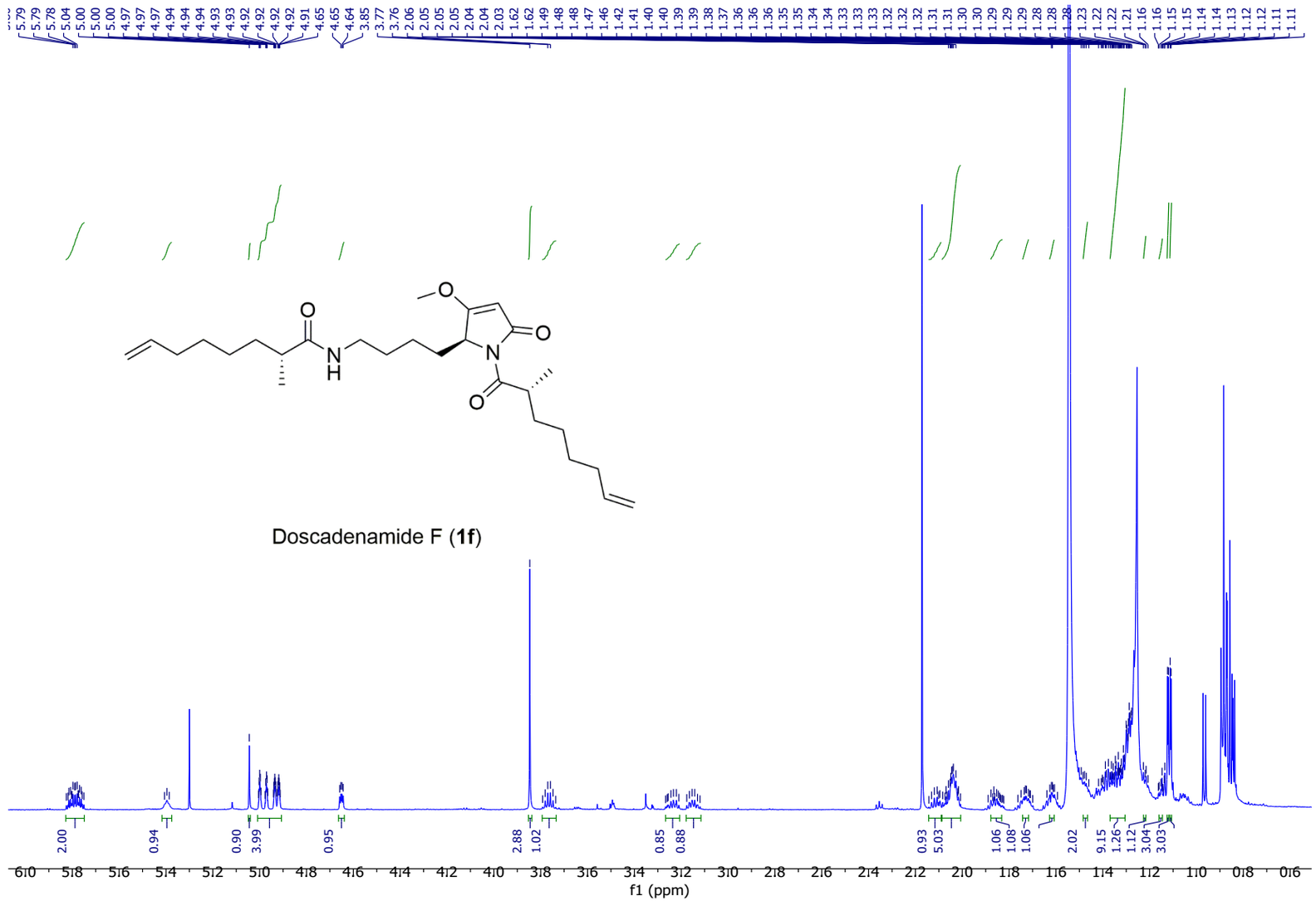


Figure S23. ^{1}H NMR spectrum of natural product doscadenamide F (**1f**) in $CDCl_3$ (600 MHz) at 27 °C.

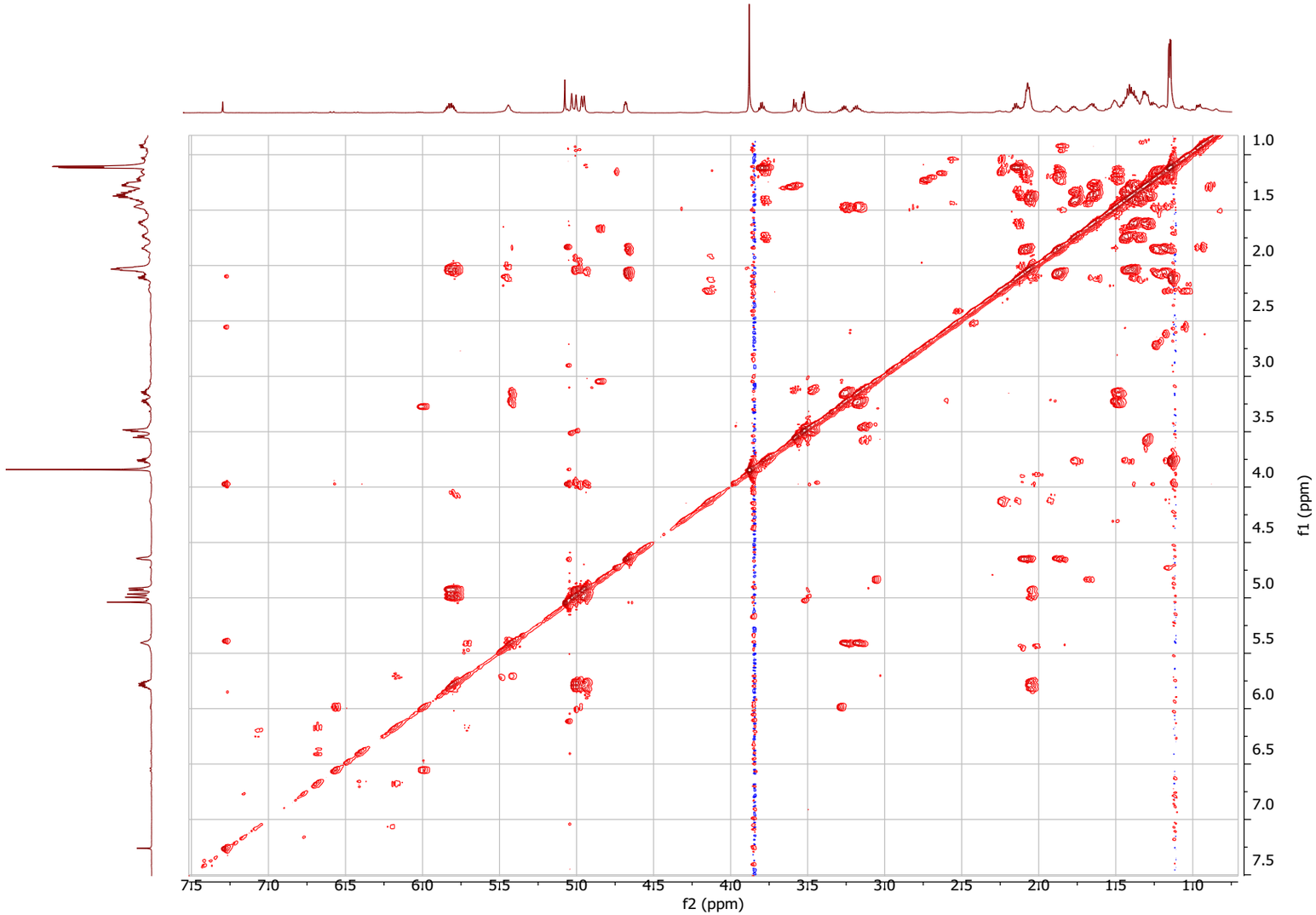


Figure S24. COSY spectrum of natural product doscadenamide F (**1f**) in $CDCl_3$ (600 MHz) at 27 °C.

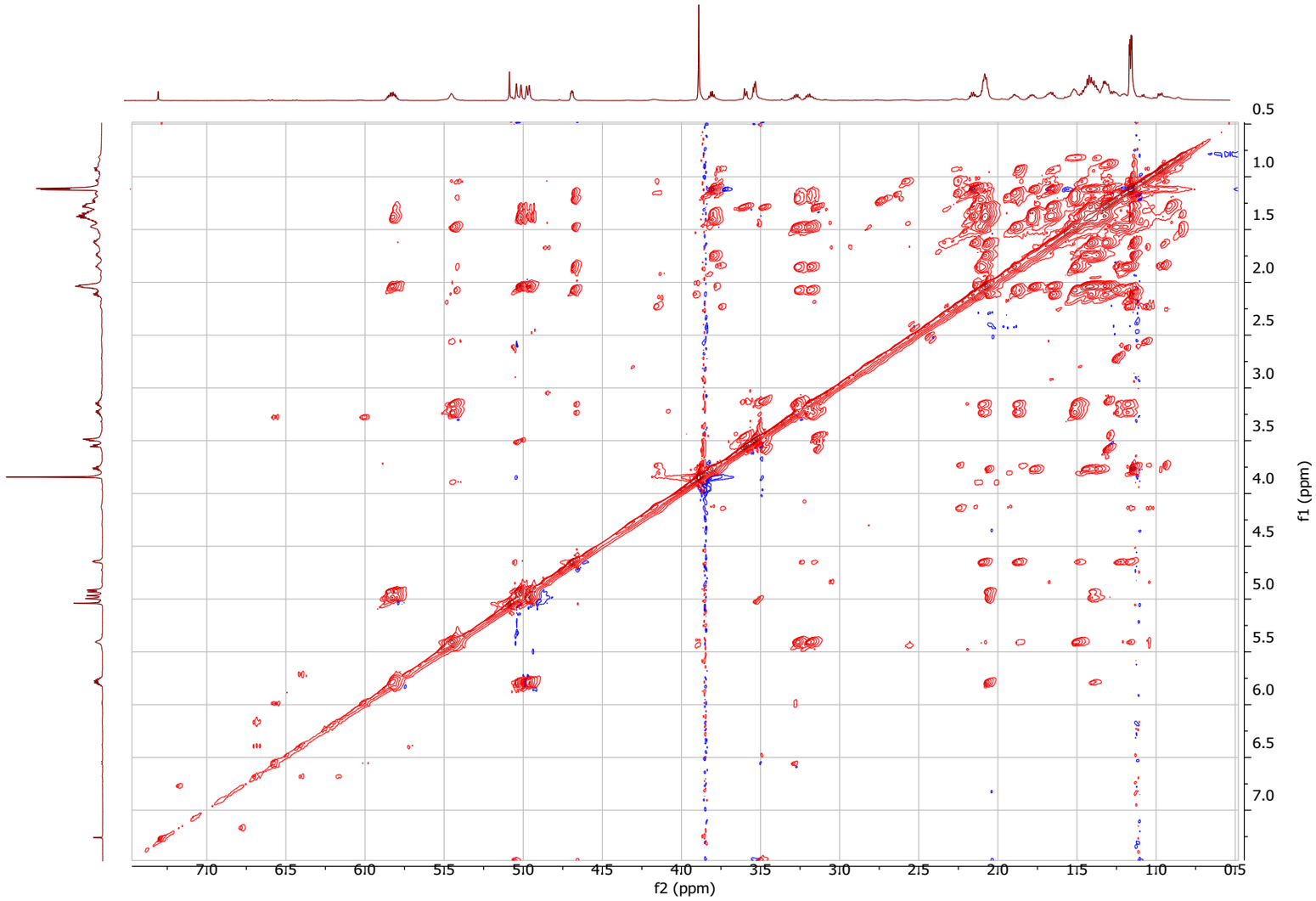


Figure S25. TOCSY spectrum of natural product doscadenamide F (**1f**) in $CDCl_3$ (600 MHz) at 27 °C.

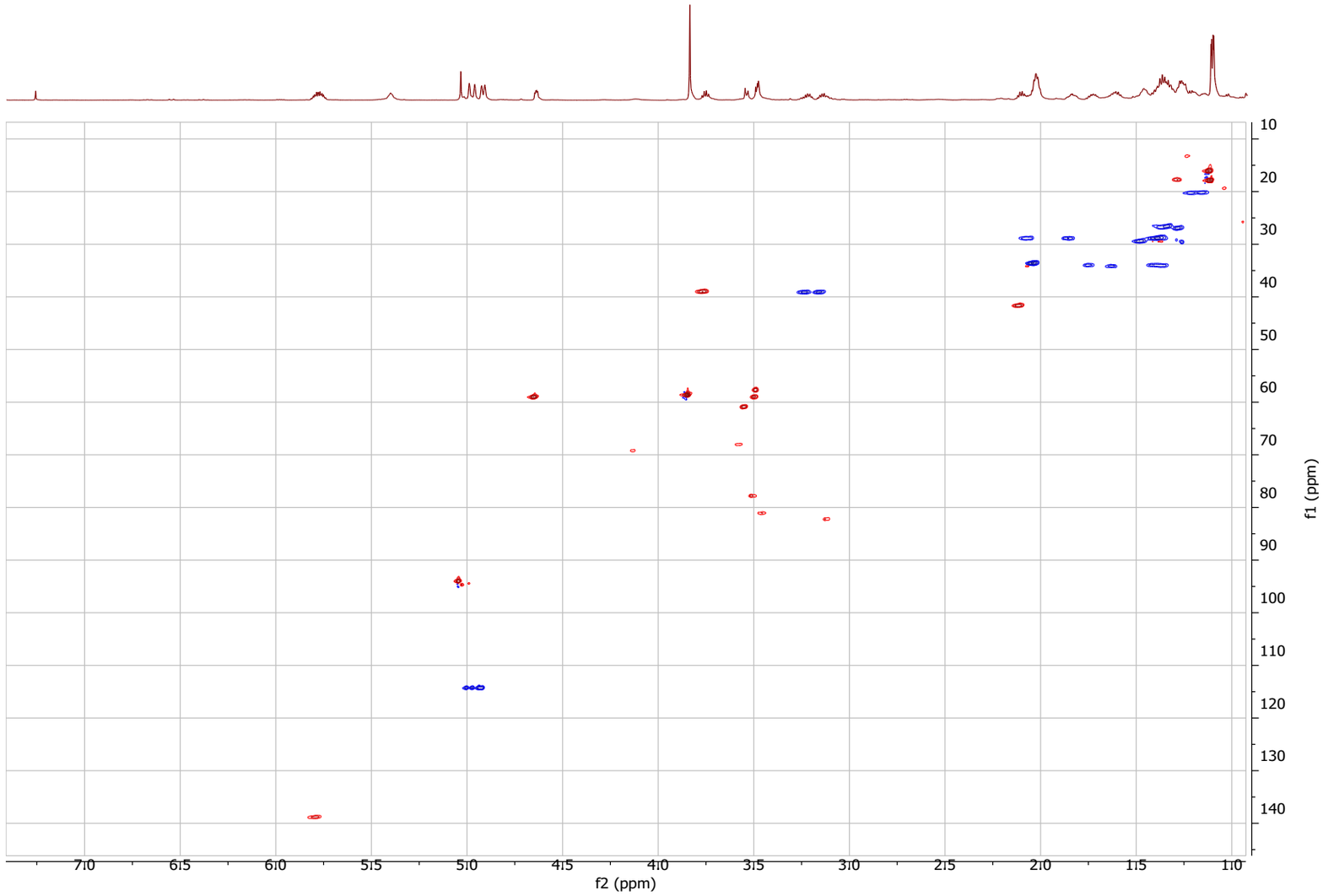


Figure S26. HSQC spectrum of natural product doscadenamide F (**1f**) in $CDCl_3$ (600 MHz) at 27 °C.

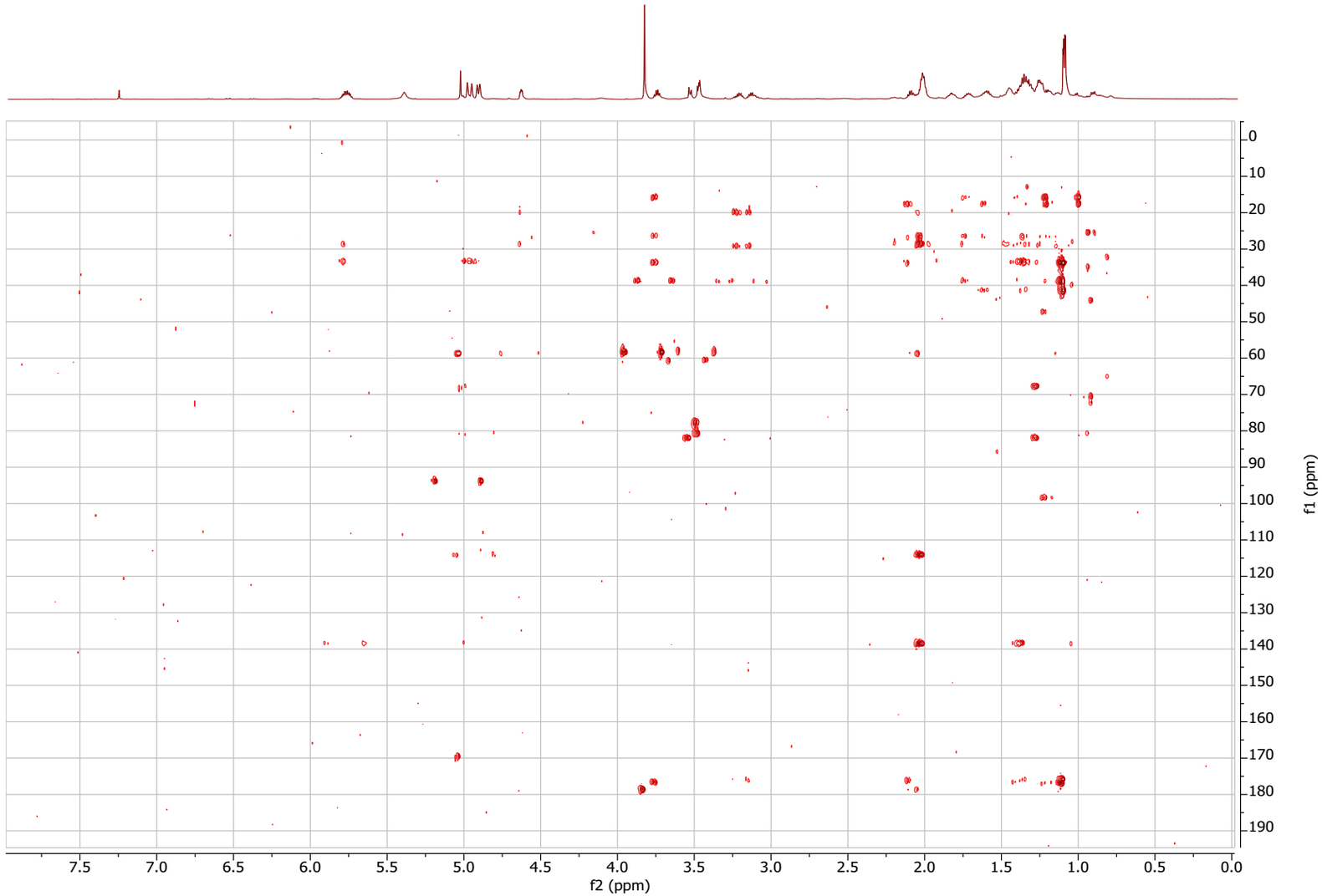


Figure S27. HMBC spectrum of natural product doscadenamide F (**1f**) in $CDCl_3$ (600 MHz) at 27 °C.

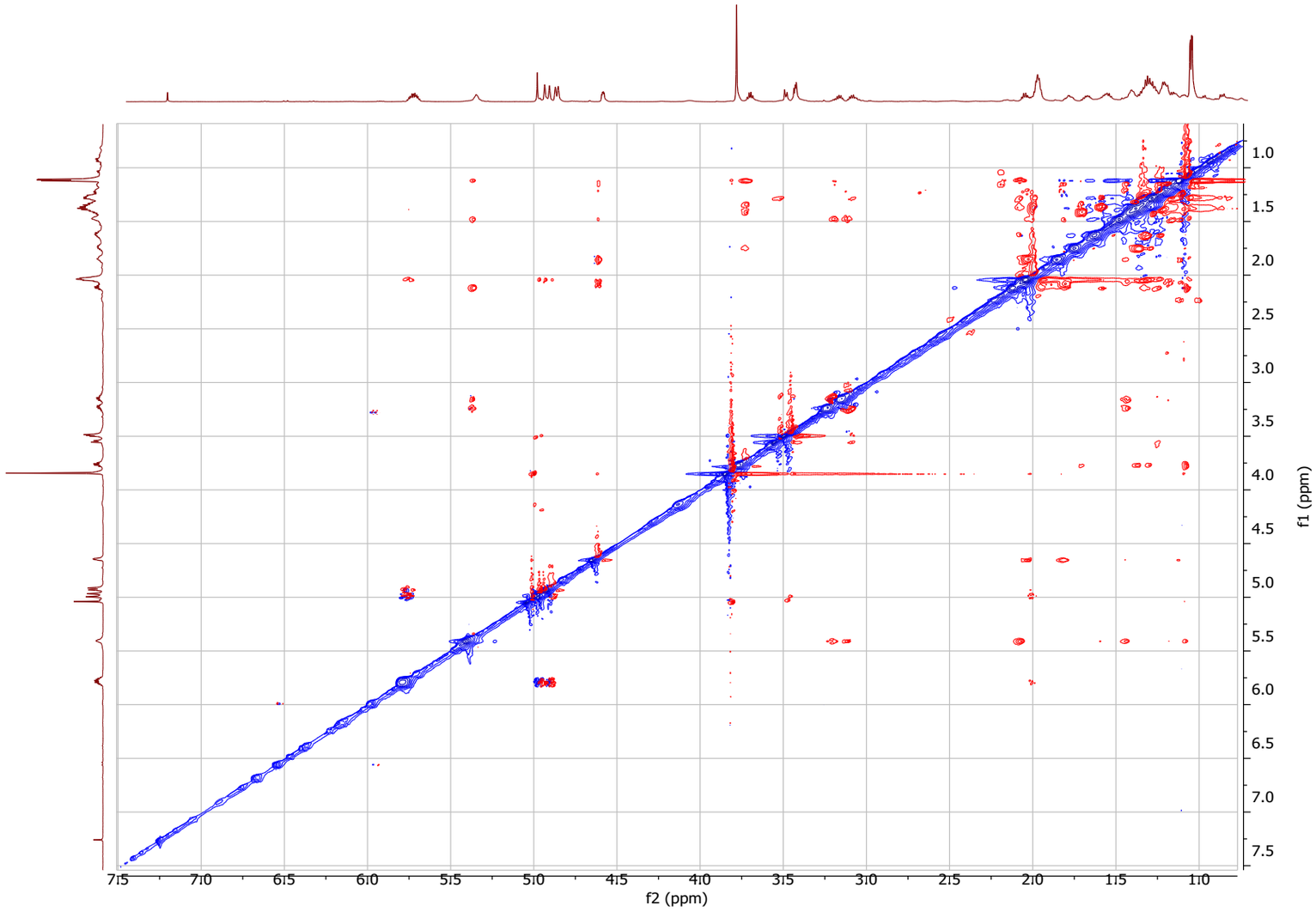


Figure S28. NOESY spectrum of natural product doscadenamide F (**1f**) in $CDCl_3$ (600 MHz) at 27 °C.

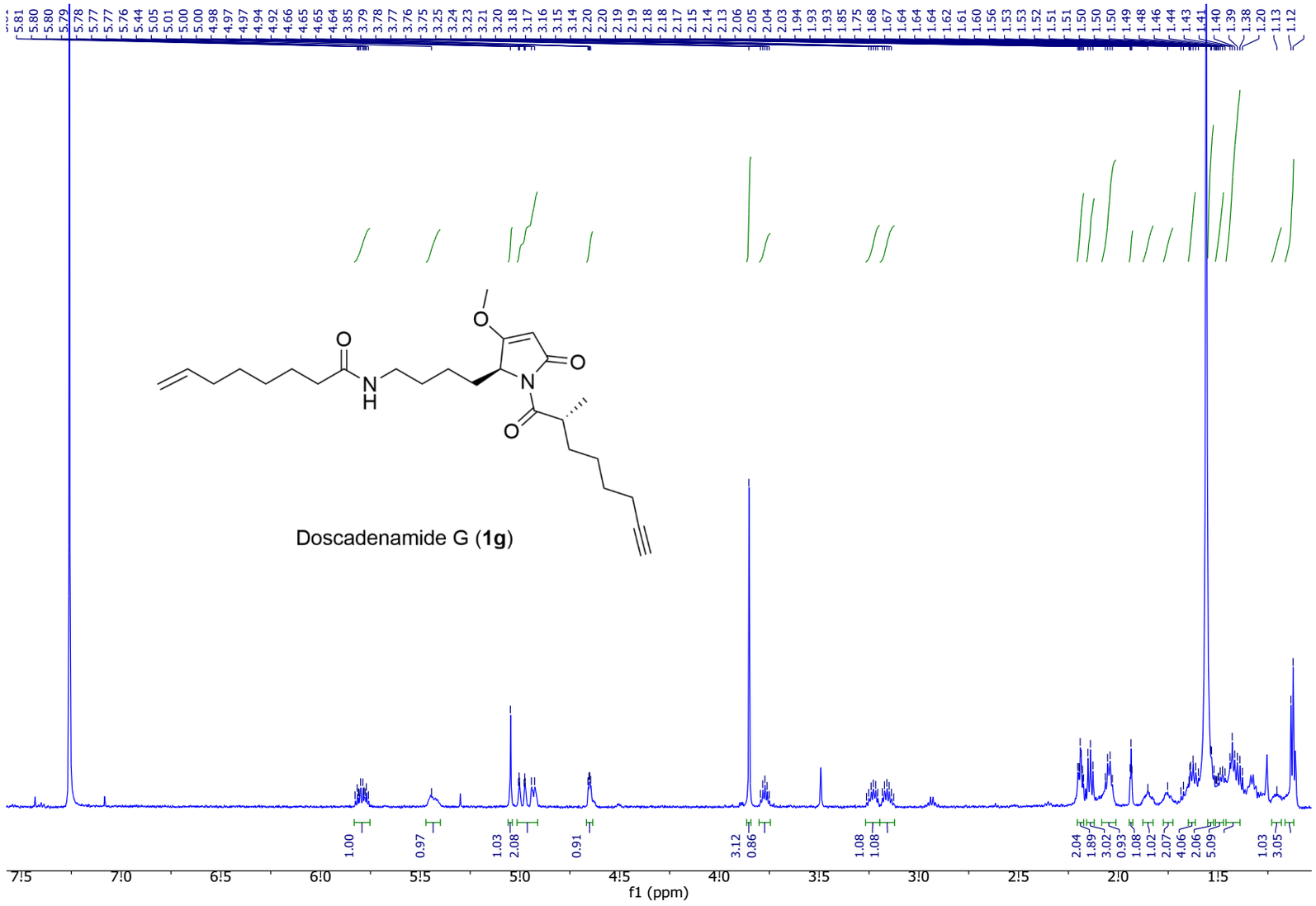


Figure S29. ^{1}H NMR spectrum of natural product doscadenamide G (**1g**) in $CDCl_3$ (600 MHz) at 27 °C.

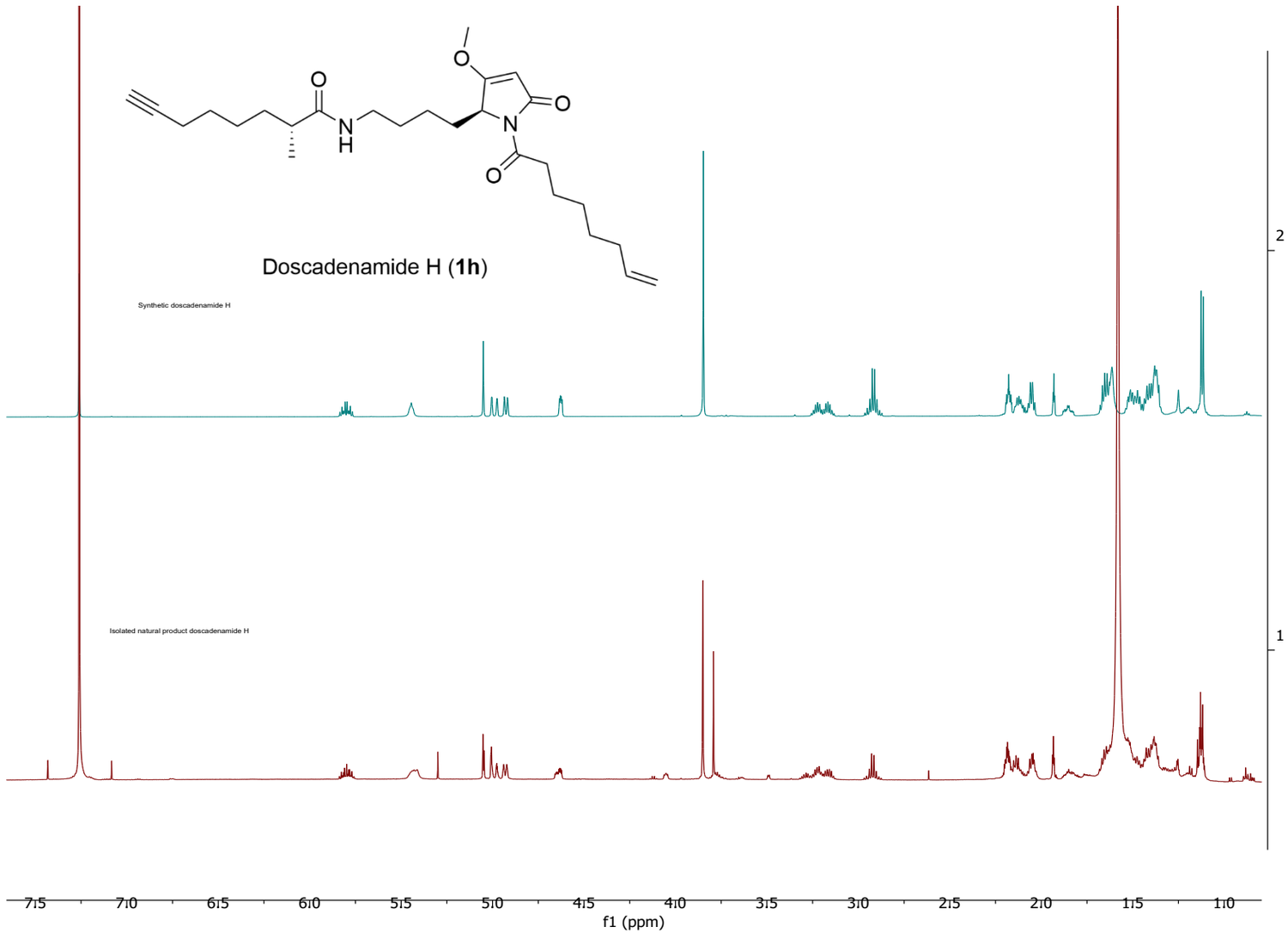


Figure S30. ^{1}H NMR spectra comparison of natural product doscadenamide H (**1h**, maroon) and synthetic doscadenamide H (teal) in $CDCl_3$ (600 MHz) at 27 °C.

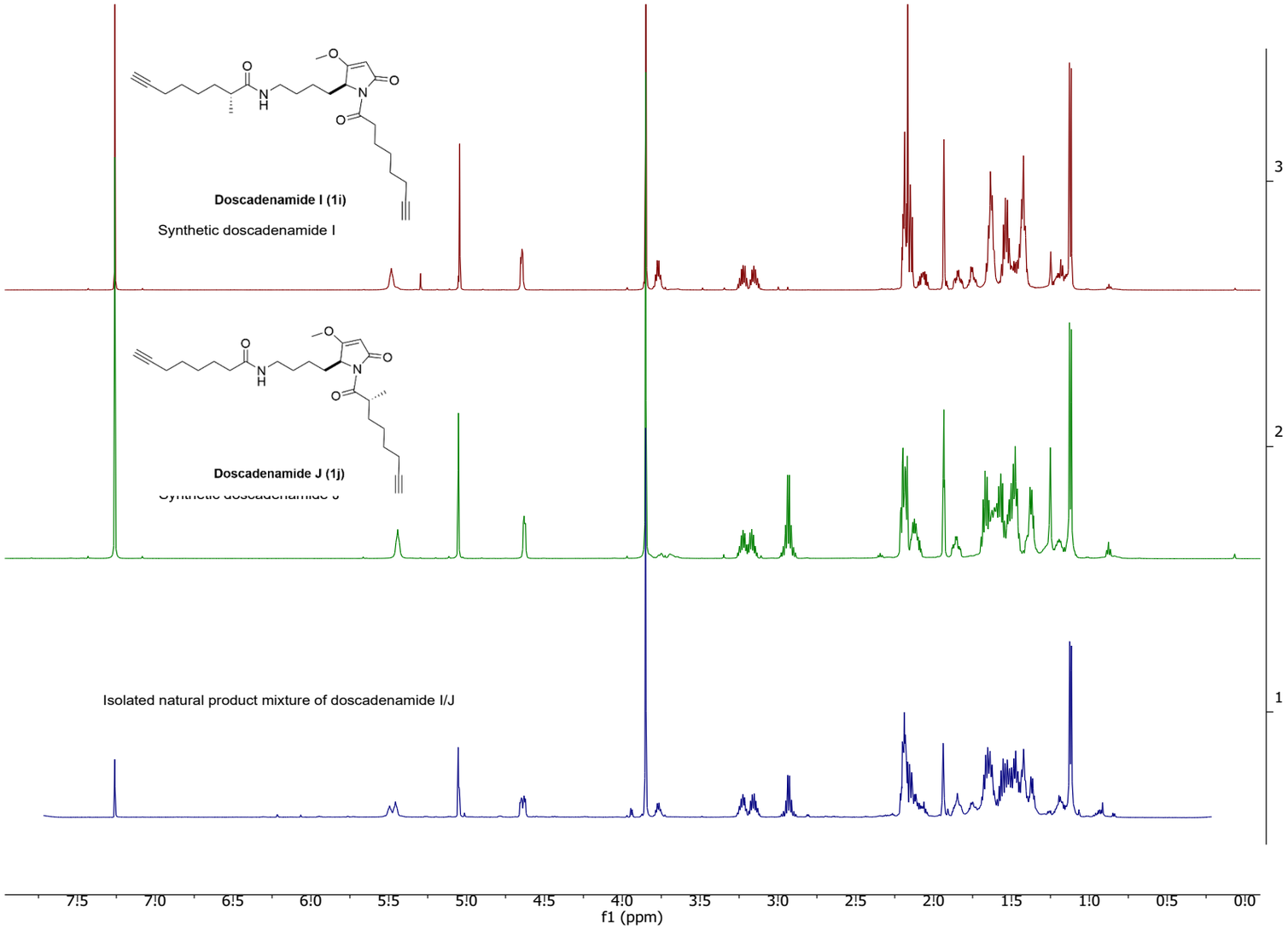


Figure S31. ^{1}H NMR spectra comparison of natural product mixture doscadenamide I/J (**1i/j**, purple) and synthetic doscadenamides I (maroon) and J (green) in $CDCl_3$ (600 MHz) at 27 °C.

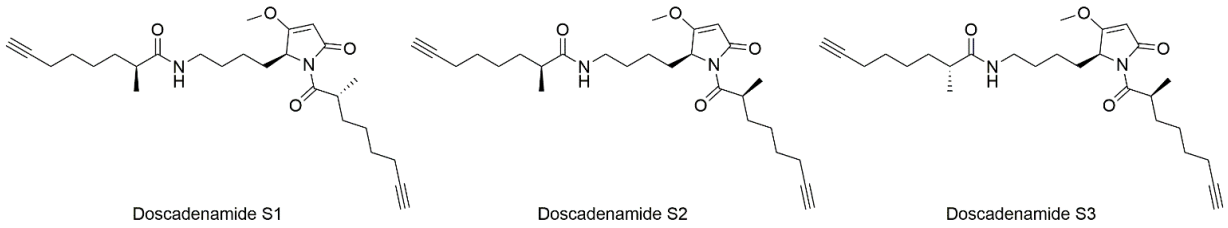


Figure S32. Structures of doscadenamide S1 – S3.

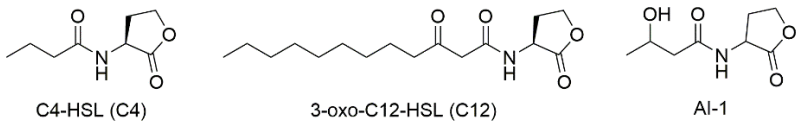


Figure S33. Structures of C4, C12 and AI-1.

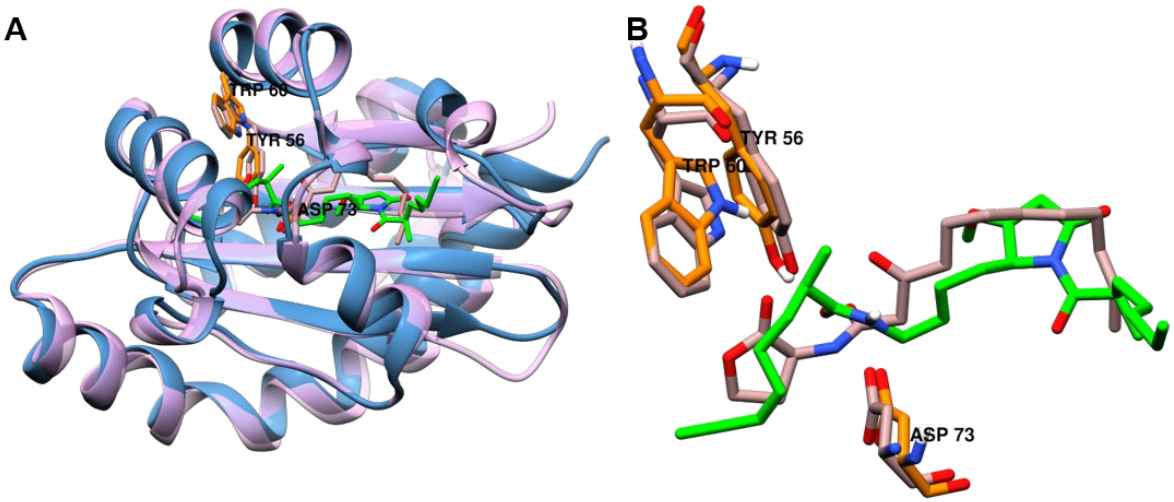


Figure S34. Comparison to the crystal structure (PDBID: 3IX3). (A) Experimental crystal structure (blue) and structure from MD simulation in pink. Ligand **1a** in green and C12 autoinducer in brown. Protein residues Tyr56, Trp60 and Asp73 are shown in brown (crystal structure) and orange (MD model). (B) Close up view of the binding site. Colors are the same as in (A).

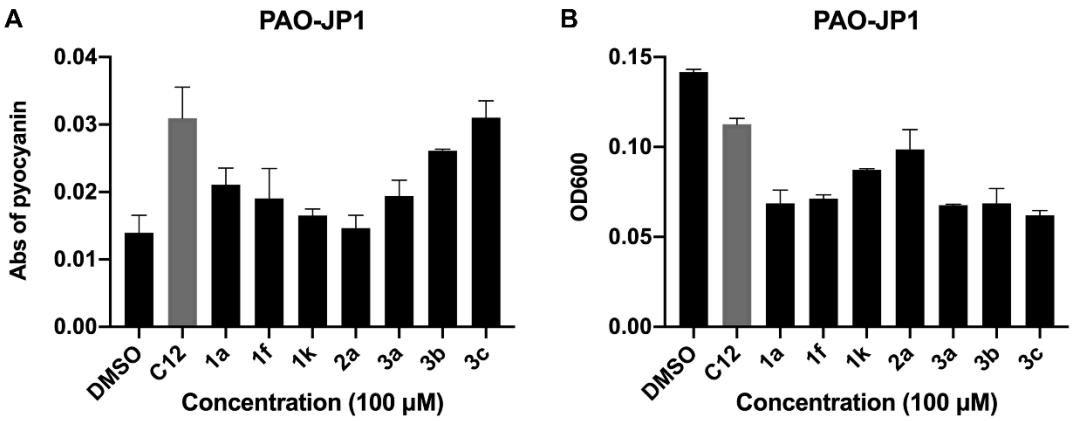


Figure S35. (A) Pyocyanin production in *P. aeruginosa* mutant PAO-JP1 after treatment with doscadenamide A (**1a**) and its structural analogs for 6 h at 100 μM and (B) the corresponding PAO-JP1 cell viability quantified by OD600. C12 was used as the positive control.

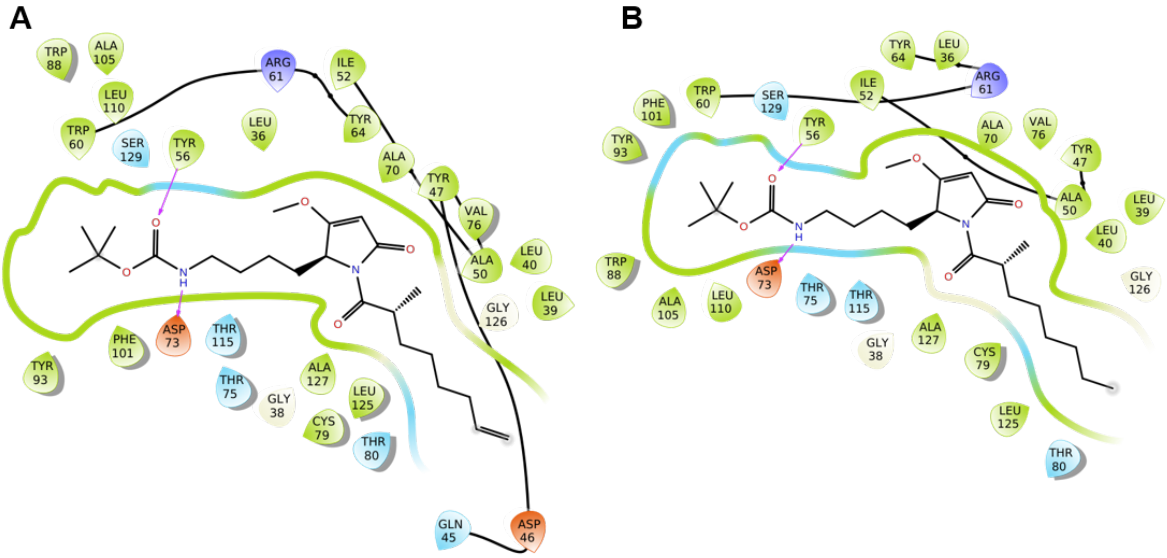


Figure S36. Diagrams showing the interactions with the surrounding residues for compounds **3b** (A), **3c** (B). Regions in green are hydrophobic, light blue are polar, red is negatively charged and dark blue are positively charged. Arrows indicate hydrogen bonds.

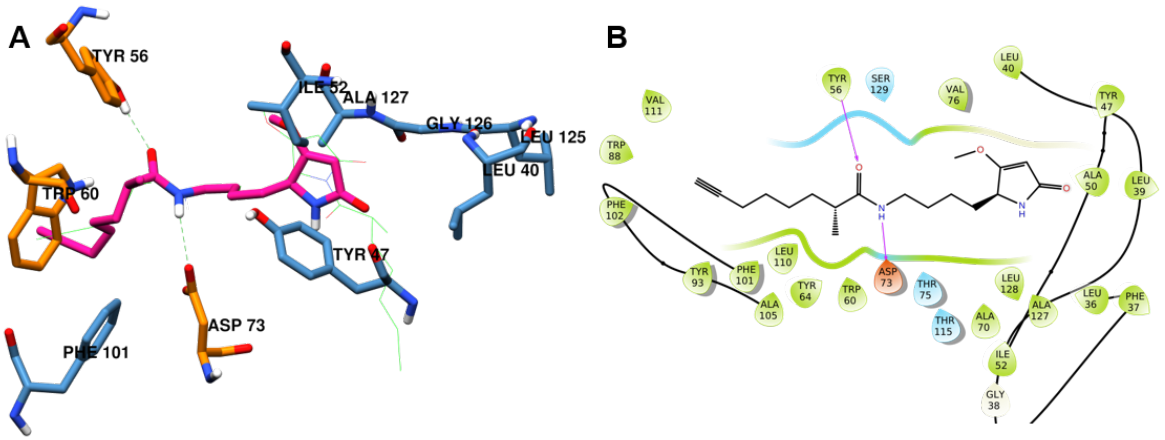


Figure S37. Three-dimensional representation (A) and diagram (B) showing the interactions with the surrounding residues for the antagonist **2a**. The agonist **1a** is depicted as green wires in (A). Regions in green are hydrophobic, light blue are polar, red is negatively charged and dark blue are positively charged. Purple arrows indicate hydrogen bonds.

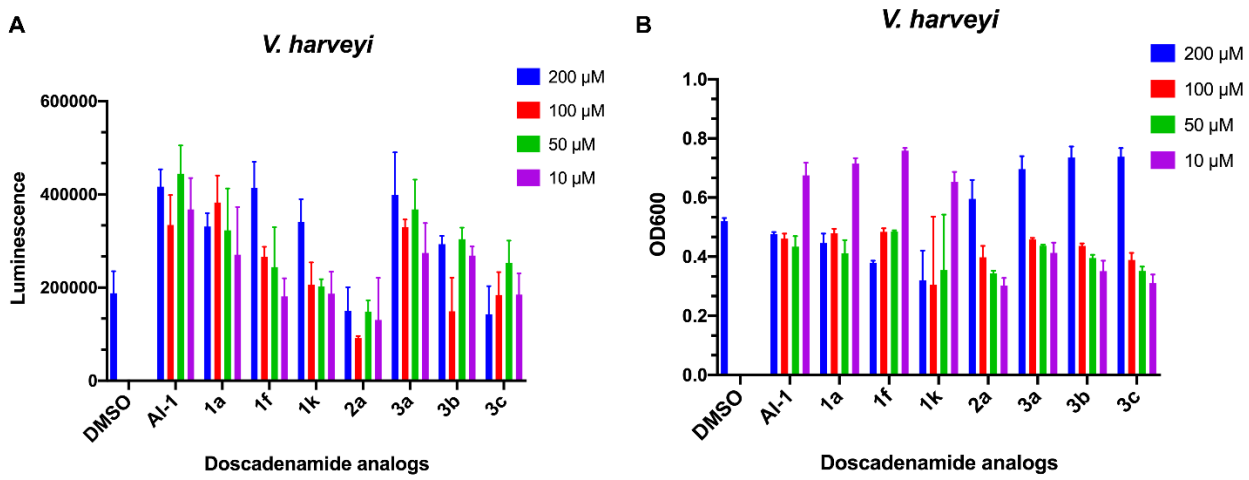
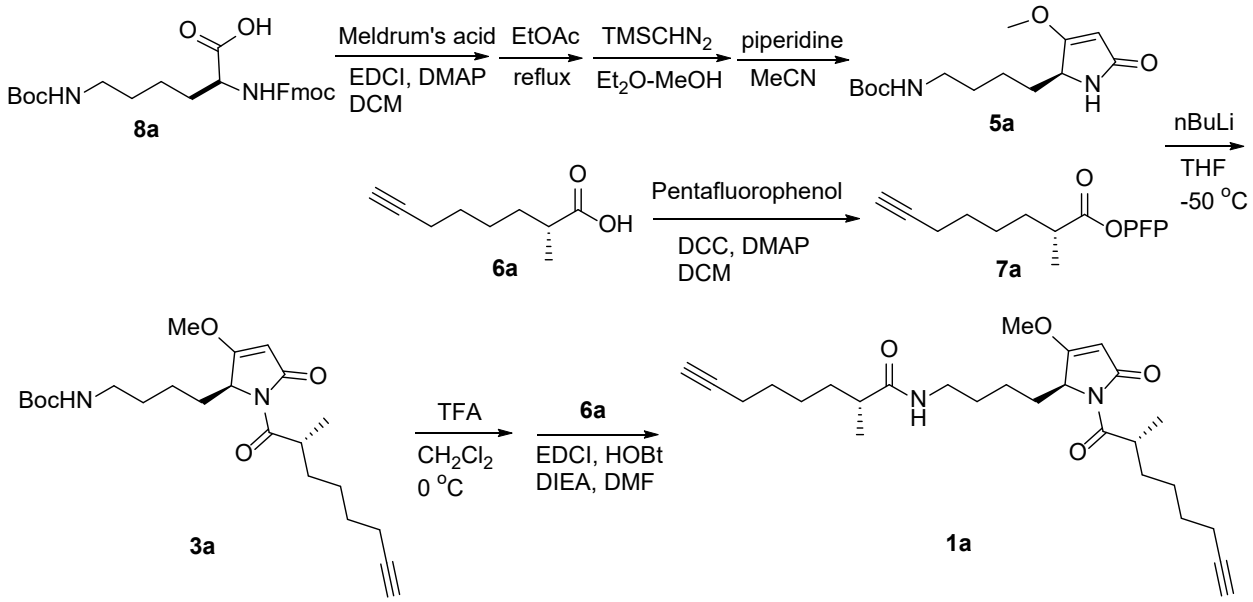


Figure S38. (A) Measurement of QS activating activity of doscadenamide A (**1a**) and its structural analogs in *V. harveyi* after 8 h treatment, presented by luminescence and (B) the corresponding cell viability quantified by OD600. AI-1 was used as the positive control.

Total Synthesis of Doscadenamides

Scheme S1. Published synthetic route for **1a**.[3]



Scheme S1 is the published synthetic route for **1a**.[3] This synthetic strategy was generalized to construct other analogs of **1-4** (Figure 1). The reaction conditions were adjusted for the minority of compounds. Various analogs of **5a** as well as **6a** (Figure S39) have been synthesized using general methods, and the combination of building blocks of **5a** analogs with **6a** analogs provided the series of target molecules (**1a-p**, **2a, b**, **3a-c**, and **4a**).

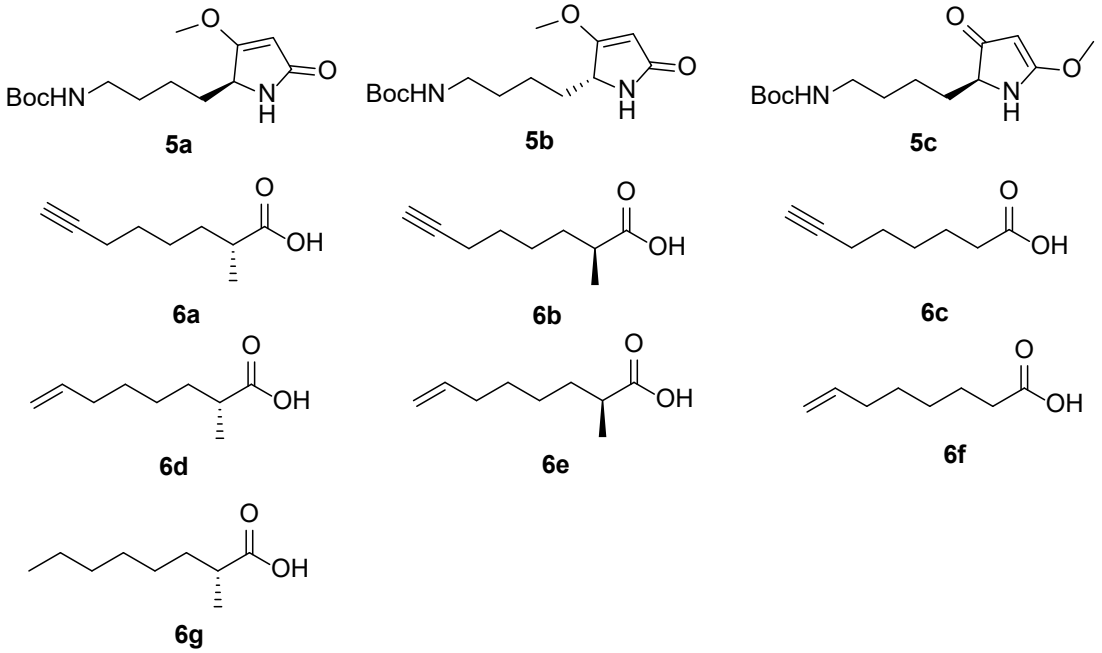
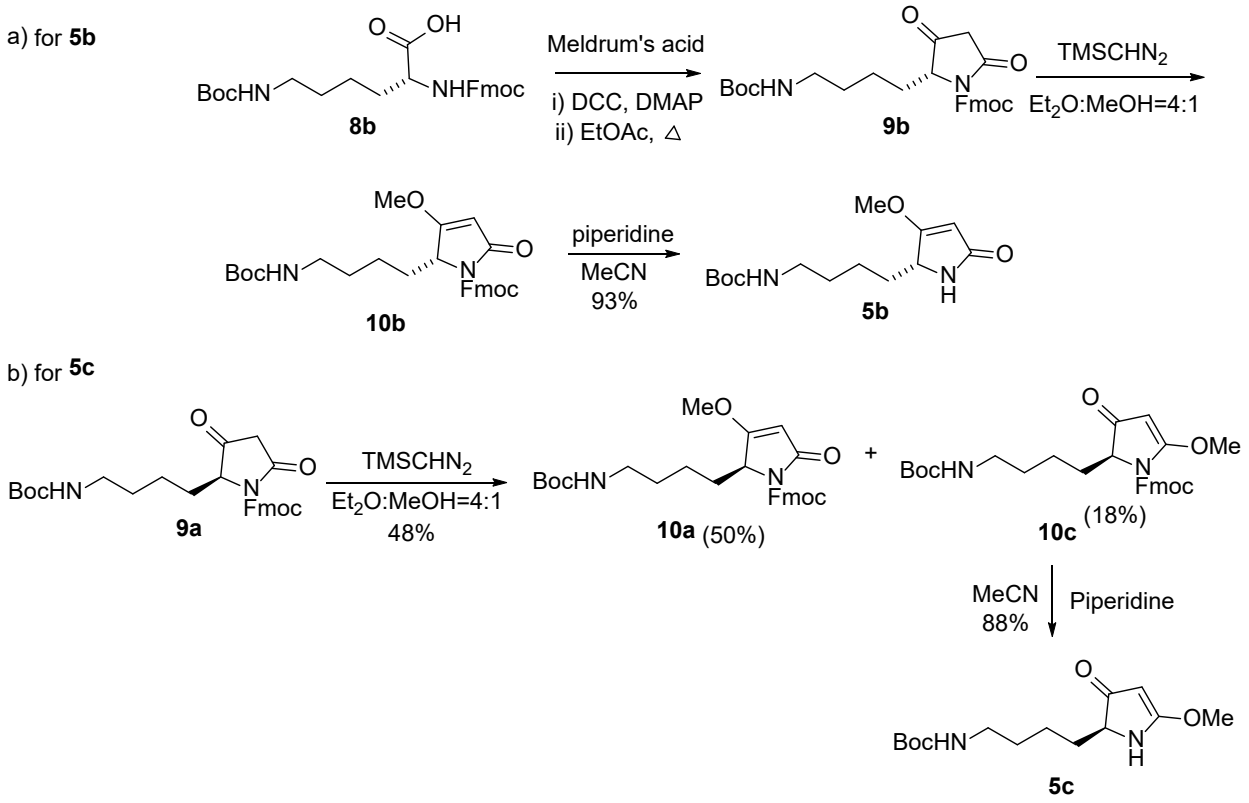


Figure S39. Designed various building blocks **5** and **6**.

Various building blocks of **5** and **6** are shown in Figure S39. Of them, **5a, 6a, b** were reported; **6c** and **6e** are commercial available. We just discuss the synthesis of **5b, c** and **6d, e, g** in here.

Synthesis of 5b, 5c

Scheme S2. Synthesis of building blocks **5b, 5c.**



Similar to the synthesis of **5a** and corresponding intermediates as reported,[3] **5b**, **5c** and corresponding intermediates were synthesized.

Synthesis of compounds 10b. To the solution of *N*-Fmoc-D-Lys (Boc)-OH (1.0 g, 2.13 mmol) and meldrum acid (338.4 mg, 2.35 mmol) in anhydrous CH_2Cl_2 (20 ml) at 0 ºC was added 4-Dimethylaminopyridine (DMAP) (391 mg, 3.20 mmol) and EDCI·HCl (530 mg, 2.77 mmol). After being stirred overnight at room temperature, the reaction solution was diluted with EtOAc (60 ml), washed by 5% citric acid (aq.) (20 ml × 4) and brine (20 ml × 2), dried over anhydrous $MgSO_4$. The filtered EtOAc phase was refluxed under heating for 30 min, then cooled down to room temperature and evaporated to give crude intermediate **9b**, which was used in next step without purification.

To a solution of the above crude **9b** in the mixture of diethyl ether (160 ml) and methanol (40 ml) was added trimethylsilyldiazomethane ($TMSCHN_2$) (4.4 ml, 8.79 mmol). The resulting mixture was stirred overnight at room temperature, then concentrated under reduced pressure. The residue was dissolved in EtOAc (150 ml), washed with 5% citric acid (aq.) (30 ml × 3), sat. $NaHCO_3$ (30

ml × 2 and brine (30 ml), dried over anhydrous $MgSO_4$, and evaporated in vacuo. Product **10b** was obtained after the crude was purified by chromatography column on silica gel (eluted by 50-70% ethyl acetate in hexane).

Compound 10b (500.0 mg, 45.0% 2 steps). $[\alpha]^{20}_D$ −72.5 (*c* 0.1, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.77-7.73 (m, 4H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 2H), 5.09 (s, 1H), 4.58 (m, 2H), 4.48 (br s, 1H), 4.36 (dd, *J* = 5.4, 3.0 Hz, 1H), 4.33 (t, *J* = 6.6 Hz, 1H), 3.83 (s, 3H), 3.08-2.98 (m, 2H), 1.85-1.79 (m, 1H), 1.71 (dddd, *J* = 14.4, 11.4, 4.8, 3.0 Hz, 1H), 1.44 (s, 9H), 1.38-1.31 (m, 2H), 1.19-1.11 (m, 1H), 1.03-0.96 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 178.0, 168.8, 155.0, 151.1, 143.8, 143.7, 141.5, 141.4, 128.0, 127.9, 127.4, 125.4, 125.4, 120.1, 120.1, 94.5, 79.3, 68.1, 59.9, 58.8, 46.9, 40.5, 29.9, 28.7, 28.6, 19.6 ppm; HRMS (ESI) *m/z* calcd for $C_{29}H_{35}N_2O_6$ $[M+H]^+$ 507.2495, found 507.2492.

Compound 10c. In the methylation of pyrrolidine **9a** previously[3], both 4- and 2- carbonyls were methylated to give corresponding products **10a** (50%) and **10c** (18%), which were separable with chromatography silica column. (18.2% from **9a**). $[\alpha]^{20}_D$ −28.0 (*c* 0.1, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 7.78-7.77 (m, 2H), 7.58-7.55 (m, 2H), 7.43-7.40 (m, 2H), 7.35-7.31 (m, 2H), 4.82 (s, 1H), 4.73 (m, 2H), 4.45 (br s, 1H), 4.25 (t, *J* = 4.8 Hz, 1H), 3.92 (s, 3H), 3.85-3.83 (m, 1H), 3.00-2.98 (m, 2H), 1.68-1.64 (m, 1H), 1.54-1.47 (m, 1H), 1.44 (s, 9H), 1.28-1.22 (m, 2H), 1.10-1.03 (m, 1H), 1.02-0.95 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): *δ* 195.9, 176.6, 156.0, 149.5, 143.5, 143.4, 141.7, 141.6, 128.1, 128.1, 127.4, 127.4, 124.6, 124.5, 120.3, 120.3, 86.6, 79.2, 67.7, 66.1, 59.7, 47.0, 40.4, 29.9, 29.4, 28.6, 19.7 ppm; HRMS (ESI) *m/z* calcd for $C_{29}H_{35}N_2O_6$ $[M+H]^+$ 507.2495, found 507.2491.

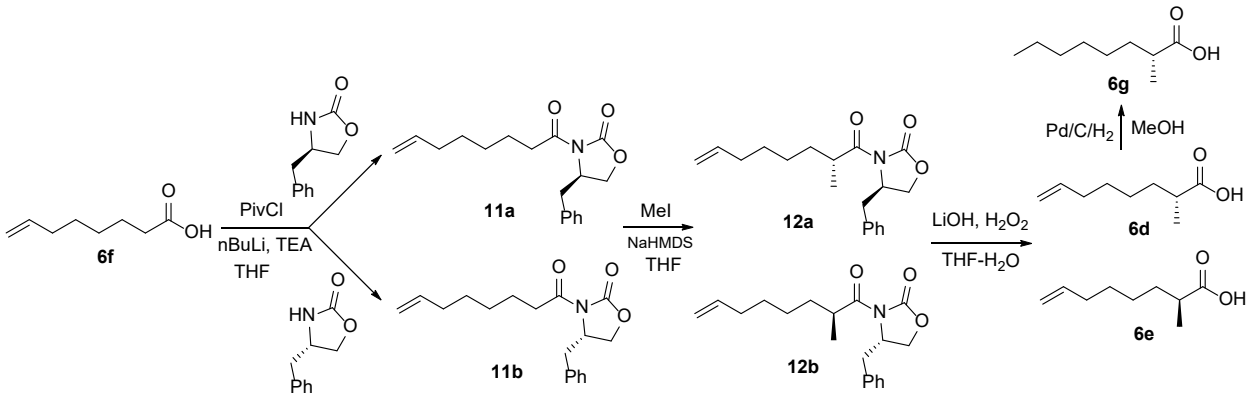
Synthesis of compounds 5b and 5c. Piperidine (2.0 ml) was added to the solution of **10b** or **10c** (366.3 mg, 0.723 mmol) at room temperature. After stirred at the same temperature for 15 min, the reaction solution was concentrated and co-evaporated with toluene for 3 times. The residue was purified by chromatography column on silica gel (eluted by EtOAc/hexane 1:1, then by 3-3.5% MeOH in CH_2Cl_2) to provide product **5b** or **5c**.

Compound 5b (93%). $[\alpha]^{20}_D$ −21.5 (*c* 0.1, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 6.23 (br s, 1H), 5.01 (s, 1H), 4.72 (t, *J* = 6.0 Hz, 1H), 4.04 (dd, *J* = 7.2, 3.6 Hz, 1H), 3.78 (s, 3H), 3.16-3.06 (m, 2H), 1.83-1.78 (m, 1H), 1.56-1.47 (m, 3H), 1.47-1.41 (m, 10H), 1.36-1.30 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): *δ* 178.3, 174.5, 156.2, 93.7, 79.3, 58.5, 57.4, 40.3, 31.5, 29.9, 28.6, 22.1 ppm; HRMS (ESI) *m/z* calcd for $C_{14}H_{25}N_2O_4$ $[M+H]^+$ 285.1814, found 285.1806.

Compound 5c (88%). $[\alpha]^{20}_D$ −39.0 (*c* 0.1, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): *δ* 5.69 (br s, 1H), 4.66-4.64 (m, 2H), 3.89 (s, 3H), 3.75-3.73 (m, 1H), 3.13-3.07 (m, 2H), 1.91-1.85 (br m, 1H), 1.66-1.60 (m, 1H), 1.53-1.47 (m, 2H), 1.44-1.37 (m, 11H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): *δ* 199.3, 181.6, 156.4, 80.4, 79.4, 63.5, 58.4, 40.1, 30.8, 30.0, 28.6, 22.2 ppm; HRMS (ESI) *m/z* calcd for $C_{14}H_{25}N_2O_4$ $[M+H]^+$ 285.1814, found 285.1807.

Synthesis of 6d, 6e and 6g

Scheme S3. Synthesis of **6d/e/g**.



Synthesis of 11a and 11b. To a solution of 7-octenoic acid (Oea) (450 mg, 3.17 mmol) and trimethylamine (Et_3N) (0.56 mL, 4.13 mmol) in THF (18 mL) at −20 °C was added neat 2,2-trimethylacetyl chloride (0.43 mL, 3.49 mmol) dropwise over 20 min. The resulting mixture was stirred at −20 °C for 30 min and 0 °C for another 30 min, then it was cooled to −78 °C by dry ice- acetone. In another reaction flask, n-butyllithium (n-BuLi) (1.6 M in n-hexane) (2.0 ml, 3.17 mmol) was added dropwise to a solution of *R*- or *S*-oxazolidione (841 mg, 4.75 mmol) in tetrahydrofuran at −78 °C. The mixture was stirred at this temperature for 20 min and then transferred to the above solution of Oya in THF at −78 °C by canula. The resulting mixture was stirred at this temperature for 30 min, then it was allowed to warm to room temperature and stirred for 1.5 h. The reaction was quenched with saturate NH_4Cl (aq) solution, extracted with EtOAc (45 mL×3), washed by 5% $NaHCO_3$ solution, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography column (eluted by 15% ethyl acetate in hexane) to give products **11a** or **11b**, corresponding to *R*- or *S*-oxazolidione, respectively.

Compound 11a (451 mg, 78%). $[\alpha]^{20}_D$ −97.0 (*c* 0.1, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35-7.32 (t m, 2H), 7.29-7.26 (t m, 1H), 7.22-7.20 (d m, 2H), 5.81 (ddt, *J* = 17.5, 10.2, 6.6 Hz, 1H), 5.02-4.93 (m, 2H), 4.67 (ddt, *J* = 10.8, 7.8, 3.0 Hz, 1H), 4.21-4.15 (m, 2H), 3.30 (dd, *J* = 13.2, 3.0 Hz, 1H), 3.00-2.87 (m, 2H), 2.77 (dd, *J* = 13.2, 9.6 Hz, 1H), 2.09-2.05 (m, 2H),, 1.75-1.65 (m, 2H), 147-1.38 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.5, 153.6, 139.0, 135.5, 129.6, 129.1, 127.5, 114.6, 66.3, 55.3, 38.1, 35.6, 33.7, 28.8, 28.7, 24.2 ppm; HRMS (ESI) *m/z* calcd for $C_{18}H_{24}NO_3$ $[M+H]^+$ 302.1756, found 302.1748.

Compound 11b (907 mg, 95%). $[\alpha]^{20}_D$ +85.0 (*c* 0.1, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35-7.32 (t m, 2H), 7.29-7.26 (t m, 1H), 7.22-7.20 (d m, 2H), 5.81 (ddt, *J* = 17.4, 10.2, 6.6 Hz, 1H), 5.02-4.93 (m, 2H), 4.67 (ddt, *J* = 10.8, 7.8, 3.0 Hz, 1H), 4.21-4.15 (m, 2H), 3.30 (dd, *J* = 13.2, 3.0 Hz, 1H), 3.00-2.87 (m, 2H), 2.77 (dd, *J* = 13.2, 9.6 Hz, 1H), 2.09-2.05 (m, 2H), 1.76-1.65 (m, 2H), 147-1.38 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.5, 153.6, 139.0, 135.5, 129.6, 129.1, 127.5, 114.6, 66.3, 55.3, 38.1, 35.6, 33.7, 28.8, 28.7, 24.2 ppm; HRMS (ESI) *m/z* calcd for $C_{18}H_{24}NO_3$ $[M+H]^+$ 302.1756, found 302.1746.

Synthesis of compounds 12a and 12b. To a solution of sodium bis(trimethylsilyl)amide (NaHMDS) (2.0 M in THF) (1.11 ml, 2.21 mmol) in anhydrous THF (9 ml) at −78 °C was added compound **11a** or **11b** (609 mg, 2.02 mmol) in THF (3.5 ml) under argon atmosphere. After the resulting reaction solution was stirred at the same temperature for 30 min, neat MeI (0.63 ml, 10.08 mmol) was added dropwise over 10 min. The reaction mixture was quenched with saturate NH_4Cl (aq.) (18 ml) after it was stirred at −78 °C for 20 h, then extracted with ethyl acetate (25 ml×3), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography column of silica gel (eluted by 8% ethyl acetate in hexane) to give product **12a or 12b**, corresponding to **11a**, **11b**, respectively.

Compound 12a (566 mg, 89%). $[\alpha]^{20}_D$ −70.0 (*c* 0.1, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34-7.31 (m, 2H), 7.29-7.26 (m, 1H), 7.22-7.21 (m, 2H), 5.79 (ddt, *J* = 17.4, 10.2, 6.6 Hz, 1H), 5.01-4.92 (m, 2H), 4.68 (ddt, *J* = 9.6, 7.8, 3.0 Hz, 1H), 4.21-4.16 (m, 2H), 3.70 (h, *J* = 6.6 Hz, 1H), 3.27 (dd, *J* = 13.2, 3.0 Hz, 1H), 2.77 (dd, *J* = 13.2, 9.6 Hz, 1H), 2.05 (qt, *J* = 7.0, 1.2 Hz, 2H), 1.78-1.72 (m, 1H), 1.46-1.36 (m, 3H), 1.36-1.29 (m, 2H), 1.22 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 177.4, 153.2, 139.0, 135.5, 129.6, 129.1, 127.5, 114.6, 66.2, 55.5, 38.1, 37.8, 33.7, 33.4, 29.0, 26.8, 17.5 ppm; HRMS (ESI) *m/z* calcd for $C_{19}H_{26}NO_3$ $[M+H]^+$ 316.1913, found 316.1901.

Compound 12b (608 mg, 69%). $[\alpha]^{20}_D$ +99.0 (*c* 0.1, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (t, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.0 Hz, 1H), 7.21 (d, *J* = 7.0 Hz, 2H), 5.79 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.00-4.92 (m, 2H), 4.70-4.65 (m, 1H), 4.21-4.15 (m, 2H), 3.70 (sextet, *J* = 6.5 Hz, 1H), 3.26 (dd, *J* = 13.5, 3.5 Hz, 1H), 2.77 (dd, *J* = 13.5, 9.5 Hz, 1H), 2.04 (q, *J* = 7.0 Hz, 2H), 1.79-1.71 (m, 1H), 1.46-1.36 (m, 3H), 1.35-1.28 (m, 2H), 1.22 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.4, 153.2, 139.0, 135.5, 129.6, 129.0, 127.5, 114.5, 66.1, 55.5, 38.0, 37.8, 33.7, 33.3, 29.0, 26.8, 17.5 ppm; HRMS (ESI) *m/z* calcd for $C_{19}H_{26}NO_3$ $[M+H]^+$ 316.1913, found 316.1902.

Synthesis of acid 6d, 6e. Hydrogen peroxide (30% in H_2O) (0.7 ml, 6.12 mmol) was added to the solution of **12a** or **12b** (480 mg, 1.52 mmol) in the mixture of THF-H_2O (10 ml-5 ml) at 0 °C. LiOH·H_2O (128.4 mg, 3.06 mmol) was added to the above reaction solution after it was stirred at 0 °C for additional 10 min. Then the resulting reaction mixture was stirred at 0 °C for 2 h and additional 1 h at room temperature, then Na_2SO_3 (965.2 mg) was added. The quenched reaction was diluted with water (25 ml) and EtOAc (25 ml). Ethyl acetate phase was separated and the separated water phase was acidified with 1M aq. HCl (to pH 2) and extracted EtOAc (25 ml × 3). The combined EtOAc phase was dried over anhydrous $MgSO_4$, concentrated *in vaccuo*, and purified by silica gel column chromatography (eluted by 17% ethyl acetate in hexane) to give product **6d** or **6e**, corresponding to **12a**, **12b**, respectively.

Acid 6d (246 mg, 92%). $[\alpha]^{20}_D$ −23.0 (*c* 0.1, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): 5.79 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H), 5.01-4.92 (m, 2H), δ 2.46 (sextet, *J* = 7.2 Hz, 1H), 2.05 (qt, *J* = 8.4, 1.2 Hz, 2H), 1.72-1.67 (m, 1H), 1.47-1.32 (m, 5H), 1.18 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 183.3, 138.9, 114.6, 39.5, 33.7, 33.5, 28.9, 26.7, 17.0 ppm; HRMS (ESI) *m/z* calcd for $C_9H_{17}O_2$ $[M+H]^+$ 157.1229, found 157.1222.

Acid 6e (148.3, 62%). $[\alpha]^{20}_D$ +13.0 (*c* 0.1, MeOH). ^{1}H NMR (600 MHz, $CDCl_3$): 5.79 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H), 5.01-4.92 (m, 2H), δ 2.46 (sextet, *J* = 7.2 Hz, xz1H), 2.05 (qt, *J* = 8.4, 1.8 Hz, 2H), 1.72-1.66 (m, 1H), 1.47-1.32 (m, 5H), 1.18 (d, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (150 MHz,

$CDCl_3$): δ 183.4, 138.9, 114.6, 39.5, 33.7, 33.5, 28.9, 26.7, 17.0 ppm. HRMS (ESI) *m/z* calcd for $C_9H_{17}O_2$ $[M+H]^+$ 157.1229, found 157.1219.

Synthesis of acid 6g. Though acid **6g** is a known and commercially available compound, we prepared it conveniently from the available material in lab. Acid **6d** (33 mg, 0.211 mmol) was stirred under hydrogen atmosphere in MeOH (2.0 mL) for 30 min, then the reaction mixture was filtered and evaporated to provide acid **6g** (30 mg, 90%).

Acid 6g (30 mg, 90%); $[\alpha]^{20}_D$ −22.0 (*c* 0.15, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.45 (ddq, J = 6.7 Hz, 1H), 1.71-1.65 (m, 1H), 1.45-1.40 (m, 1H), 1.34-1.27 (m, 8H), 1.17 (d, J = 7.0 Hz, 3H), 0.88 (t, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 182.9, 39.6, 33.8, 31.8, 29.3, 27.3, 22.8, 17.0, 14.2 ppm; HRMS (ESI) *m/z* calcd for $C_9H_{17}O_2$ $[M-H]^-$ 157.1229, found 157.1232.

Synthesis of 3a-g and 1a-o (Scheme S4 and S5)

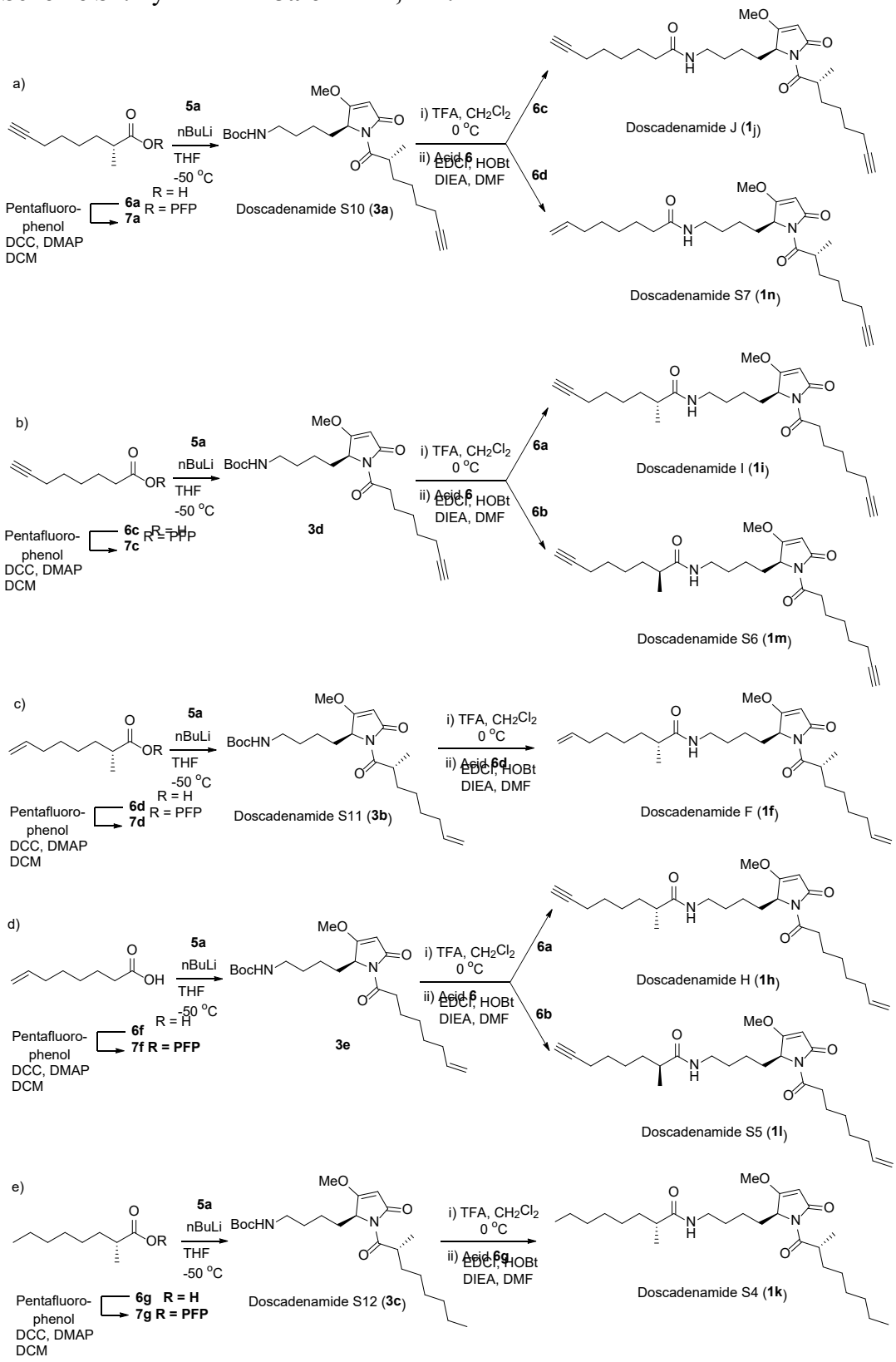
General procedure for the synthesis of PFP ester 7 (Scheme S4). To the solution of an acid **6** (0.1 mmol) in anhydrous CH_2Cl_2 (3.0 mL) at 0 °C was added pentafluorophenol (40.1 mg, 0.22 mmol) in anhydrous CH_2Cl_2 (0.5 mL), DMAP (2.4 mg, 0.02 mmol) and DCC (49.5 mg, 0.24 mmol). The resulting reaction mixture was stirred at room temperature overnight and concentrated under reduced pressure. The residue was stirred in cooled EtOAc (3.0 mL), and the suspending solid was filtered off. The filtrate was evaporated *in vacuo* and purified with silica gel column chromatography (eluted by 7% EtOAc in hexane) to yield the corresponding PFP ester **7** as white solid.

General procedure for the synthesis of 3a-e (Scheme S4). To a solution of **5a** (6.2 mg, 0.02 mmol) in anhydrous THF (1.0 mL) at –55 °C was added nBuLi (1.6 M in n-hexane) (0.021 mL, 0.033 mmol), the solution was stirred the same temperature for 30 min. Subsequently, the activated carboxylic corresponding acid **7** (0.03 mmol) in anhydrous THF (0.5 mL) was added dropwise at –55 °C. The resulting reaction mixture was stirred at the same temperature for 3 h and then room temperature overnight. The reaction was quenched on the next day with saturate NH_4Cl (aq, 3.0 mL) and then extracted with EtOAc (5 mL × 3). The combined organic phase was washed with saturate $NaHCO_3$ (aq, 5 mL × 2) and brine (5 mL), dried over anhydrous $MgSO_4$, and purified by preparative TLC plate of silica gel to yield corresponding product **3** as white solid.

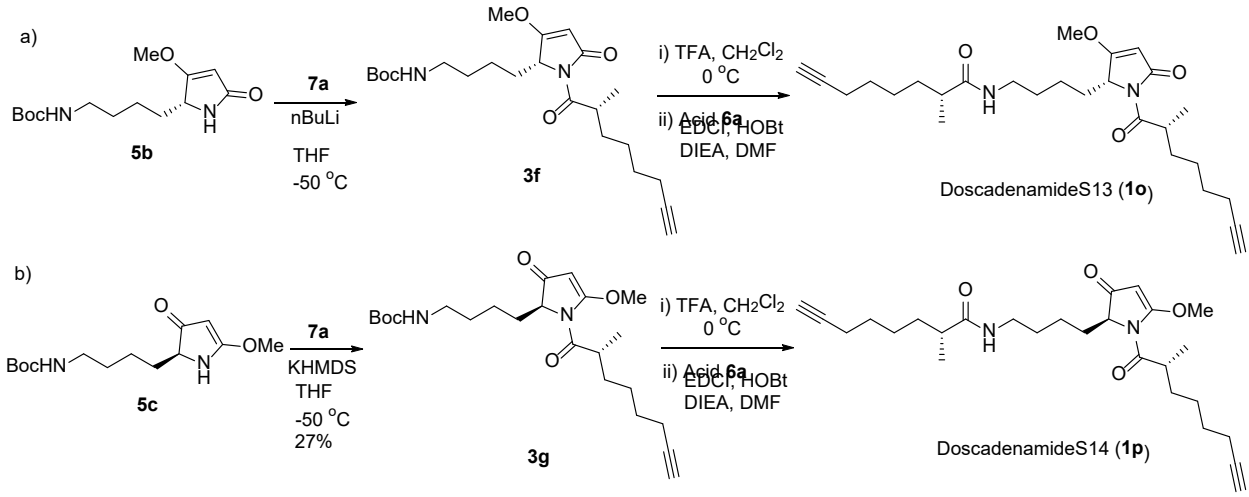
For the synthesis of **3f** (**Scheme S5 a**)), use **5b** instead of **5a** to couple with PFP ester **7a** following the above general procedure. For the synthesis of **3g** (**Scheme S5 b**), nBuLi was replaced by KHMDS (0.7 M in toluene) and use **5c** instead of **5a** to couple with PFP ester **7a** following the above general procedure.

General procedure for the synthesis of 1a-g (Scheme S4 and S5). To the solution of corresponding **3** (0.010 mmol) in CH_2Cl_2 (1.5 mL) was added TFA (0.75 mL) at 0 °C and the mixture was stirred the same temperature for 30 min. The reaction was diluted with toluene (1 mL) and evaporated *in vacuo* (3 times) to produce an intermediate crude, which was used in next step without purification. To the intermediate crude in anhydrous DMF (1.0 mL) was added corresponding acid **6** (0.011 mmol), EDCI·HCl (3.4 mg, 0.017 mmol), HOBt·H_2O (2.8 mg, 0.018 mmol) and DIEA (6.0 µL). The reaction mixture was stirred at room temperature for 20 h and then was evaporated *in vacuo* and purified by preparative TLC plate to yield corresponding product doscadenamide **1** as white solid.

Scheme S4. Synthesis of **3a-e** and **1f, h-n.**



Scheme S5. Synthesis of **1o** and **1p**.



PFP ester 7a was reported previously.[3]

PFP ester 7c (91.5%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.68 (t, J = 7.2 Hz, 2H), 2.23 (td, J = 6.6, 2.4 Hz, 2H), 1.96 (t, J = 3.0 Hz, 1H), 1.80 (p, J = 7.8 Hz, 2H), 1.62-1.52 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.5, 142.1 (m), 140.5 (m), 138.8 (m), 137.2 (m), 125.3 (m), 84.2, 68.7, 33.3, 28.1, 28.0, 24.4, 18.4 ppm; HRMS (ESI) *m/z* calcd for $C_{14}H_{12}F_5O_2$ $[M+H]^+$ 307.0757, found 307.0760.

PFP ester 7d (85%). $[\alpha]^{20}_D$ −96.0 (*c* 0.03, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.81 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.03-4.94 (m, 2H), 2.81 (ddq, J = 7.0 Hz, 1H), 2.10-2.06 (m, 2H), 1.86-1.80 (m, 1H), 1.63-1.56 (m, 1H), 1.48-1.40 (m, 4H), 1.33 (d, J = 7.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.8, 142.2 (m), 140.4(m), 138.7 (m), 138.7, 137.2 (m), 125.4 (m), 114.7, 39.4, 33.7, 33.6, 28.8, 26.6, 17.1 ppm; HRMS (ESI) *m/z* calcd for $C_{15}H_{16}F_5O_2$ $[M+H]^+$ 323.1070, found 323.1068.

PFP ester 7f (84%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.81 (ddt, J = 17.4, 10.8, 6.6 Hz, 1H), 5.03-4.95 (m, 2H), 2.67 (t, J = 7.2 Hz, 2H), 2.10-2.06 (m, 2H), 1.81-1.76 (m, 2H), 1.48-1.42 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.7, 142.1 (m), 140.5 (m), 138.9 (m), 138.7, 137.2 (m), 125.3 (m), 114.8, 33.6, 33.4, 28.5, 28.4, 24.8 ppm; HRMS (ESI) *m/z* calcd for $C_{14}H_{14}F_5O_2$ $[M+H]^+$ 309.0914, found 309.0918.

PFP ester 7g (90%). $[\alpha]^{20}_D$ −25.0 (*c* 0.15, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.80 (ddq, J = 7.0 Hz, 1H), 1.81 (dq, J = 13.6, 7.7, 1H), 1.62-1.57 (m, 1H), 1.42-1.36 (m, 2H), 1.36-1.28 (m, 9H), 0.89 (t, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.9, 142.2 (m), 140.5 (m), 138.8 (m), 138.8, 137.2 (m), 125.5 (m), 114.7, 39.5, 33.7, 31.8, 29.2, 27.1, 22.7, 17.1, 14.2 ppm; HRMS (ESI) *m/z* calcd for $C_{15}H_{18}F_5O_2$ $[M+H]^+$ 325.1227, found 325.1222.

Doscadenamide S10 (3a) was reported previously.[3]

Doscadenamide S11 (3b) (67%). $[\alpha]^{20}_D$ +24.0 (*c* 0.04, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.78 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.04 (s, 1H), 5.00-4.90 (m, 2H), 4.65 (dd, J = 5.7, 3.0 Hz,

1H), 4.48 (br s, 1H), 3.84 (s, 3H), 3.10-3.01 (m, 2H), 2.08 (ddt, *J* = 18.3, 9.9, 4.7 Hz, 1H), 2.03 (dt, *J* = 7.1, 7.1 Hz, 2H), 1.83 (dddd, *J* = 14.2, 11.3, 5.4, 3.1 Hz, 1H), 1.74-1.72 (m, 1H), 1.67-1.63 (m, 1H), 1.45-1.37 (m, 14H), 1.36-1.29 (m, 2H), 1.20-1.14 (m, 1H), 1.13-1.08 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.1, 177.1, 170.0, 156.0, 139.0, 114.5, 94.3, 79.3, 59.2, 58.8, 40.5, 39.2, 34.1, 33.8, 29.9, 29.0, 28.8, 28.6, 26.7, 20.0, 16.3 ppm; HRMS (ESI) *m/z* calcd for $C_{23}H_{38}N_2O_5Na$ $[M+Na]^+$ 445.2678, found 445.2670.

Doscadenamide S12 (3c) (56%). $[\alpha]^{20}_D$ +48.0 (*c* 0.033, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.04 (s, 1H), 5.00-4.90 (m, 2H), 4.66 (dd, *J* = 5.6, 3.0 Hz, 1H), 4.48 (br s, 1H), 3.84 (s, 3H), 3.76 (ddq, *J* = 6.7, 6.7, 6.7 Hz, 2H), 3.10-3.01 (m, 2H), 2.08 (ddt, *J* = 13.9, 10.9, 5.3 Hz, 1H), 1.83 (dddd, *J* = 14.1, 11.3, 5.5, 3.1 Hz, 1H), 1.75-1.70 (m, 1H), 1.48-1.37 (m, 13H), 1.30-1.25 (m, 7H), 1.19-1.15 (m, 1H), 1.14-1.06 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.0, 177.2, 170.0, 156.0, 94.3, 79.3, 59.2, 58.8, 40.5, 39.2, 34.4, 32.0, 29.5, 28.8, 28.6, 27.2, 22.8, 20.0, 16.3, 14.2 ppm. HRMS (ESI) *m/z* calcd for $C_{23}H_{40}N_2O_5Na$ $[M+Na]^+$ 447.2835, found 447.2825.

Compound 3d (71%). $[\alpha]^{20}_D$ +60.0 (*c* 0.1, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.05 (s, 1H), 4.64 (dd, *J* = 5.4, 3.0 Hz, 1H), 4.49 (br s, 1H), 3.85 (s, 3H), 3.08-3.03 (m, 2H), 2.99-2.88 (m, 2H), 2.20 (td, *J* = 6.6, 2.4 Hz, 2H), 2.12 (ddt, *J* = 13.8, 11.4, 5.4 Hz, 1.93 (t, *J* = 3.0 Hz, 1H), 1.84 (dddd, *J* = 13.8, 11.4, 5.4, 3.0 Hz, 1H), 1.67 (p, *J* = 7.2 Hz, 2H), 1.59-1.55 (m, 2H), 1.50-1.45 (m, 4H), 1.43 (s, 9H), 1.25-1.14 (m, 1H), 1.13-1.05 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.1, 173.0, 170.3, 156.1, 94.2, 84.7, 79.3, 68.4, 59.2, 58.8, 40.5, 37.1, 30.0, 28.8, 28.6, 28.5, 28.4, 24.1, 20.0, 18.4 ppm; HRMS (ESI) *m/z* calcd for $C_{22}H_{35}N_2O_5$ $[M+H]^+$ 407.2546, found 407.2549.

Compound 3e (62%). $[\alpha]^{20}_D$ +65.0 (*c* 0.1, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.80 (ddt, *J* = 17.4, 10.8, 6.6 Hz, 1H), 5.05 (s, 1H), 5.01-4.91 (m, 2H), 4.64 (dd, *J* = 5.4, 3.0 Hz, 1H), 4.48 (br s, 1H), 3.85 (s, 3H), 3.09-3.02 (m, 2H), 2.98-2.87 (m, 2H), 2.12 (ddt, *J* = 13.8, 11.4, 5.4 Hz, 1H), 2.08-2.03 (m, 2H), 1.84 (dddd, *J* = 13.8, 11.4, 5.4, 3.0 Hz, 1H), 1.66 (p, *J* = 7.8 Hz, 2H), 1.46-1.36 (m, 15H), 1.20-1.14 (m, 1H), 1.12-1.05 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.1, 173.2, 170.3, 156.1, 130.1, 114.5, 94.2, 79.3, 59.2, 58.8, 37.2, 33.8, 29.9, 28.9, 28.9, 28.8, 28.6, 24.5, 20.0 ppm; HRMS (ESI) *m/z* calcd for $C_{22}H_{37}N_2O_5$ $[M+H]^+$ 409.2697, found 409.2692.

Compound 3f (63%). $[\alpha]^{20}_D$ −13.3 (*c* 0.06, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.06 (s, 1H), 4.65 (dd, *J* = 5.4, 3.0 Hz, 1H), 4.48 (br s, 1H), 3.85 (s, 3H), 3.77 (sextet, *J* = 6.6 Hz, 1H), 3.07-3.04 (m, 2H), 2.17 (td, *J* = 7.2, 2.4 Hz, 2H), 2.12 (ddt, *J* = 13.8, 11.4, 5.4 Hz, 1H), 1.92 (t, *J* = 3.0 Hz, 1H), 1.82 (dddd, *J* = 13.8, 11.4, 5.4, 3.0 Hz, 1H), 1.78-1.73 (m, 1H), 1.56-1.49 (m, 2H), 1.48-1.36 (m, 14H), 1.19 (d, *J* = 6.6 Hz, 3H), 1.17-1.14 (m, 1H), 1.12-1.07 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.1, 177.0, 170.0, 156.0, 94.3, 84.7, 79.3, 68.5, 68.3, 59.2, 58.8, 39.3, 32.4, 29.9, 28.7, 28.6, 26.6, 19.8, 18.5, 18.2 ppm; HRMS (ESI) *m/z* calcd for $C_{23}H_{37}N_2O_5$ $[M+H]^+$ 421.2702, found 421.2693.

Compound 3g (27%). $[\alpha]^{20}_D$ −43.5 (*c* 0.1, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.90 (s, 1H), 4.52 (br s, 1H), 4.40 (dd, *J* = 6.0, 3.0 Hz, 1H), 4.04 (s, 3H), 3.20 (h, *J* = 6.6 Hz, 1H), 3.07 (br s, 2H), 2.21 (td, *J* = 7.2, 2.4 Hz, 2H), 2.06-2.00 (m, 1H), 1.99-1.92 (m, 2H), 1.66-1.62 (m, 1H), 1.55-1.50 (m, 3H), 1.48-1.39 (m, 14H), 1.31-1.25 (m, 3H), 1.14 (d, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.1, 177.0, 170.0, 156.1, 94.3, 84.6, 79.3, 68.5, 59.2, 58.8, 40.5, 39.1, 33.7, 30.0, 28.8, 28.6, 28.5, 26.4, 20.0, 18.5, 18.3 ppm; HRMS (ESI) *m/z* calcd for $C_{23}H_{37}N_2O_5$ $[M+H]^+$ 421.2702, found 421.2689.

Doscadenamide F (1f) (80%). $[\alpha]^{20}_{D}$ +23.0 (*c* 0.21, MeOH) (natural product doscadenamide $[\alpha]^{20}_{D}$ +114); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.78 (m, 2H), 5.43 (br t, *J* = 5.8 Hz, 1H), 5.04 (s, 1H), 5.00-4.91 (m, 4H), 4.64 (dd, *J* = 5.8, 3.0 Hz, 1H), 3.84 (s, 3H), 3.76 (ddq, *J* = 6.8, 6.8, 6.8, 1H), 3.26-3.20 (m, 1H), 3.17-3.11 (m, 1H), 2.1 (ddq, *J* = 7.2 Hz, 1H), 2.08-2.00 (m, 5H), 1.84 (dddd, *J* = 14.2, 11.2, 5.5, 3.1 Hz, 1H), 1.77-1.71 (m, 1H), 1.64-1.59 (m, 1H), 1.51-1.43 (m, 2H), 1.43-1.30 (m, 8H), 1.29-1.24 (m, 2H), 1.23-1.13 (m, 2H), 1.11 (d, *J* = 6.6 Hz, 3H), 1.11 (d, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.2, 177.2, 176.6, 170.0, 139.0, 139.0, 114.5, 114.5, 94.2, 59.2, 58.8, 41.8, 39.3, 39.2, 34.3, 34.1, 33.8, 33.7, 29.6, 29.0, 29.0, 27.1, 26.8, 20.4, 18.1, 16.3 ppm; HRMS (ESI) *m/z* calcd for $C_{26}H_{43}N_2O_4$ $[M+H]^+$ 447.3379, found 447.3369.

Doscadenamide H (1h) (69%). $[\alpha]^{20}_{D}$ +54.3 (*c* 0.07, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.80 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H), 5.44 (br t, *J* = 6.0 Hz, 1H), 5.05 (s, 1H), 5.01-4.91 (m, 2H), 4.63 (dd, *J* = 5.4, 3.0 Hz, 1H), 3.85 (s, 3H), 3.26-3.20 (m, 1H), 3.19-3.13 (m, 1H), 2.96-2.87 (m, 2H), 2.19-2.16 (m, 2H), 2.15-2.08 (m, 2H), 2.07-2.03 (m, 2H), 1.93 (t, *J* = 2.4 Hz, 1H), 1.85 (dddd, *J* = 13.8, 11.4, 5.4, 3.0 Hz, 1H), 1.68-1.63 (m, 3H), 1.54-1.45 (m, 4H), 1.44-1.34 (m, 7H), 1.23-1.17 (m, 1H), 1.15-1.09 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.2, 176.4, 173.2, 170.3, 139.1, 114.5, 94.2, 84.6, 68.5, 59.1, 58.9, 41.8, 39.3, 37.2, 33.9, 33.8, 29.5, 28.9, 28.9, 28.8, 28.5, 26.7, 24.5, 20.3, 18.4, 18.1 ppm; HRMS (ESI) *m/z* calcd for $C_{26}H_{41}N_2O_4$ $[M+H]^+$ 445.3066, found 445.3059.

Doscadenamide I (1i) (79%). $[\alpha]^{20}_{D}$ +59.3 (*c* 0.07, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.44 (br t, *J* = 6.0 Hz, 1H), 5.05 (s, 1H), 4.63 (dd, *J* = 6.0, 3.0 Hz, 1H), 3.85 (s, 3H), 3.26-3.20 (m, 1H), 3.19-3.13 (m, 1H), 2.99-2.89 (m, 2H), 2.20-2.16 (m, 4H), 2.15-2.08 (m, 2H), 1.93 (t, *J* = 3.0 Hz, 2H), 1.85 (dddd, *J* = 13.8, 11.4, 5.4, 3.0 Hz, 1H), 1.70-1.62 (m, 3H), 1.59-1.54 (m, 2H), 1.53-1.45 (m, 6H), 1.41-1.34 (m, 3H), 1.23-1.17 (m, 1H), 1.15-1.08 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.2, 176.4, 173.1, 170.3, 94.2, 84.7, 84.6, 68.5, 68.4, 59.1, 58.9, 41.8, 39.3, 37.1, 33.9, 29.9, 29.6, 28.9, 28.5, 28.5, 28.4, 26.8, 26.7, 24.1, 20.3, 18.5, 18.4, 18.1 ppm; HRMS (ESI) *m/z* calcd for $C_{26}H_{39}N_2O_4$ $[M+H]^+$ 443.2910, found 443.2902.

Doscadenamide J (1j) (100%). $[\alpha]^{20}_{D}$ +52.9 (*c* 0.07, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.48 (br t, *J* = 6.0 Hz, 1H), 5.04 (s, 1H), 4.65 (dd, *J* = 6.0, 3.0 Hz, 1H), 3.85 (s, 3H), 3.78 (h, *J* = 6.6 Hz, 1H), 3.26-3.21 (m, 1H), 3.18-3.12 (m, 1H), 2.20-2.17 (m, 4H), 2.15 (t, *J* = 7.2 Hz, 2H), 2.07 (ddt, *J* = 13.8, 11.4, 5.4 Hz, 1H), 1.93 (t, *J* = 3.0 Hz, 1H), 1.84 (dddd, *J* = 13.8, 11.4, 5.4, 3.0 Hz, 1H), 1.78-1.73 (m, 1H), 1.65-1.62 (m, 1H), 1.56-1.51 (m, 4H), 1.50-1.47 (m, 2H), 1.46-1.40 (m, 6H), 1.23-1.14 (m, 2H), 1.12 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.2, 177.0, 172.9, 170.0, 94.2, 84.7, 84.6, 68.5, 68.5, 59.2, 58.9, 39.5, 39.1, 36.8, 33.7, 29.5, 29.0, 28.5, 28.5, 28.3, 26.4, 25.4, 20.4, 18.5, 18.4, 16.3 ppm; HRMS (ESI) *m/z* calcd for $C_{26}H_{39}N_2O_4$ $[M+H]^+$ 443.2910, found 443.2903.

Doscadenamide S4 (1k) (83%). $[\alpha]^{20}_{D}$ +44.0 (*c* 0.12, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.78 (m, 2H), 5.43 (br t, *J* = 5.8 Hz, 1H), 5.04 (s, 1H), 5.00-4.91 (m, 4H), 4.64 (dd, *J* = 5.8, 3.0 Hz, 1H), 3.84 (s, 3H), 3.76 (ddq, *J* = 6.8, 6.8, 6.8, 1H), 3.26-3.20 (m, 1H), 3.17-3.11 (m, 1H), 2.1 (ddq, *J* = 7.2 Hz, 1H), 2.08-2.00 (m, 5H), 1.84 (dddd, *J* = 14.2, 11.2, 5.5, 3.1 Hz, 1H), 1.77-1.71 (m, 1H), 1.64-1.59 (m, 1H), 1.51-1.43 (m, 2H), 1.43-1.30 (m, 8H), 1.29-1.24 (m, 2H), 1.23-1.13 (m, 2H), 1.11 (d, *J* = 6.6 Hz, 3H), 1.11 (d, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.2, 177.2, 176.6, 170.0, 139.0, 139.0, 114.5, 114.5, 94.2, 59.2, 58.8, 41.8, 39.3, 39.2, 34.3, 34.1,

33.8, 33.7, 29.6, 29.0, 29.0, 27.1, 26.8, 20.4, 18.1, 16.3 ppm; HRMS (ESI) *m/z* calcd for $C_{27}H_{49}N_2O_4$ $[M+H]^+$ 465.3692, found 465.3685.

Doscadenamide S5 (1l) (77.5%). $[\alpha]^{20}_D$ +102.1 (*c* 0.07, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.80 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H), 5.45 (br t, *J* = 5.4 Hz, 1H), 5.05 (s, 1H), 5.01-4.91 (m, 2H), 4.63 (dd, *J* = 5.4, 3.0 Hz, 1H), 3.85 (s, 3H), 3.25-3.15 (m, 2H), 2.96-2.87 (m, 2H), 2.19-2.16 (m, 2H), 2.14-2.08 (m, 2H), 2.07-2.03 (m, 2H), 1.93 (t, *J* = 2.4 Hz, 1H), 1.85 (dddd, *J* = 13.8, 11.4, 5.4, 3.0 Hz, 1H), 1.68-1.63 (m, 3H), 1.54-1.45 (m, 4H), 1.44-1.34 (m, 7H), 1.23-1.16 (m, 1H), 1.16-1.08 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.1, 176.4, 173.2, 170.2, 139.1, 114.5, 94.2, 84.6, 68.5, 59.1, 58.9, 41.7, 39.2, 37.2, 33.9, 33.8, 29.5, 28.9, 28.9, 28.8, 28.5, 26.7, 24.5, 20.3, 18.4, 18.1 ppm; HRMS (ESI) *m/z* calcd for $C_{26}H_{41}N_2O_4$ $[M+H]^+$ 445.3066, found 445.3058.

Doscadenamide S6 (1m) (60%). $[\alpha]^{20}_D$ +82.9 (*c* 0.07, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.47 (br t, *J* = 7.2 Hz, 1H), 5.05 (s, 1H), 4.63 (dd, *J* = 5.4, 3.0 Hz, 1H), 3.85 (s, 3H), 3.25-3.15 (m, 2H), 2.99-2.89 (m, 2H), 2.21-2.16 (m, 4H), 2.14-2.08 (m, 2H), 1.94-1.93 (m, 2H), 1.85 (dddd, *J* = 13.8, 11.4, 5.4, 3.0 Hz, 1H), 1.69-1.63 (m, 3H), 1.59-1.56 (m, 2H), 1.56-1.42 (m, 6H), 1.41-1.35 (m, 3H), 1.22-1.14 (m, 1H), 1.13-1.09 (m, 4H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.2, 176.4, 173.1, 170.3, 94.1, 84.7, 84.6, 68.5, 68.4, 59.2, 58.9, 41.8, 39.3, 37.1, 33.9, 29.5, 28.9, 28.5, 28.5, 28.5, 28.4, 26.7, 24.1, 20.2, 18.4, 18.1 ppm; HRMS (ESI) *m/z* calcd for $C_{26}H_{39}N_2O_4$ $[M+H]^+$ 443.2910, found 443.2903.

Doscadenamide S7 (1n) (58.1%). $[\alpha]^{20}_D$ +42.9 (*c* 0.07, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.79 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H), 5.46 (br t, *J* = 5.4 Hz, 1H), 5.05 (s, 1H), 5.01-4.92 (m, 2H), 4.65 (dd, *J* = 6.6, 3.0 Hz, 1H), 3.85 (s, 3H), 3.80-3.75 (m, 1H), 3.26-3.20 (m, 1H), 3.18-3.12 (m, 1H), 2.18 (td, *J* = 7.2, 2.4 Hz, 2H), 2.14 (t, *J* = 7.2 Hz, 2H), 2.10-2.02 (m, 3H), 1.93 (t, *J* = 2.4 Hz, 1H), 1.85 (dddd, *J* = 13.8, 11.4, 5.4, 3.0 Hz, 1H), 1.78-1.73 (m, 1H), 1.65-1.60 (m, 5H), 1.57-1.49 (m, 3H), 1.49-1.37 (m, 7H), 1.35-1.29 (m, 2H), 1.23-1.14 (m, 2H), 1.12 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.2, 177.0, 173.1, 170.0, 138.9, 114.6, 94.2, 84.7, 68.5, 59.2, 58.9, 39.5, 39.1, 36.9, 33.7, 29.5, 29.0, 28.9, 28.7, 28.5, 26.4, 25.8, 20.4, 18.5, 16.3 ppm; HRMS (ESI) *m/z* calcd for $C_{26}H_{41}N_2O_4$ $[M+H]^+$ 445.3066, found 445.3059.

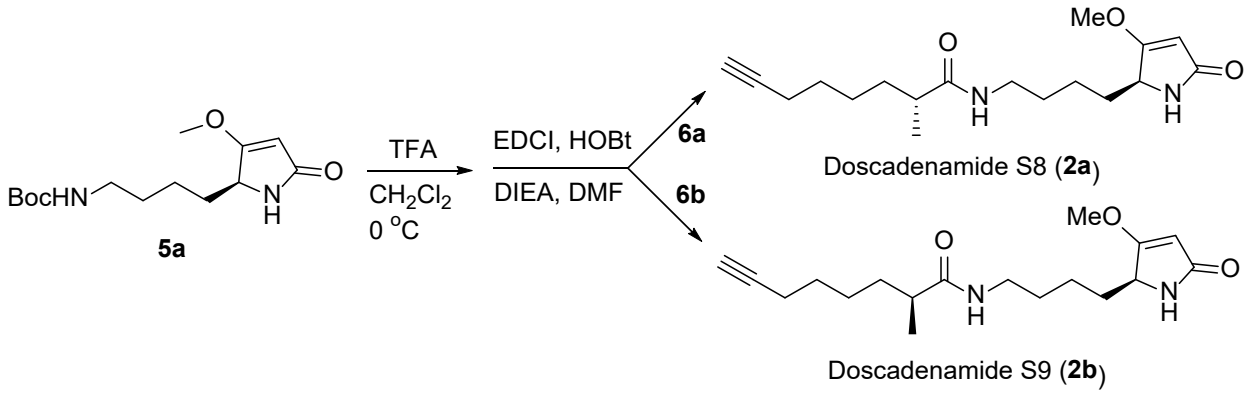
Doscadenamide S13 (1o) (66%**)**. $[\alpha]^{20}_D$ −40.0 (*c* 0.09, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.42 (br t, *J* = 6.0 Hz, 1H), 5.06 (s, 1H), 4.64 (dd, *J* = 5.4, 3.0 Hz, 1H), 3.85 (s, 3H), 3.77 (sextet, *J* = 6.6 Hz, 1H), 3.25-3.20 (m, 1H), 3.19-3.14 (m, 1H), 2.20-2.16 (m, 4H), 2.14-2.08 (m, 2H), 1.93 (t, *J* = 2.4 Hz, 1H), 1.92 (t, *J* = 2.4 Hz, 1H), 1.83 (dddd, *J* = 13.8, 11.4, 5.4, 3.0 Hz, 1H), 1.77-1.72 (m, 1H), 1.65-1.61 (m, 1H), 1.53-1.46 (m, 6H), 1.45-1.34 (m, 3H), 1.32-1.28 (m, 3H), 1.18 (d, *J* = 7.2 Hz, 3H), 1.16-1.13 (m, 2H), 1.12 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 179.2, 177.0, 176.4, 170.0, 94.2, 84.7, 84.6, 68.5, 68.3, 59.2, 58.9, 41.7, 39.3, 39.3, 33.9, 32.5, 32.1, 29.5, 29.2, 29.0, 28.7, 28.5, 26.8, 26.6, 20.2, 18.5, 18.4, 18.1, 18.1 ppm; HRMS (ESI) *m/z* calcd for $C_{27}H_{41}N_2O_4$ $[M+H]^+$ 457.3066, found 457.3056.

Doscadenamide S14 (1p) (38%). $[\alpha]^{20}_D$ +41.4 (*c* 0.07, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.59 (br t, 1H), 4.90 (s, 1H), 4.40 (dd, *J* = 6.0, 3.6 Hz, 1H), 4.04 (s, 3H), 3.27-3.15 (m, 3H), 2.22-2.13 (m, 5H), 2.04-1.93 (m, 4H), 1.79-1.72 (m, 1H), 1.67-1.60 (m, 1H), 1.56-1.47 (m, 6H), 1.46-1.40 (m, 3H), 1.39-1.35 (m, 3H), 1.33-1.28 (m, 2H), 1.14 (d, *J* = 6.6 Hz, 3H), 1.11 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 196.9, 176.5, 175.2, 174.0, 86.6, 84.7, 84.4, 68.7, 68.5,

65.7, 59.9, 41.7, 40.3, 39.1, 33.9, 29.4, 29.2, 28.6, 28.4, 26.8, 26.5, 20.5, 19.3, 18.5, 18.4, 18.1, 16.9 ppm; HRMS (ESI) *m/z* calcd for $C_{27}H_{41}N_2O_4$ $[M+H]^+$ 457.3066, found 457.3055.

Synthesis of 2a and 2b

Scheme S6. Synthesis of **2a and 2b**.



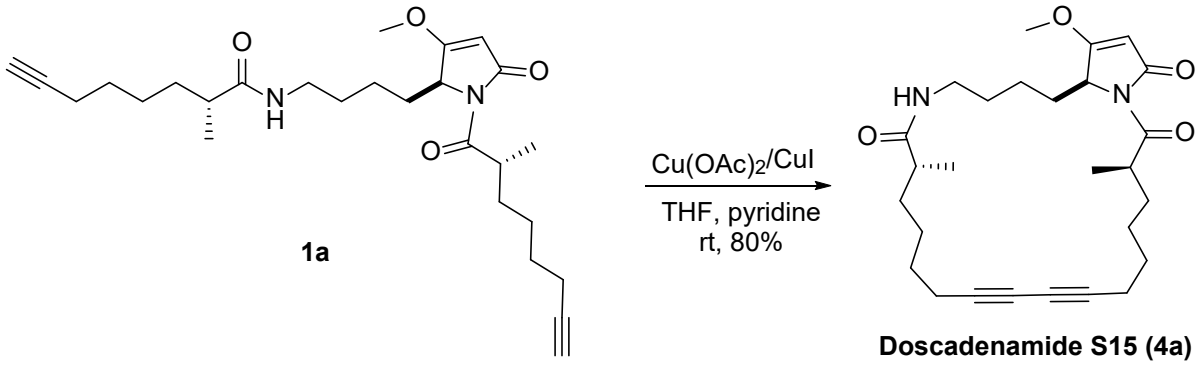
Synthesis 2a or 2b (Scheme S6). To the solution of compound **5a** (4.5 mg, 0.016 mmol) in CH_2Cl_2 (0.8 mL) was added TFA (0.4 mL) at 0 °C and the mixture was stirred the same temperature for 30 min. The reaction residue was diluted with toluene (1 mL) and evaporated *in vacuo* (3 times) to produce an intermediate crude that was used in next step without purification. To the solution of this intermediate crude in anhydrous DMF (1.0 mL) was added corresponding acid **6** (2.5 mg, 0.016 mmol), EDCI·HCl (4.6 mg, 0.024 mmol), HOBt·H_2O (3.9 mg, 0.025 mmol) and DIEA (8.4 μL). The reaction mixture was stirred at room temperature for 20 h and then was evaporated *in vacuo* and purified by preparative TLC plate to yield corresponding product **2** as white solid.

Doscadenamide S8 (2a) (33% 2 steps). $[\alpha]^{20}_D$ −5.0 (*c* 0.1, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.93 (br s, 1H), 5.47 (br t, *J* = 5.4 Hz, 1H), 5.00 (s, 1H), 4.05 (dd, *J* = 7.2, 3.6 Hz, 1H), 3.79 (s, 3H), 3.32-3.27 (m, 1H), 3.24-3.18 (m, 1H), 2.20-2.13 (m, 3H), 1.93 (t, *J* = 2.4 Hz, 1H), 1.86-1.80 (m, 1H), 1.67-1.64 (m, 1H), 1.58-1.49 (m, 5H), 1.44-1.36 (m, 4H), 1.36-1.28 (m, 1H), 1.14 (d, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 178.3, 176.7, 174.5, 93.7, 84.6, 68.5, 58.5, 57.4, 41.7, 39.0, 31.3, 29.6, 28.5, 26.8, 22.0, 18.5, 18.2 ppm; HRMS (ESI) *m/z* calcd for $C_{18}H_{29}N_2O_3$ $[M+H]^+$ 321.2178, found 321.2169.

Doscadenamide S9 (2b) (43% 2 steps). $[\alpha]^{20}_D$ +17.0 (*c* 0.1, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.19 (br s, 1H), 5.68 (br t, *J* = 5.4 Hz, 1H), 4.99 (s, 1H), 4.05 (dd, *J* = 7.8, 4.2 Hz, 1H), 3.79 (s, 3H), 3.32-3.27 (m, 1H), 3.23-3.18 (m, 1H), 2.20-2.13 (m, 3H), 1.93 (t, *J* = 3.0 Hz, 1H), 1.85-1.80 (m, 1H), 1.67-1.64 (m, 1H), 1.57-1.48 (m, 5H), 1.44-1.36 (m, 4H), 1.36-1.29 (m, 1H), 1.13 (d, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ 178.4, 176.7, 174.6, 93.7, 84.6, 68.5, 58.5, 57.4, 41.7, 39.0, 33.9, 31.3, 29.5, 28.5, 26.8, 22.1, 18.5, 18.1 ppm; HRMS (ESI) *m/z* calcd for $C_{18}H_{29}N_2O_3$ $[M+H]^+$ 321.2178, found 321.2169.

Synthesis of 4a

Scheme S7. Synthesis of **4a**.



To the solution of **1a** (1.0 mg, 0.0022 mmol) in anhydrous THF (0.5 mL) was added pyridine (0.25 mL), Cu(OAc)2 (23.8 mg, 0.131 mmol) and CuI (6.3 mg, 0.033 mmol) sequentially. The reaction was stirred at room temperature overnight and the purification with preparative TLC to provide product **4a** (0.8 mg, 80%).

Doscadenamide S15 (4a): $[\alpha]^{20}_{D}$ +14.0 (*c* 0.07, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm: 5.61 (br t, *J* = 5.90 Hz, 1H), 5.06 (s, 1H), 4.69 (dd, *J* = 5.8, 3.0 Hz, 1H), 3.90 (ddt, *J* = 6.8, 5.0, 3.3 Hz, 1H), 3.86 (s, 3H), 3.28-3.19 (m, 2H), 2.31-2.24 (m, 4H), 2.19 (dqd, *J* = 10.3, 6.7, 3.9, 1H), 2.10 (ddt, *J* = 14.1, 10.9, 5.2, 1H), 1.90 (dddd, *J* = 14.3, 11.5, 5.6, 3.2 Hz, 1H), 1.80 (dtd, *J* = 13.5, 9.3, 5.2 Hz, 1H), 1.67-1.65 (m, 1H), 1.52-1.42 (m, 9H), 1.32-1.28 (m, 3H), 1.19-1.15 (m, 2H), 1.12 (d, *J* = 6.8, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm: 179.2, 176.9, 176.2, 170.1, 94.2, 77.7, 77.7, 66.1, 65.4, 59.1, 58.9, 41.7, 41.2, 39.6, 38.8, 34.0, 29.7, 29.5, 28.2, 27.1, 26.3, 26.1, 20.6, 19.4, 19.2, 18.6, 17.2; HRMS (ESI) *m/z* calcd for $C_{27}H_{39}N_2O_4$ $[M+H]^+$ 455.2910, found 455.2899.

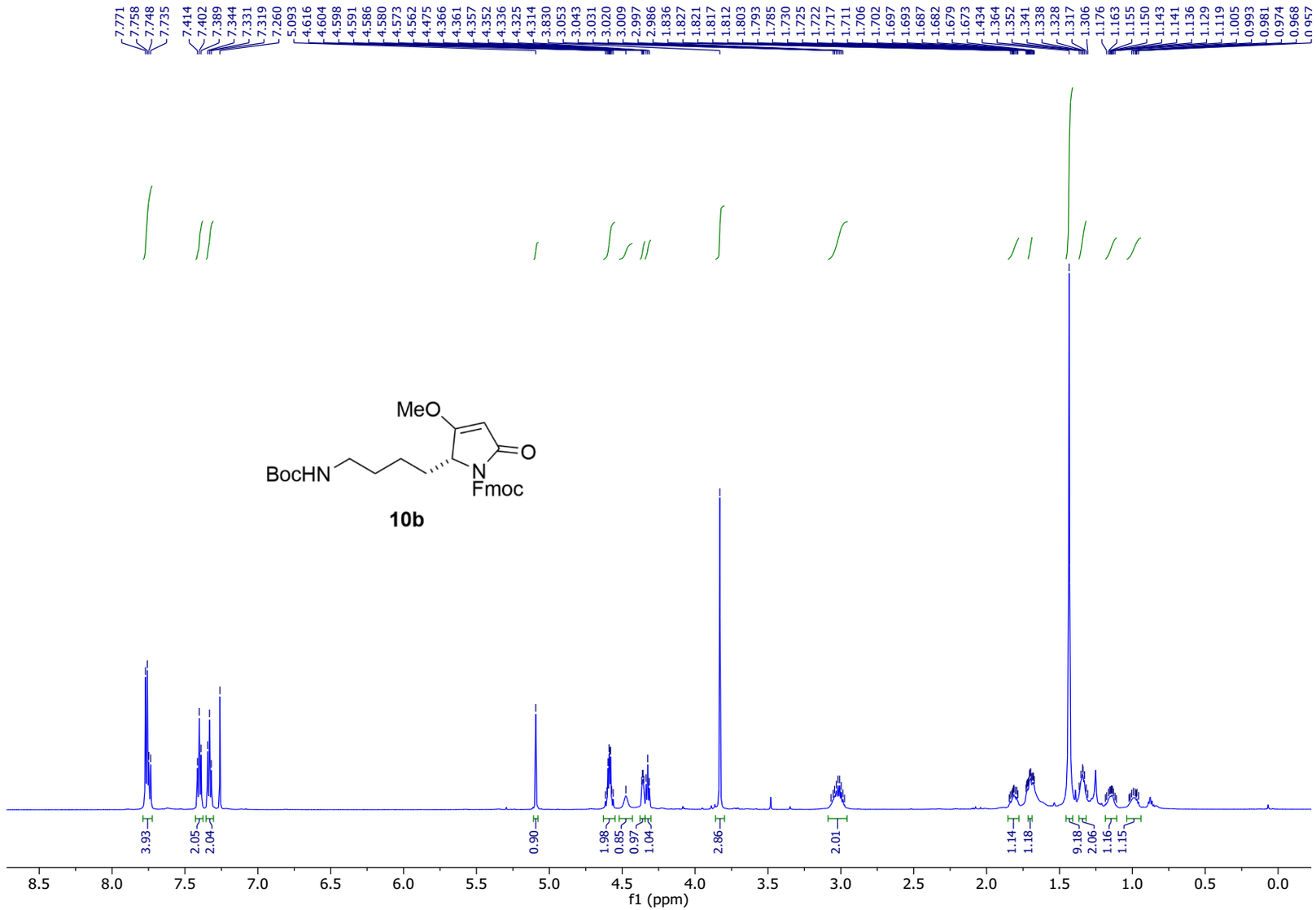


Figure S40. ^{1}H NMR spectrum of **10b** in $CDCl_3$ (600 MHz) at 27 °C.

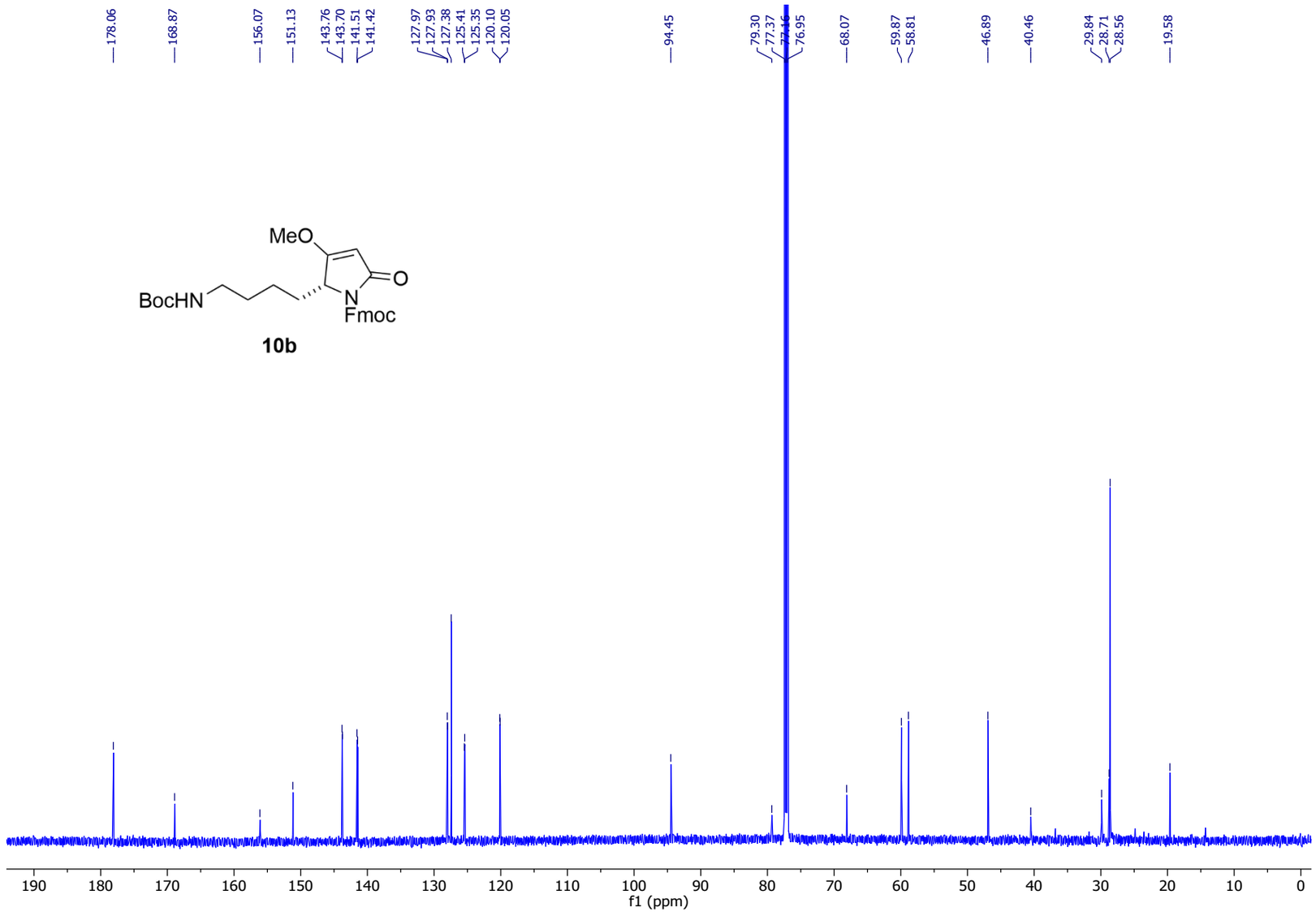


Figure S41. ^{13}C NMR spectrum of **10b** in $CDCl_3$ (150 MHz) at 27 °C.

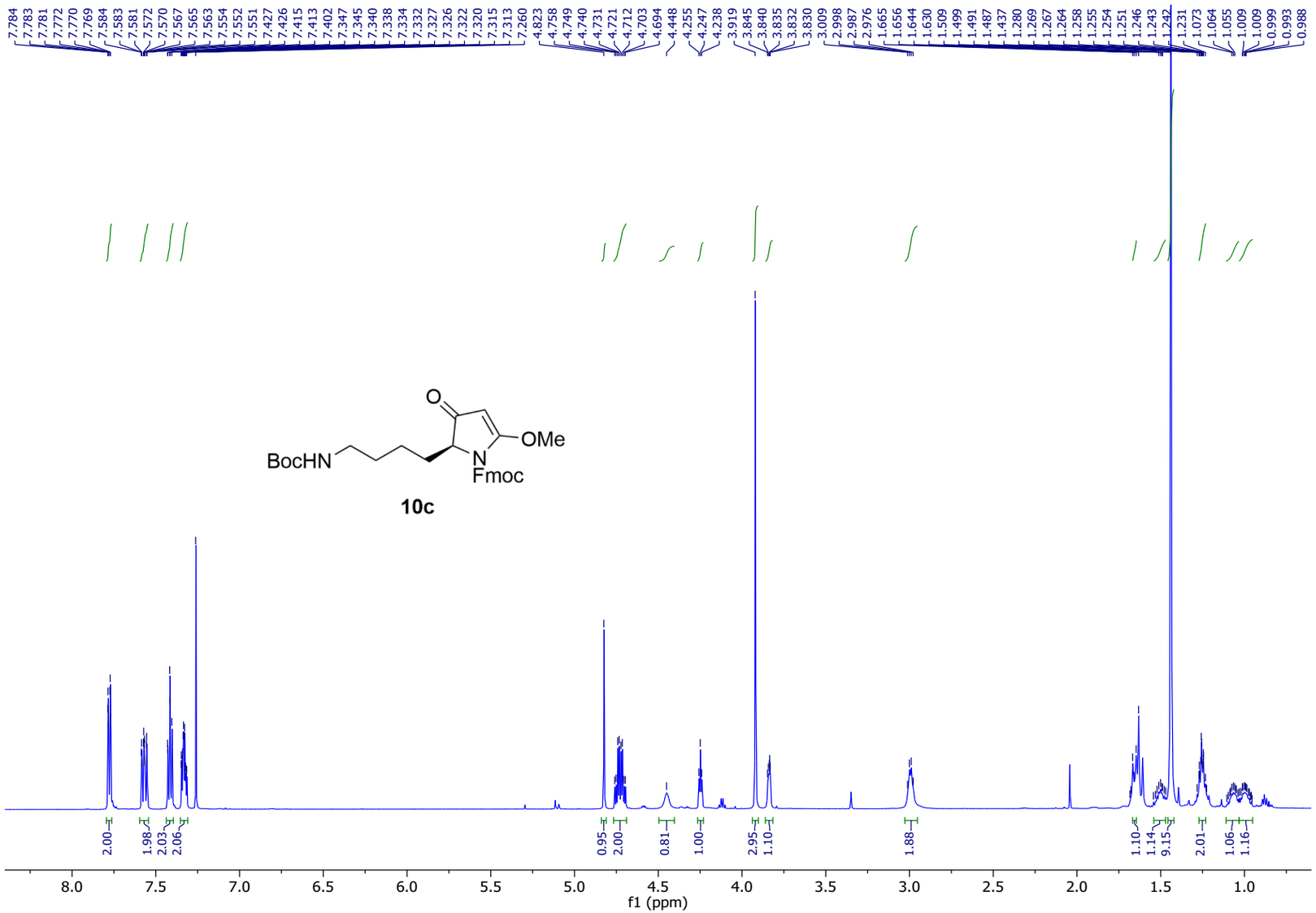


Figure S42. ^{1}H NMR spectrum of **10c** in $CDCl_3$ (600 MHz) at 27 °C.

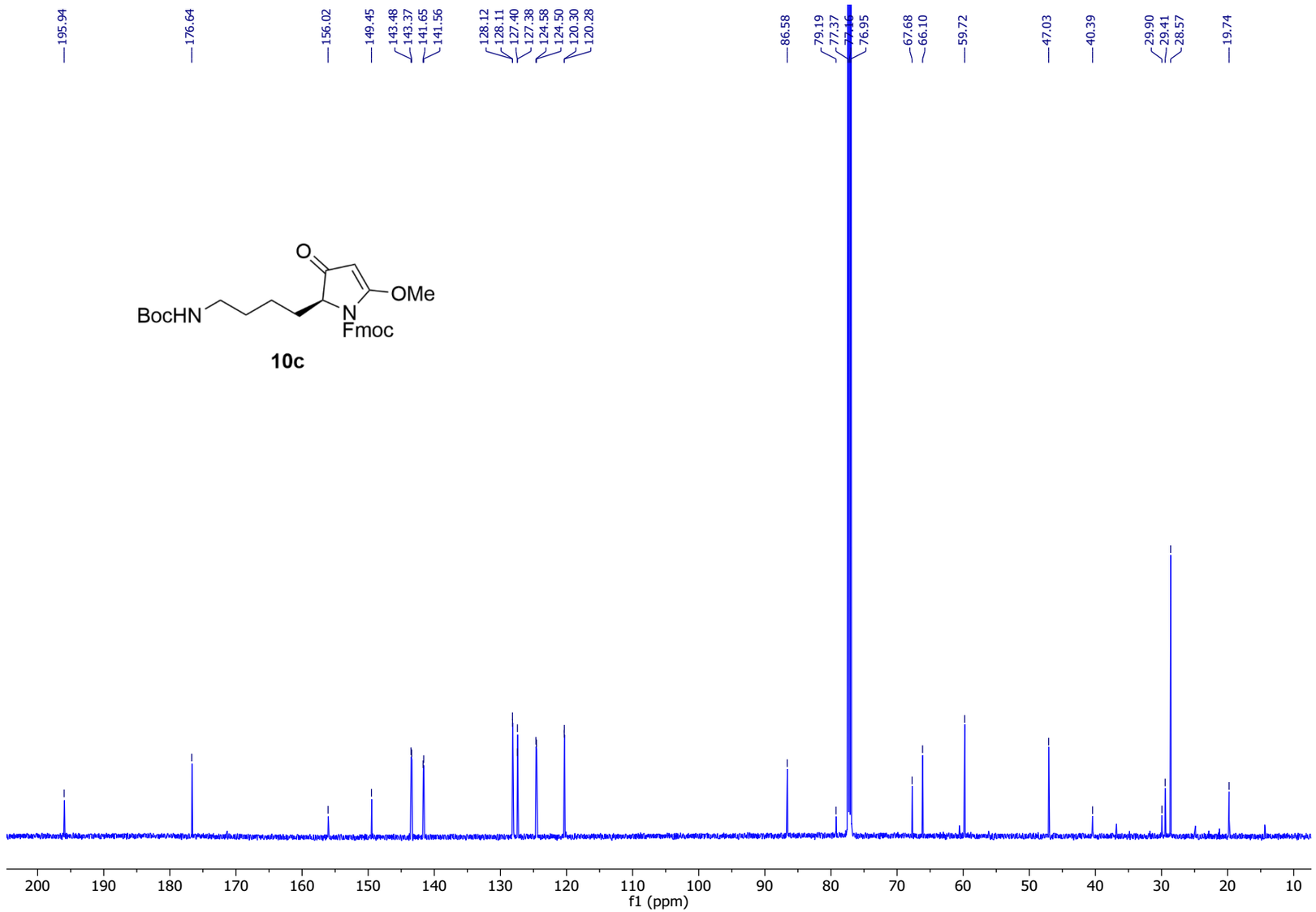


Figure S43. ^{13}C NMR spectrum of **10c** in $CDCl_3$ (150 MHz) at 27 °C.

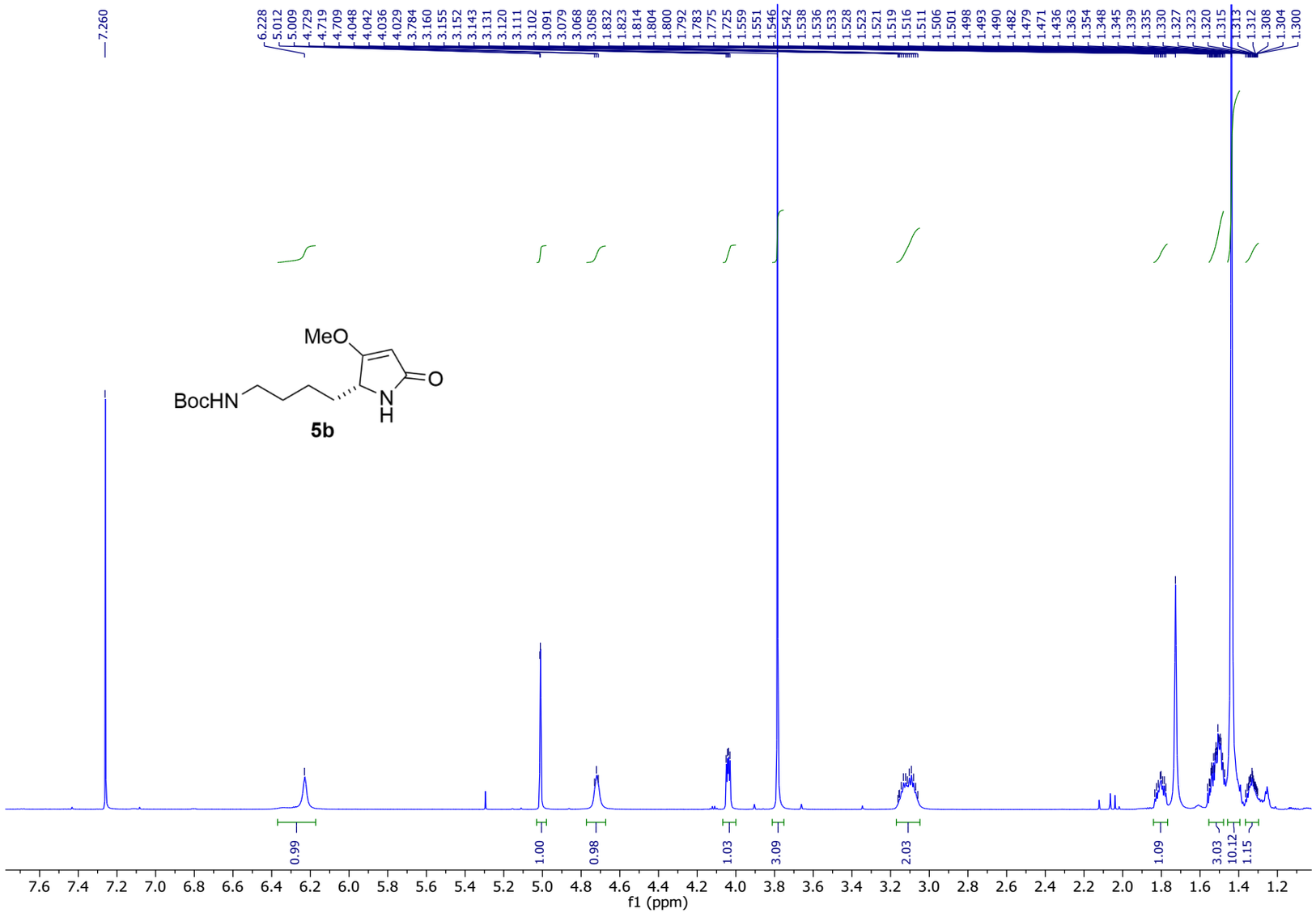


Figure S44. ^{1}H NMR spectrum of **5b** in $CDCl_3$ (600 MHz) at 27 °C.

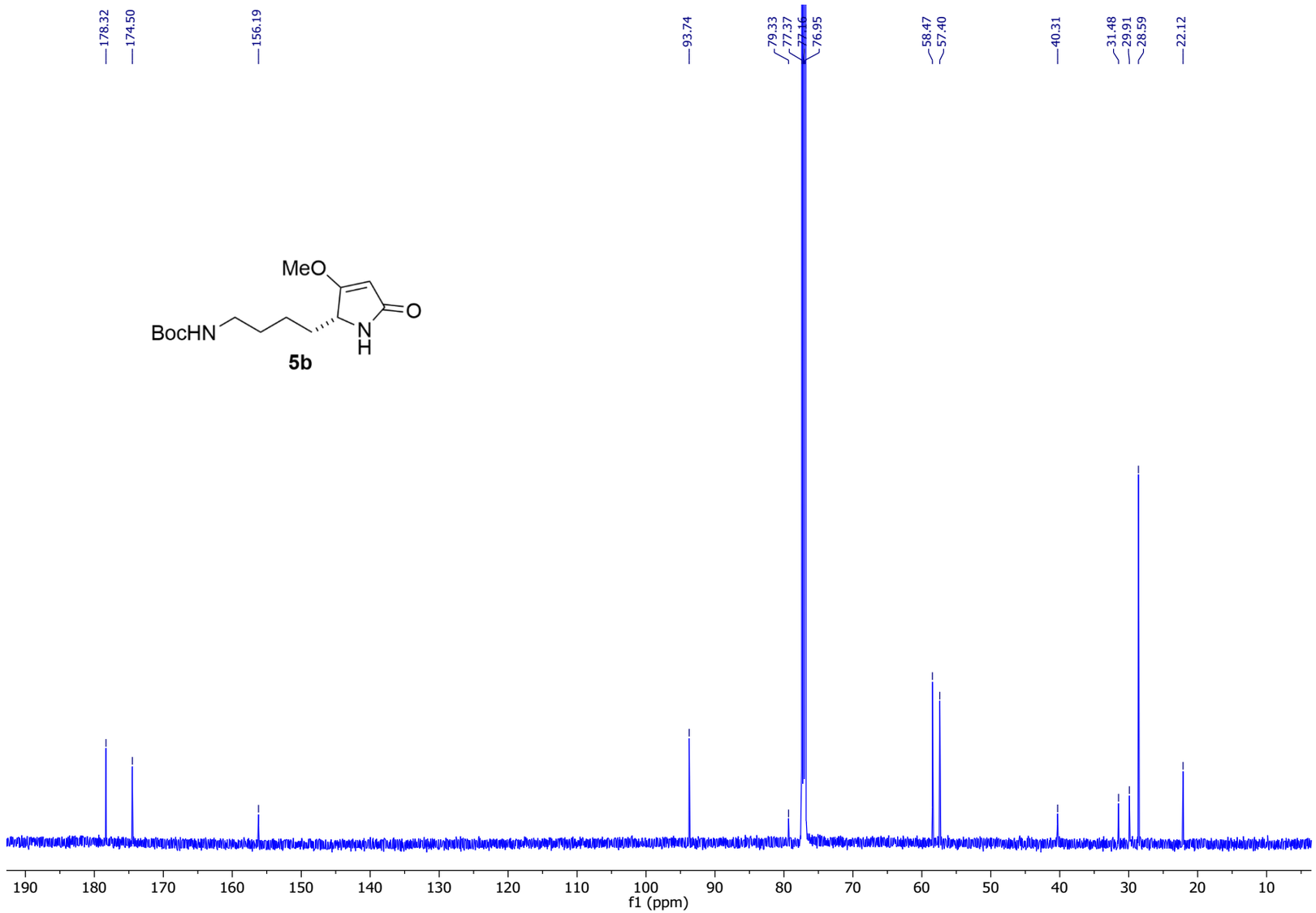


Figure S45. ^{13}C NMR spectrum of **5b** in $CDCl_3$ (150 MHz) at 27 °C.

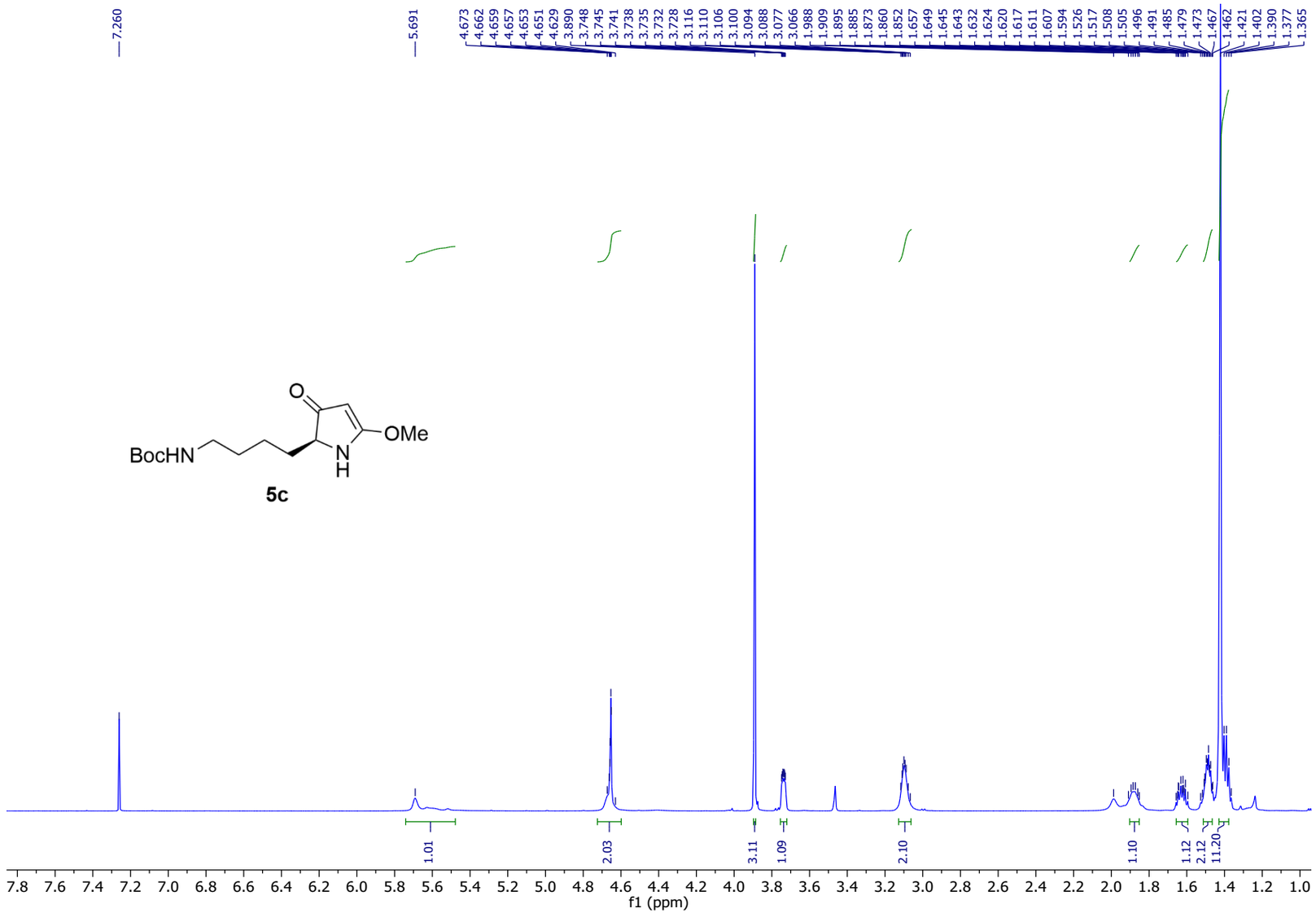


Figure S46. ^{1}H NMR spectrum of **5c** in $CDCl_3$ (600 MHz) at 27 °C.

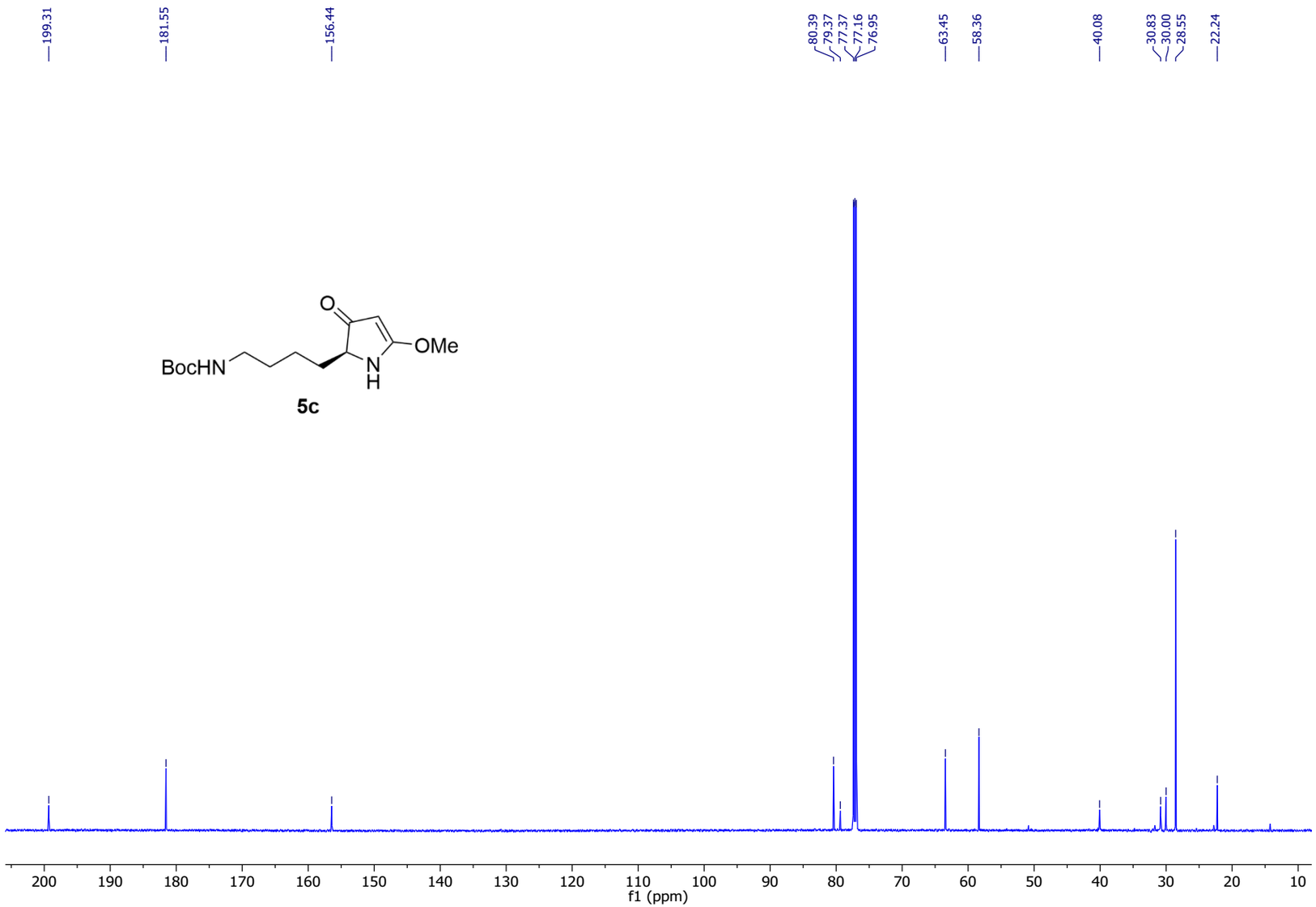


Figure S47. ^{13}C NMR spectrum of **5c** in $CDCl_3$ (150 MHz) at 27 °C.

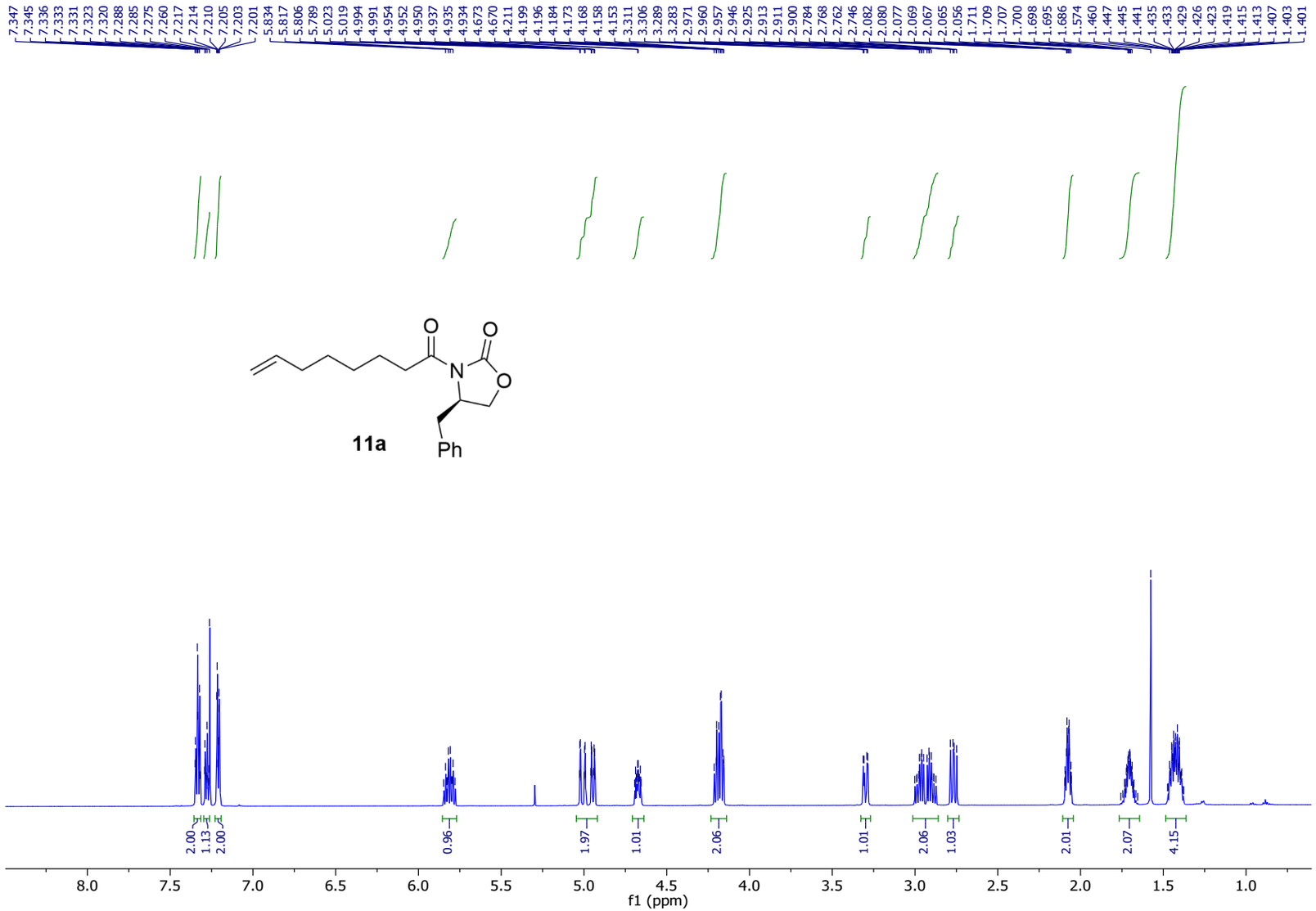


Figure S48. ^{1}H NMR spectrum of **11a** in $CDCl_3$ (600 MHz) at 27 °C.

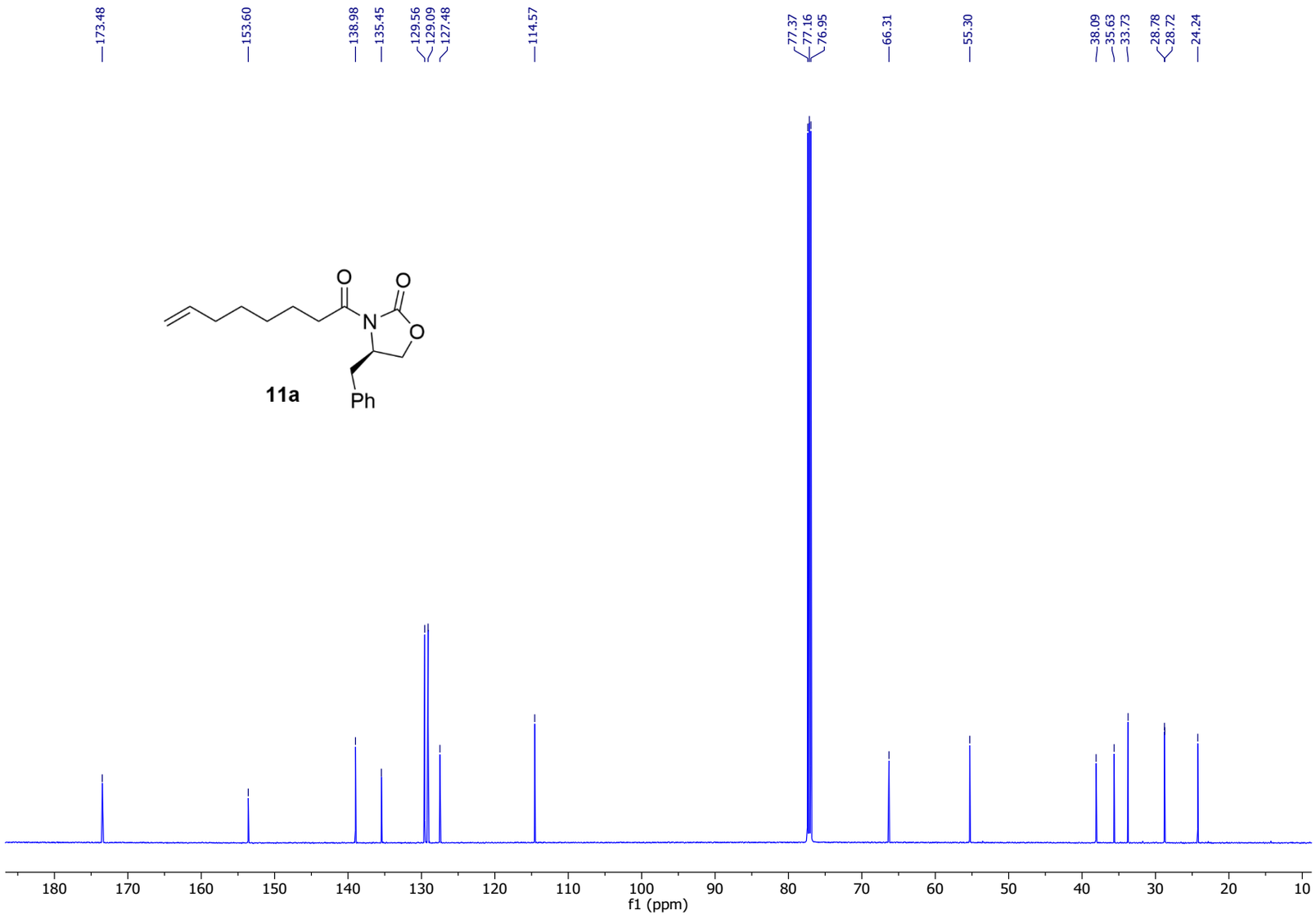


Figure S49. ^{13}C NMR spectrum of **11a** in $CDCl_3$ (150 MHz) at 27 °C.

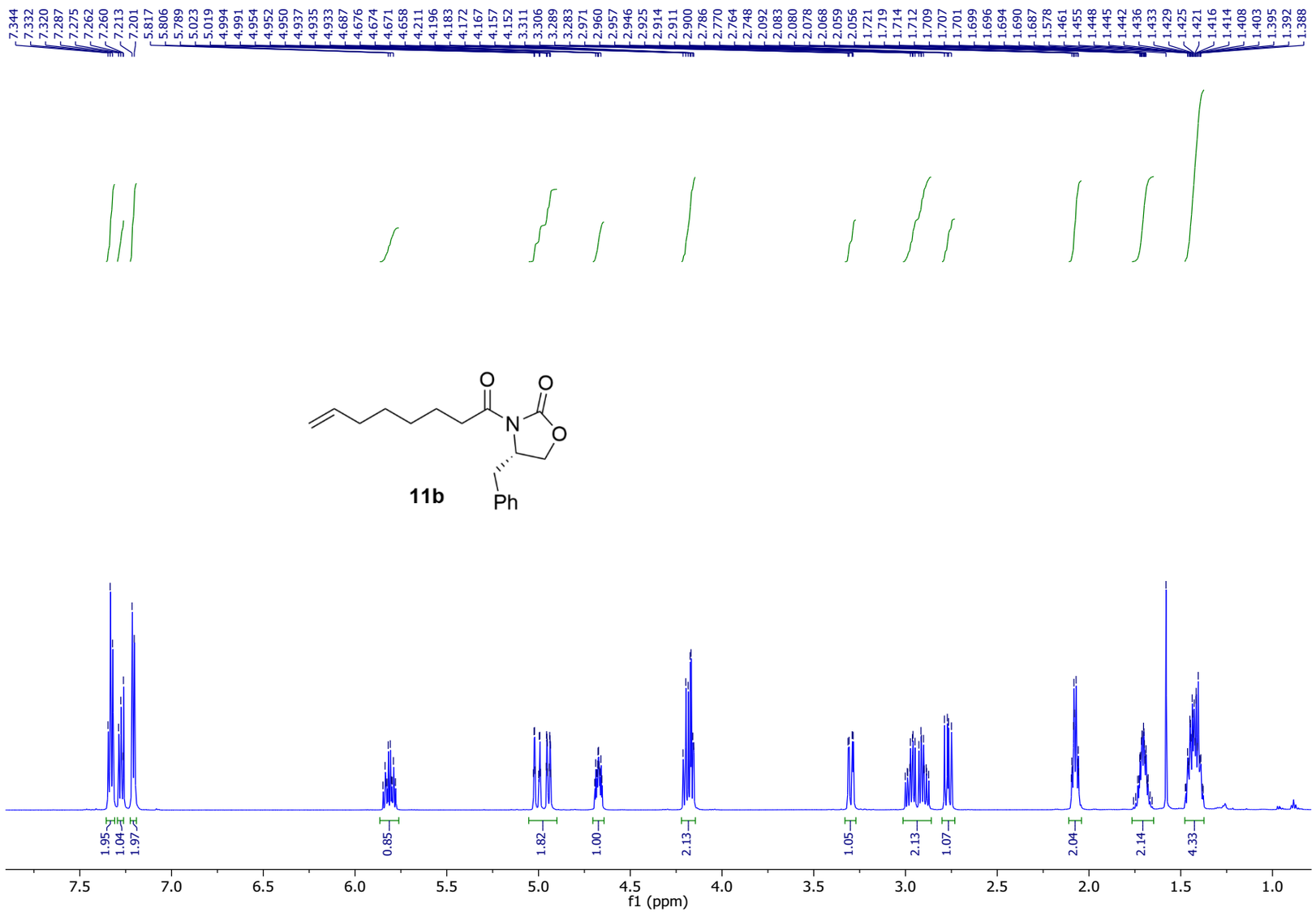


Figure S50. ^{1}H NMR spectrum of **11b** in $CDCl_3$ (600 MHz) at 27 °C.

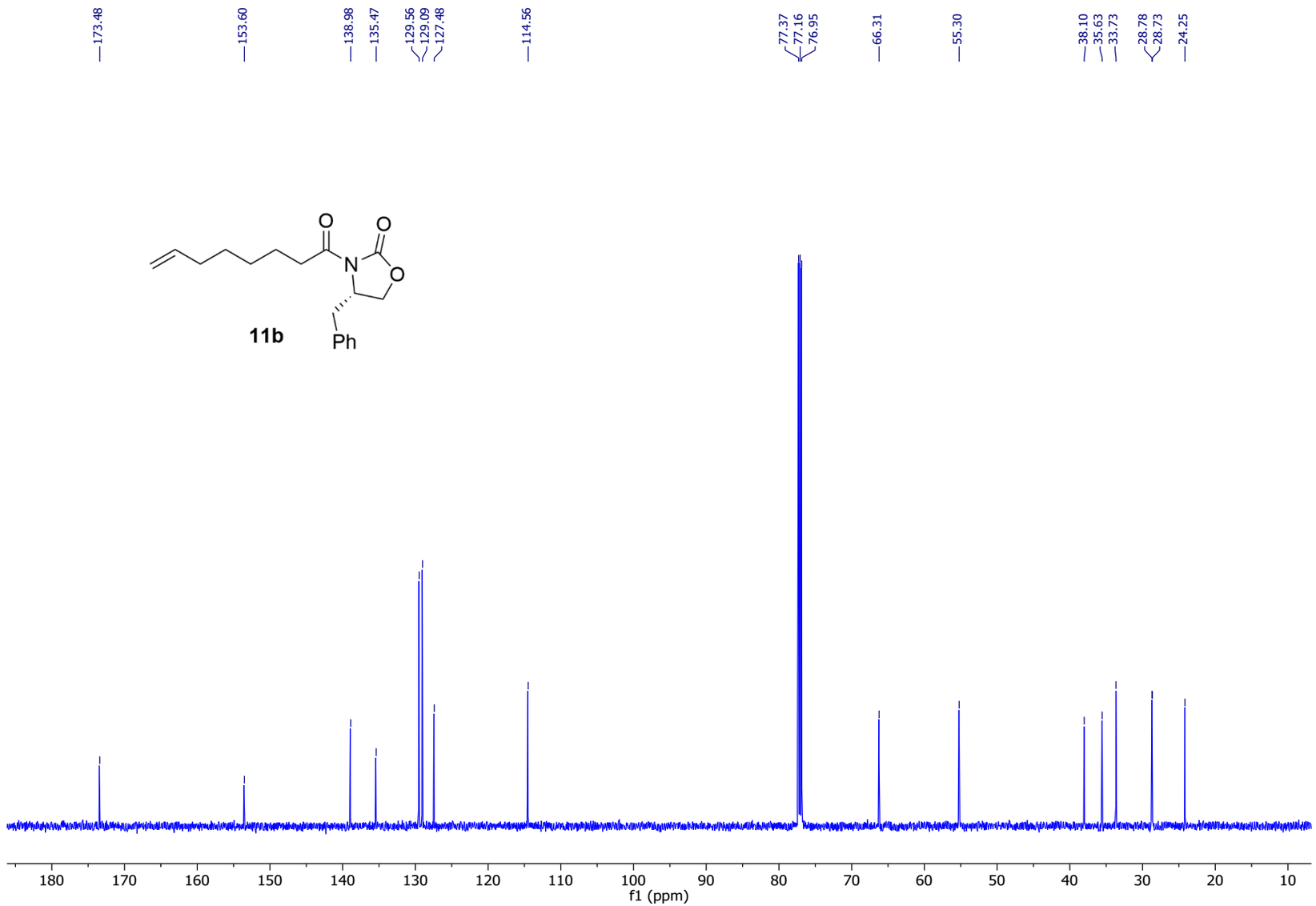


Figure S51. ^{13}C NMR spectrum of **11b** in $CDCl_3$ (150 MHz) at 27 °C.

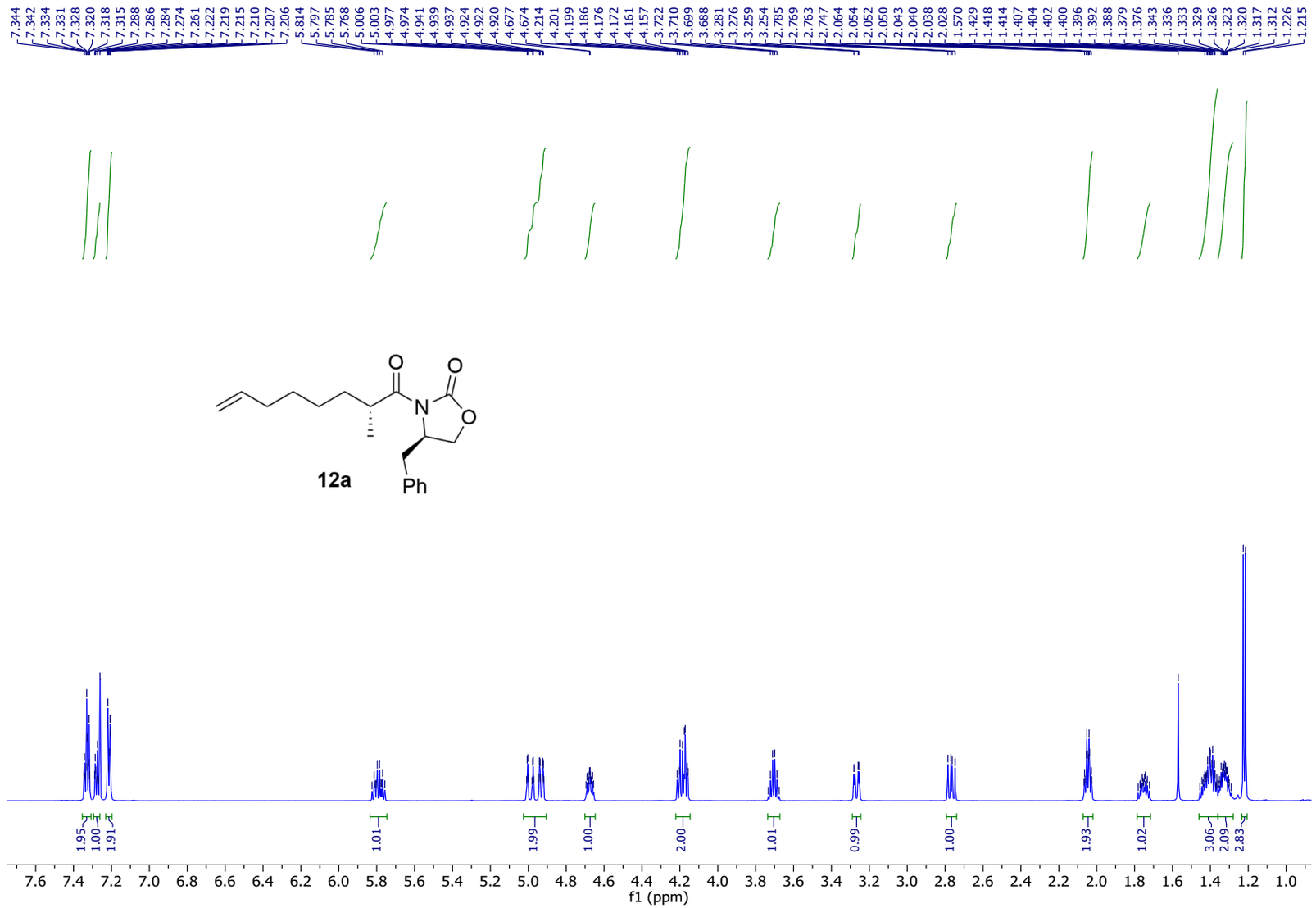


Figure S52. ^{1}H NMR spectrum of **12a** in $CDCl_3$ (600 MHz) at 27 °C.

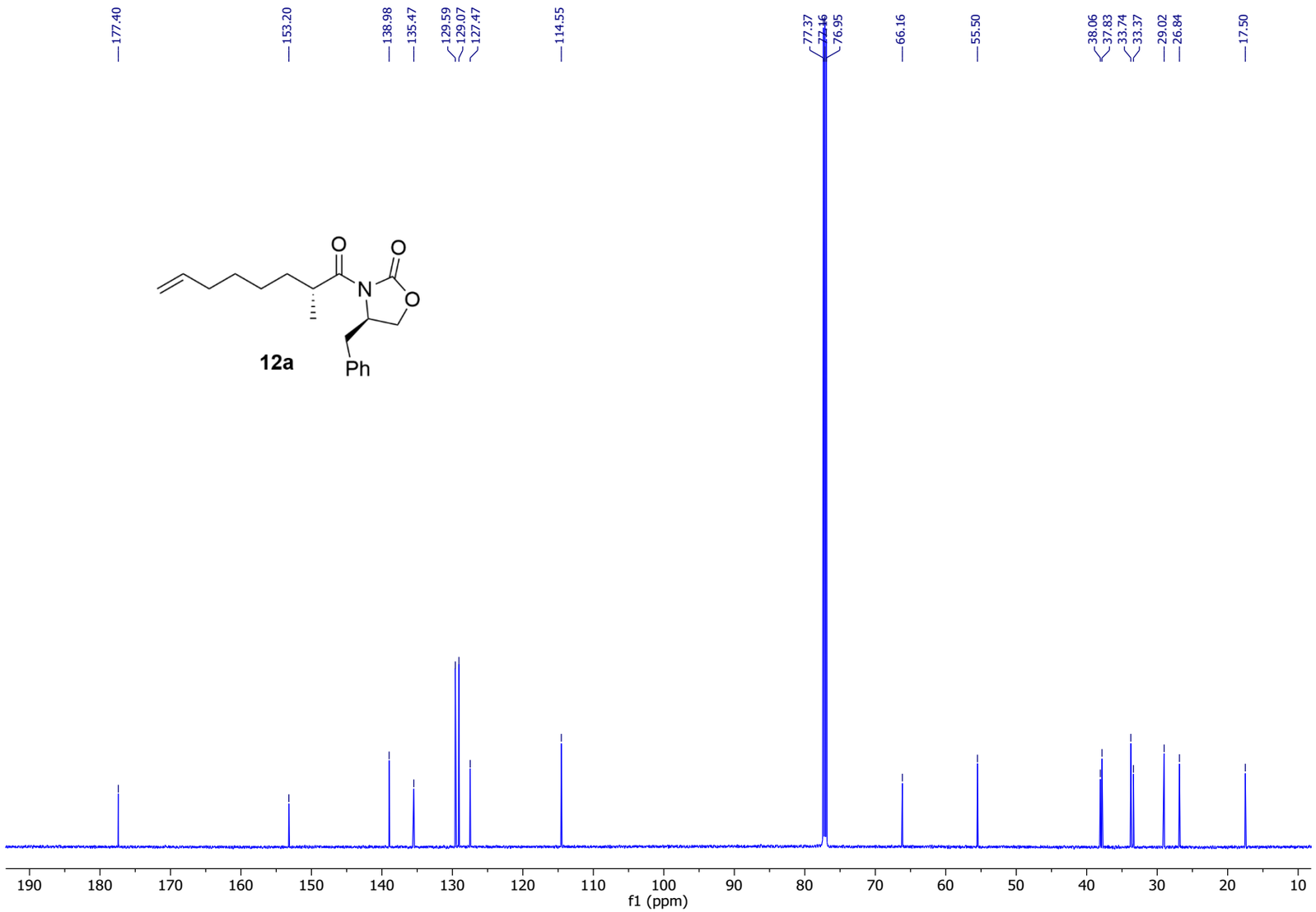


Figure S53. ^{13}C NMR spectrum of **12a** in $CDCl_3$ (150 MHz) at 27 °C.

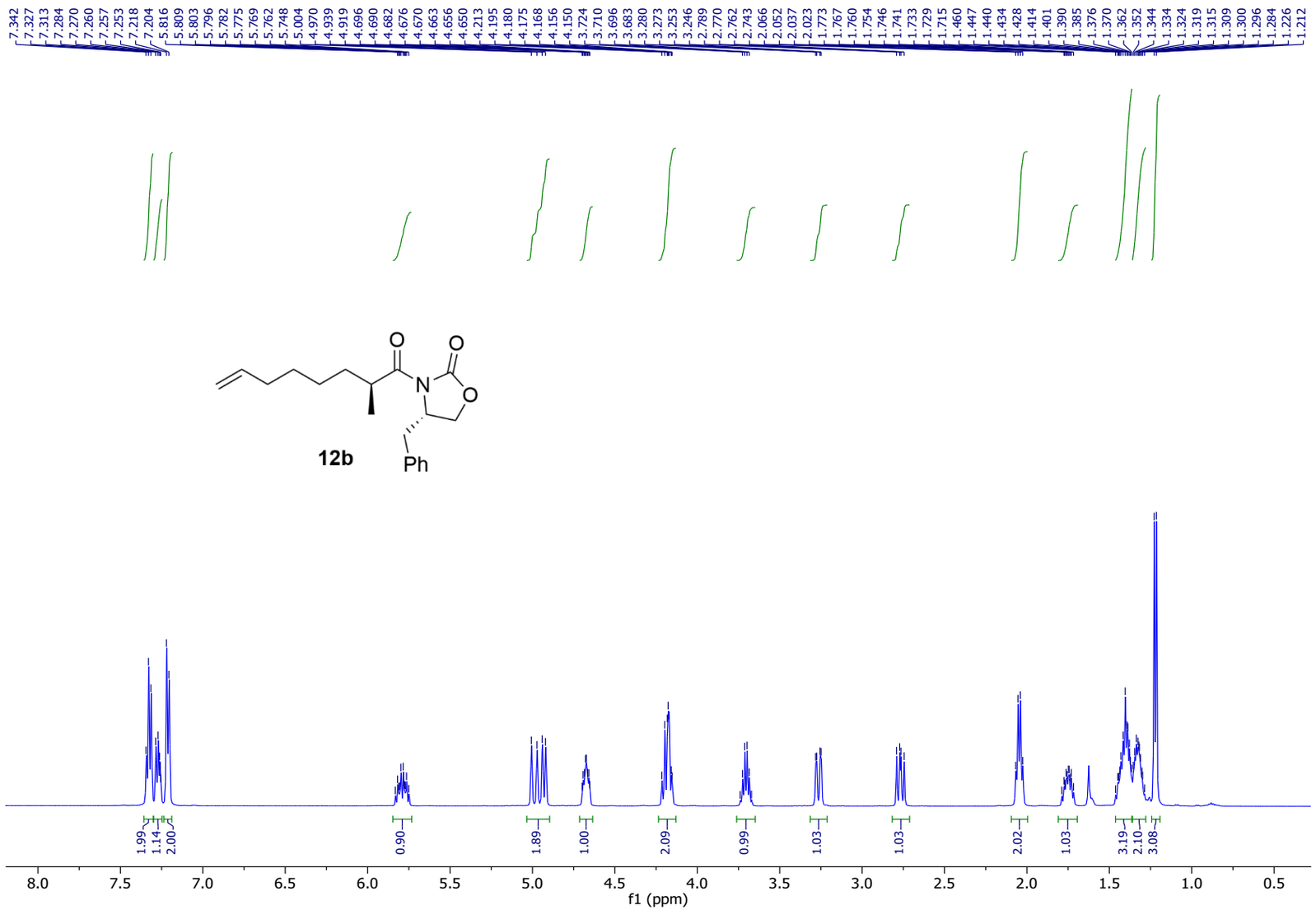


Figure S54. ^{1}H NMR spectrum of **12b** in $CDCl_3$ (600 MHz) at 27 °C.

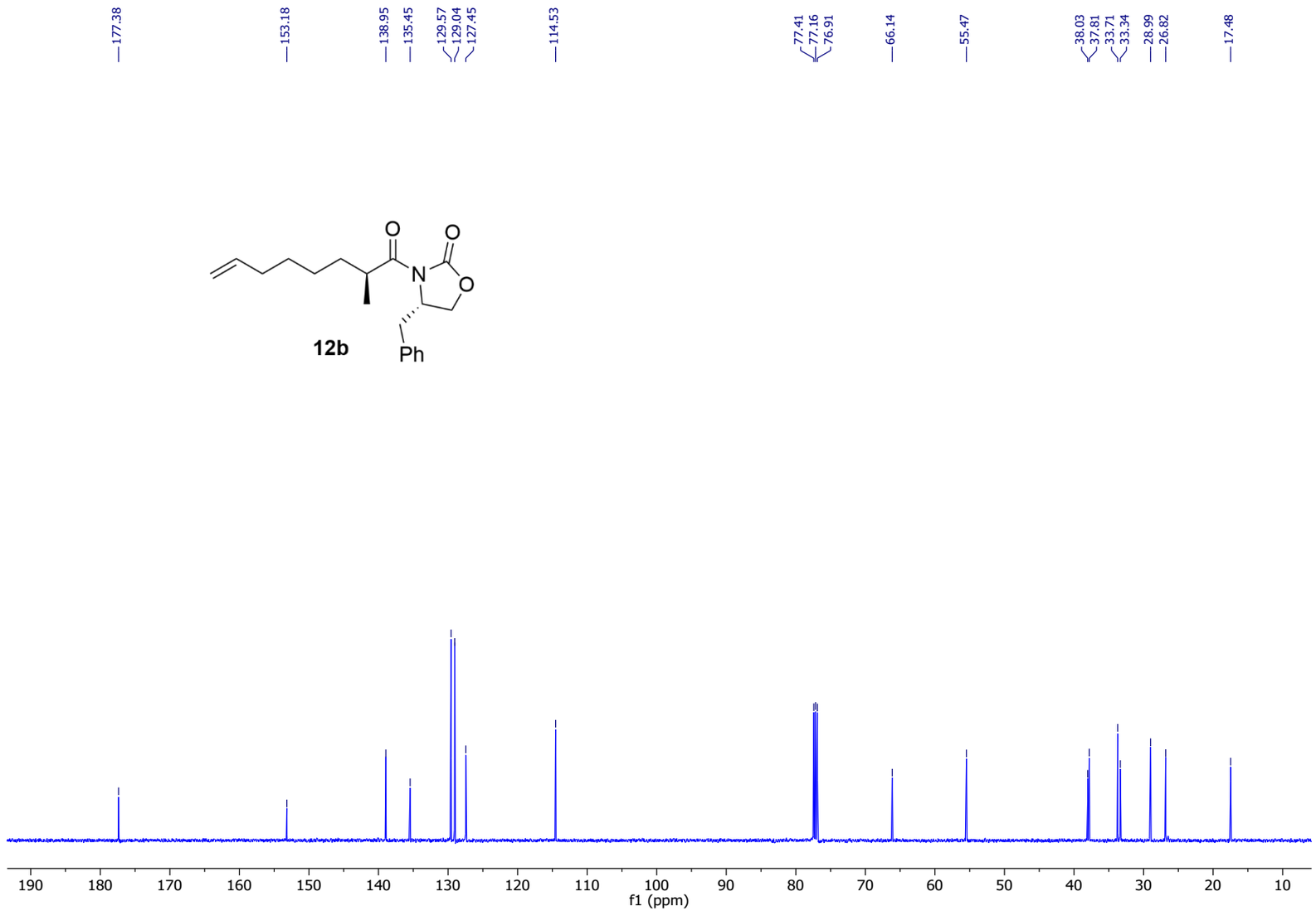


Figure S55. ^{13}C NMR spectrum of **12b** in $CDCl_3$ (150 MHz) at 27 °C.

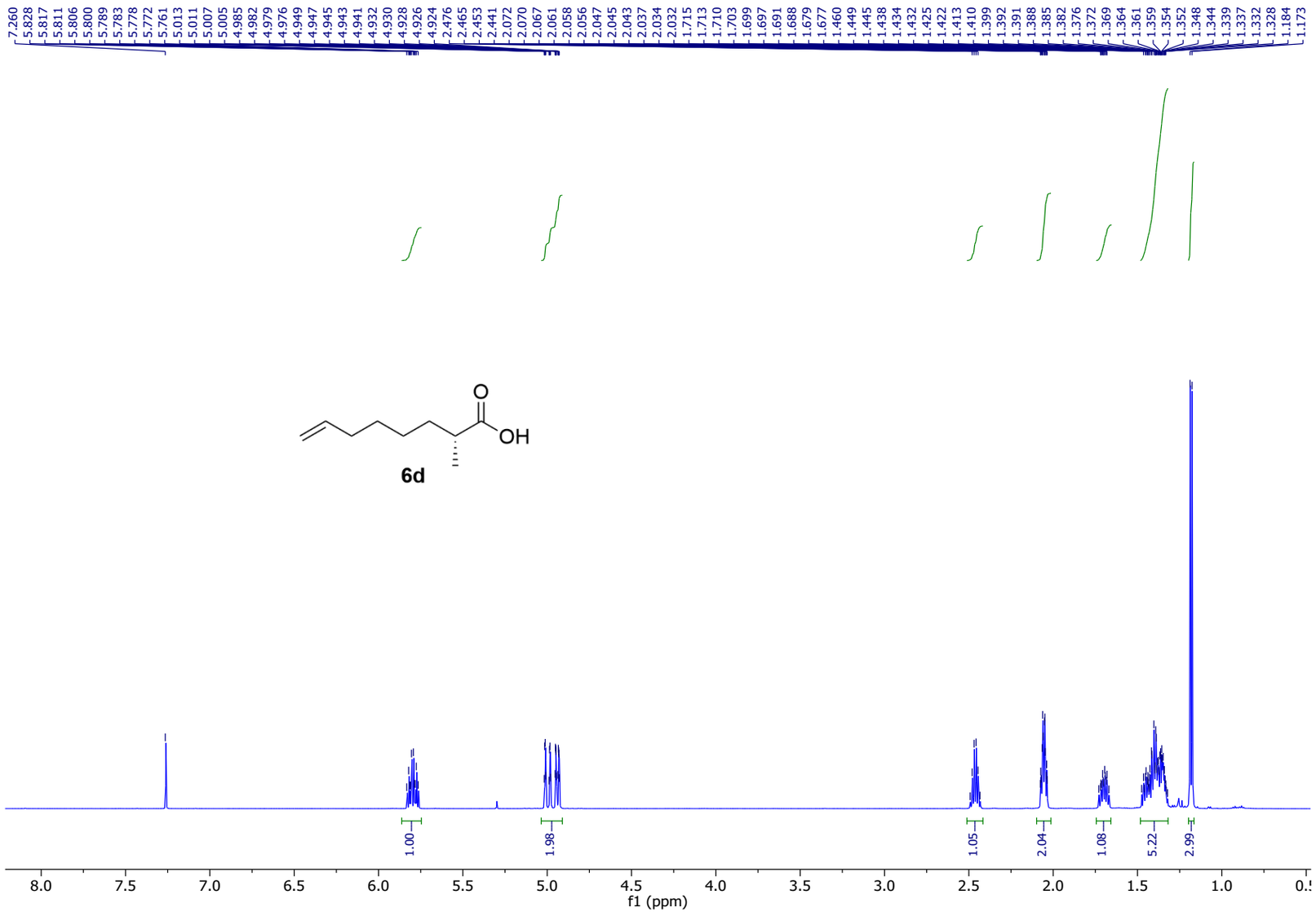


Figure S56. ^{1}H NMR spectrum of **6d** in $CDCl_3$ (600 MHz) at 27 °C.

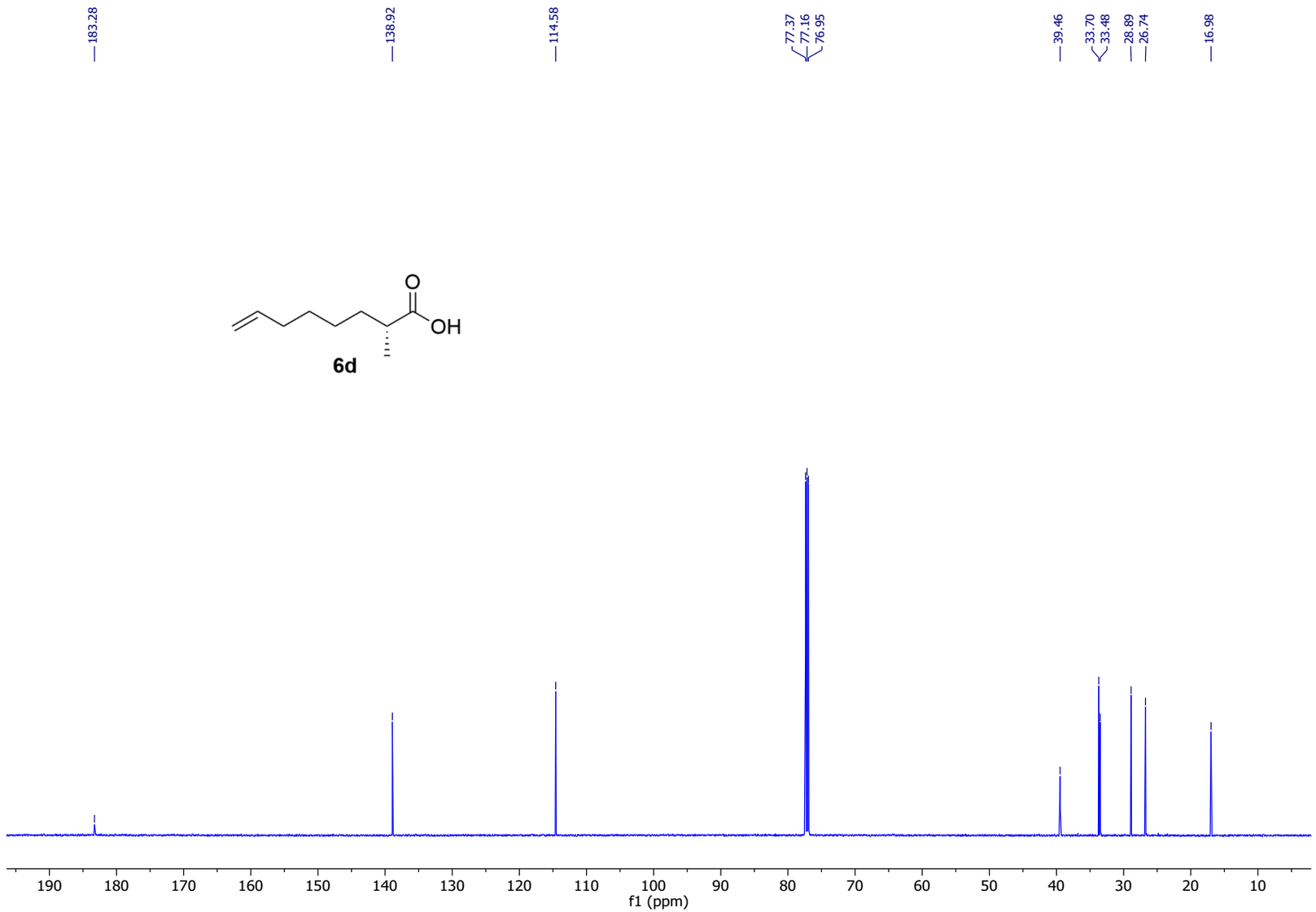


Figure S57. ^{13}C NMR spectrum of **6d** in $CDCl_3$ (150 MHz) at 27 °C.

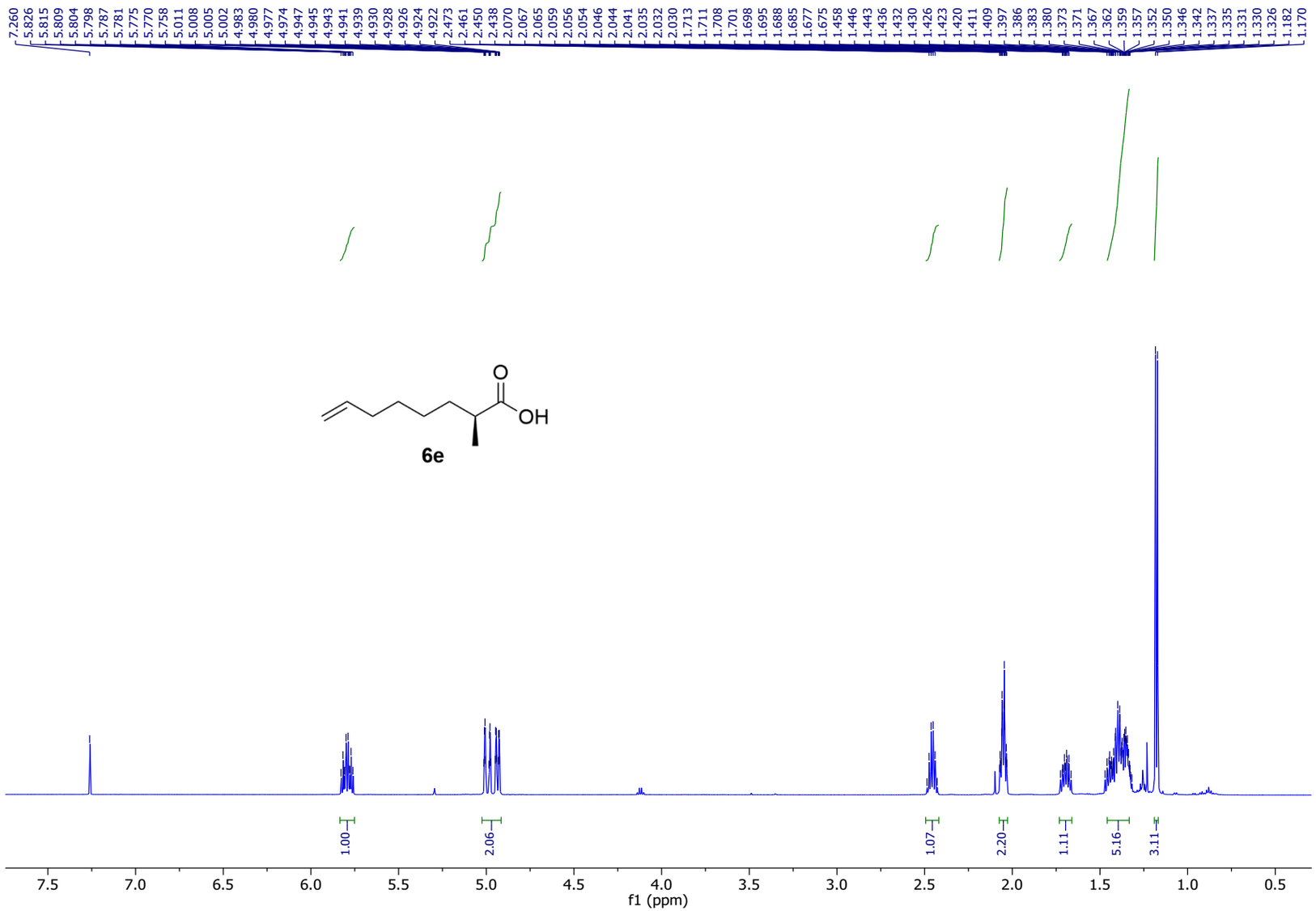


Figure S58. ^{1}H NMR spectrum of **6e** in $CDCl_3$ (600 MHz) at 27 °C.

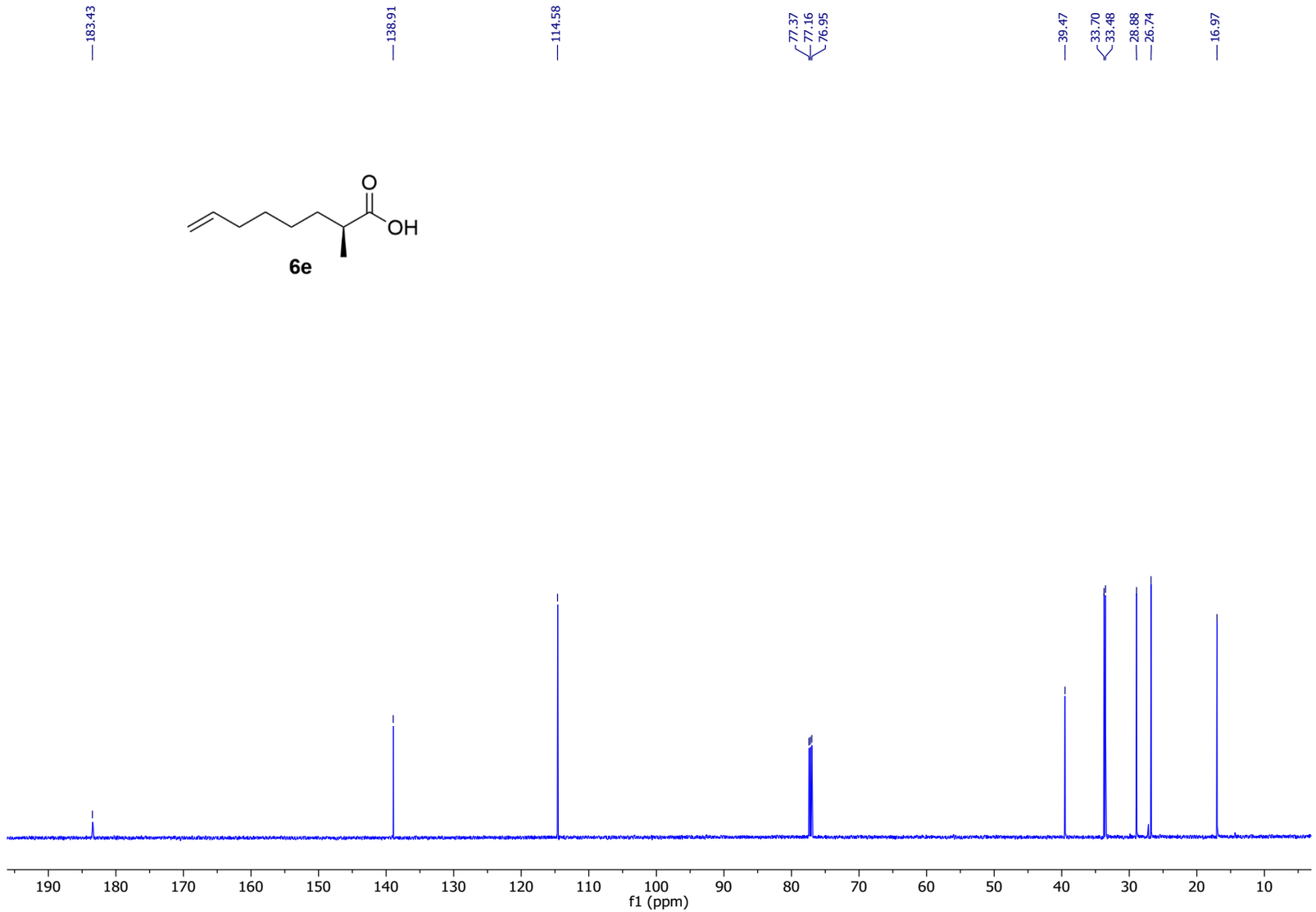


Figure S59. ^{13}C NMR spectrum of **6e** in $CDCl_3$ (150 MHz) at 27 °C.

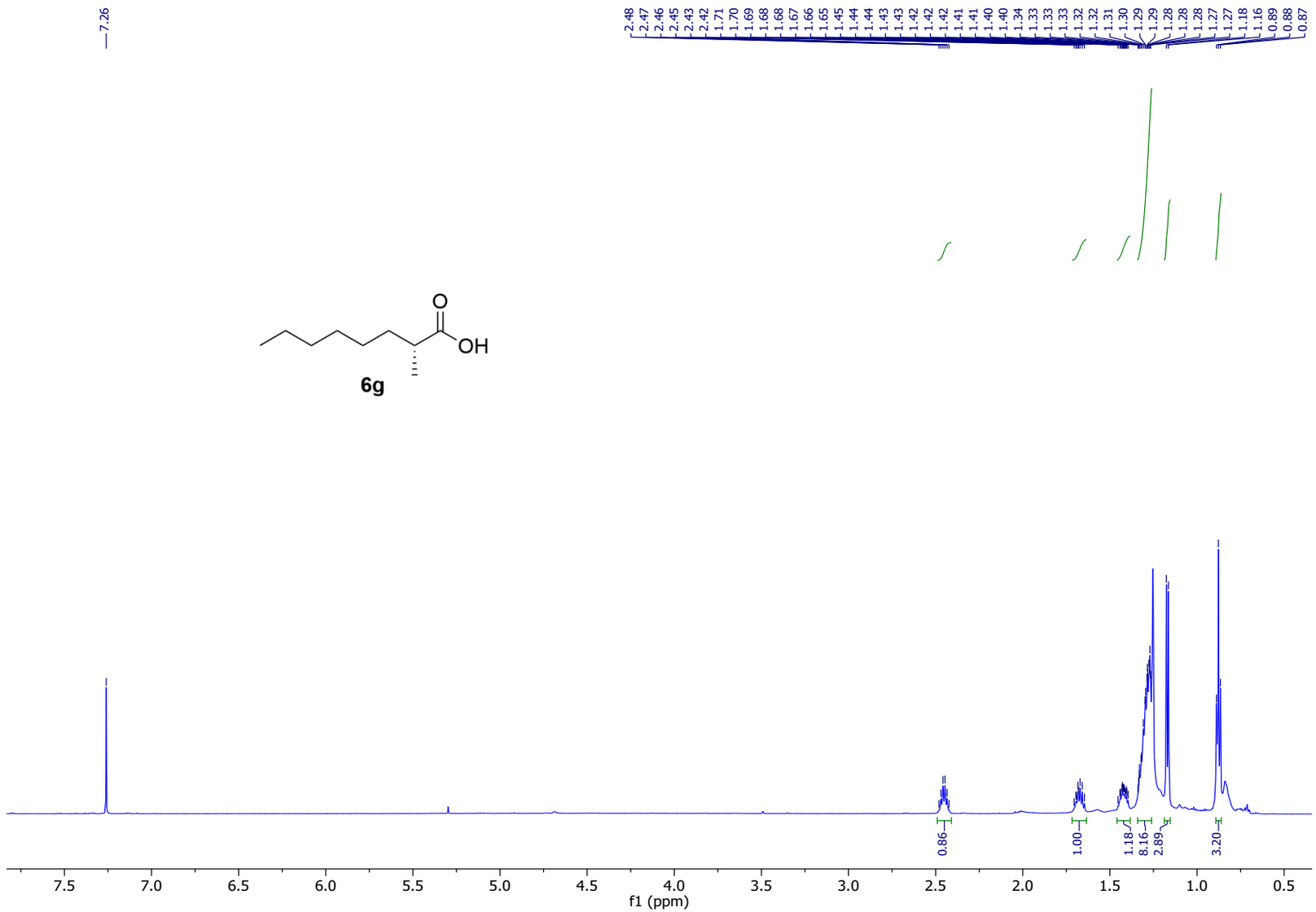


Figure S60. ^{1}H NMR spectrum of **6g** in $CDCl_3$ (600 MHz) at 27 °C.

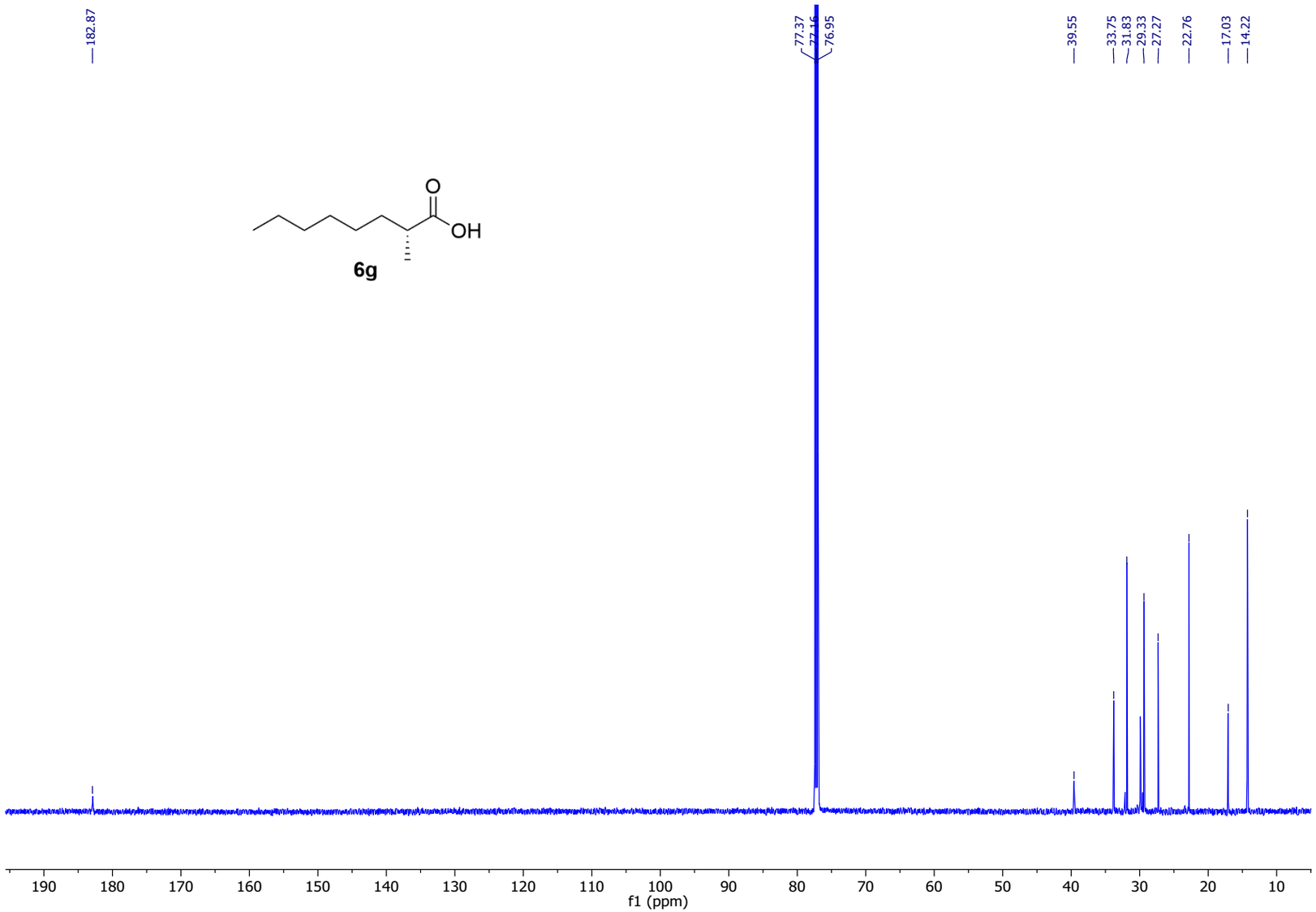


Figure S61. ^{13}C NMR spectrum of **6g** in $CDCl_3$ (150 MHz) at 27 °C.

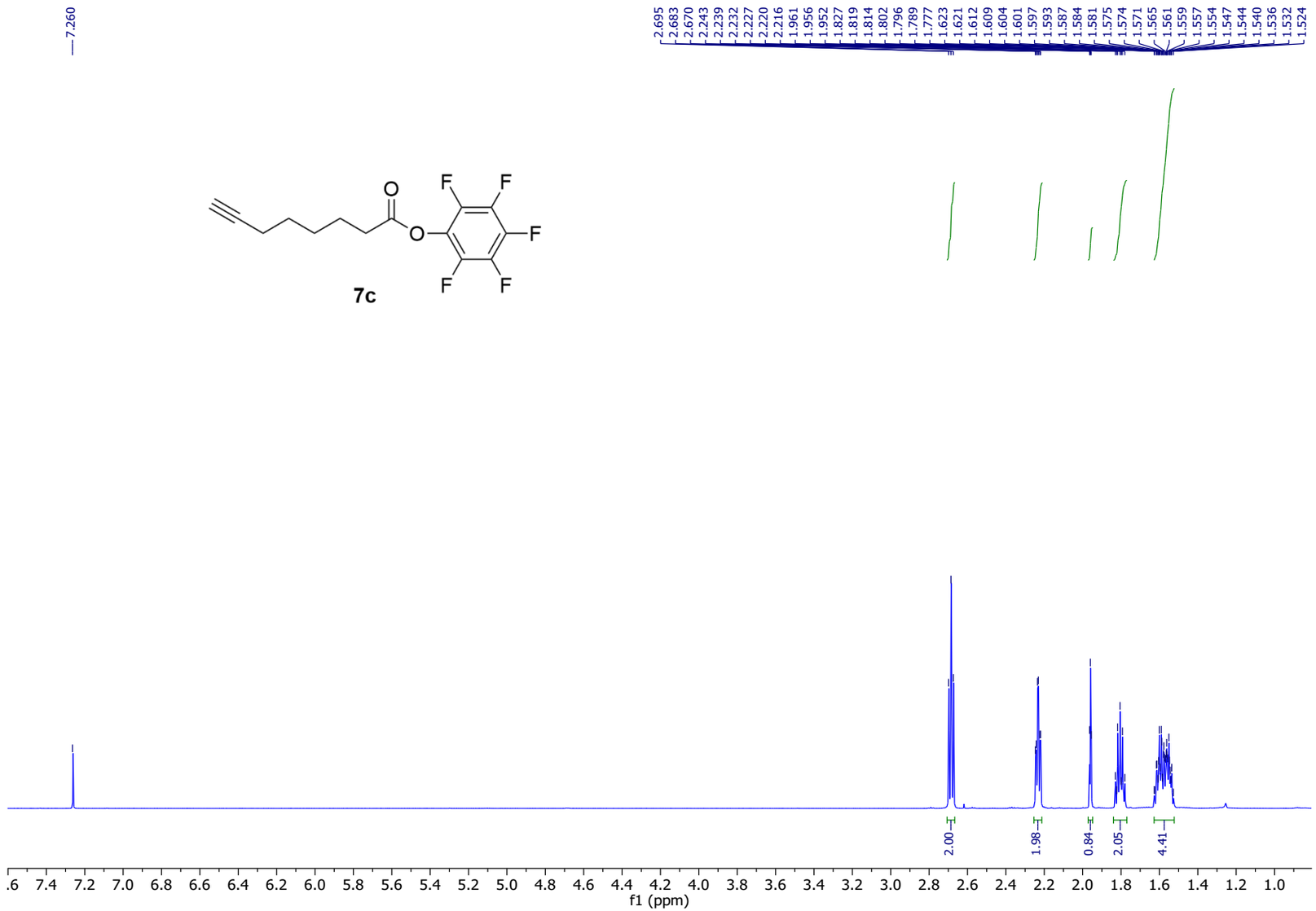


Figure S62. ^{1}H NMR spectrum of **7c** in $CDCl_3$ (600 MHz) at 27 °C.

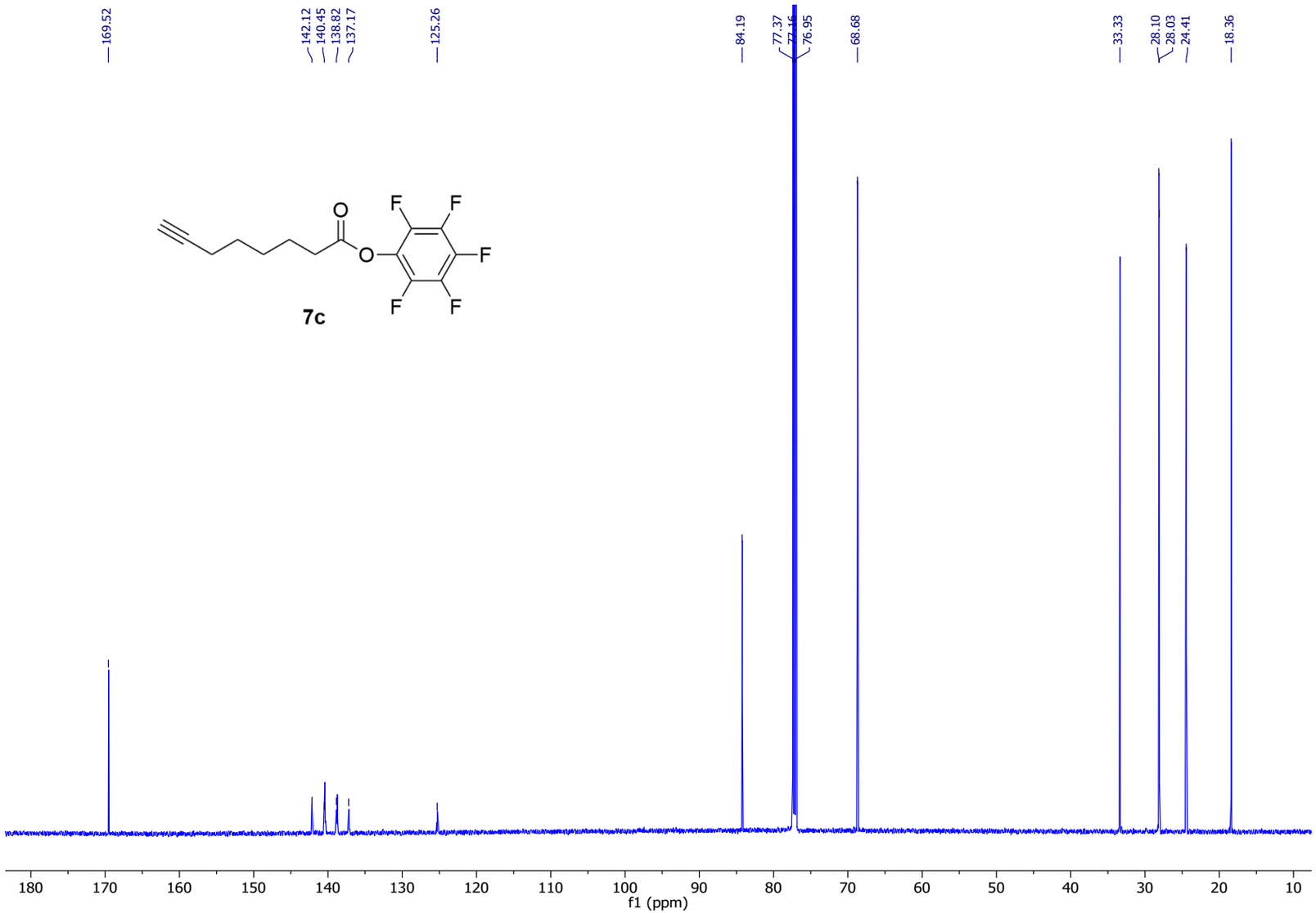


Figure S63. ^{13}C NMR spectrum of **7c** in $CDCl_3$ (150 MHz) at 27 °C.

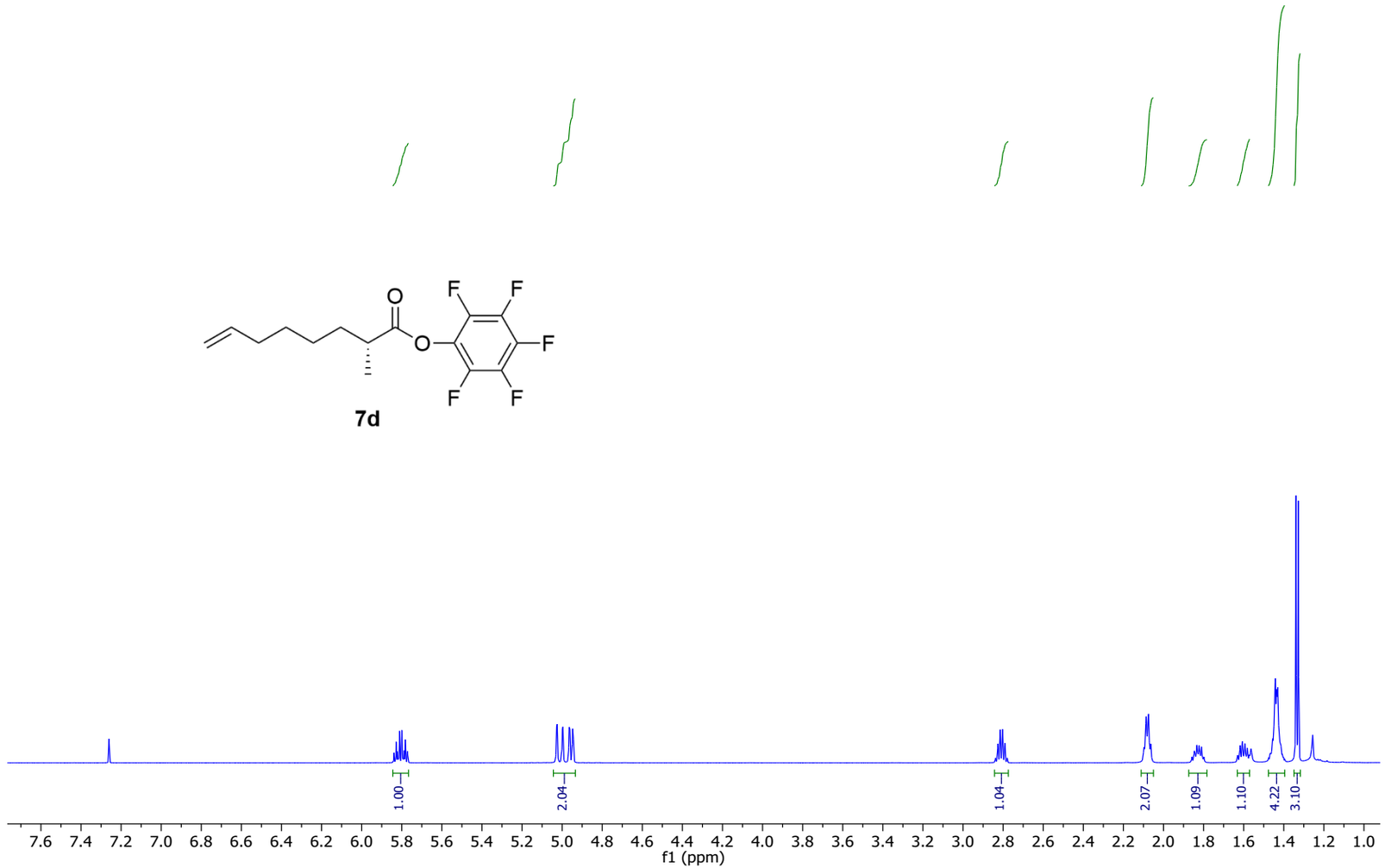


Figure S64. ^{1}H NMR spectrum of **7d** in $CDCl_3$ (600 MHz) at 27 °C.

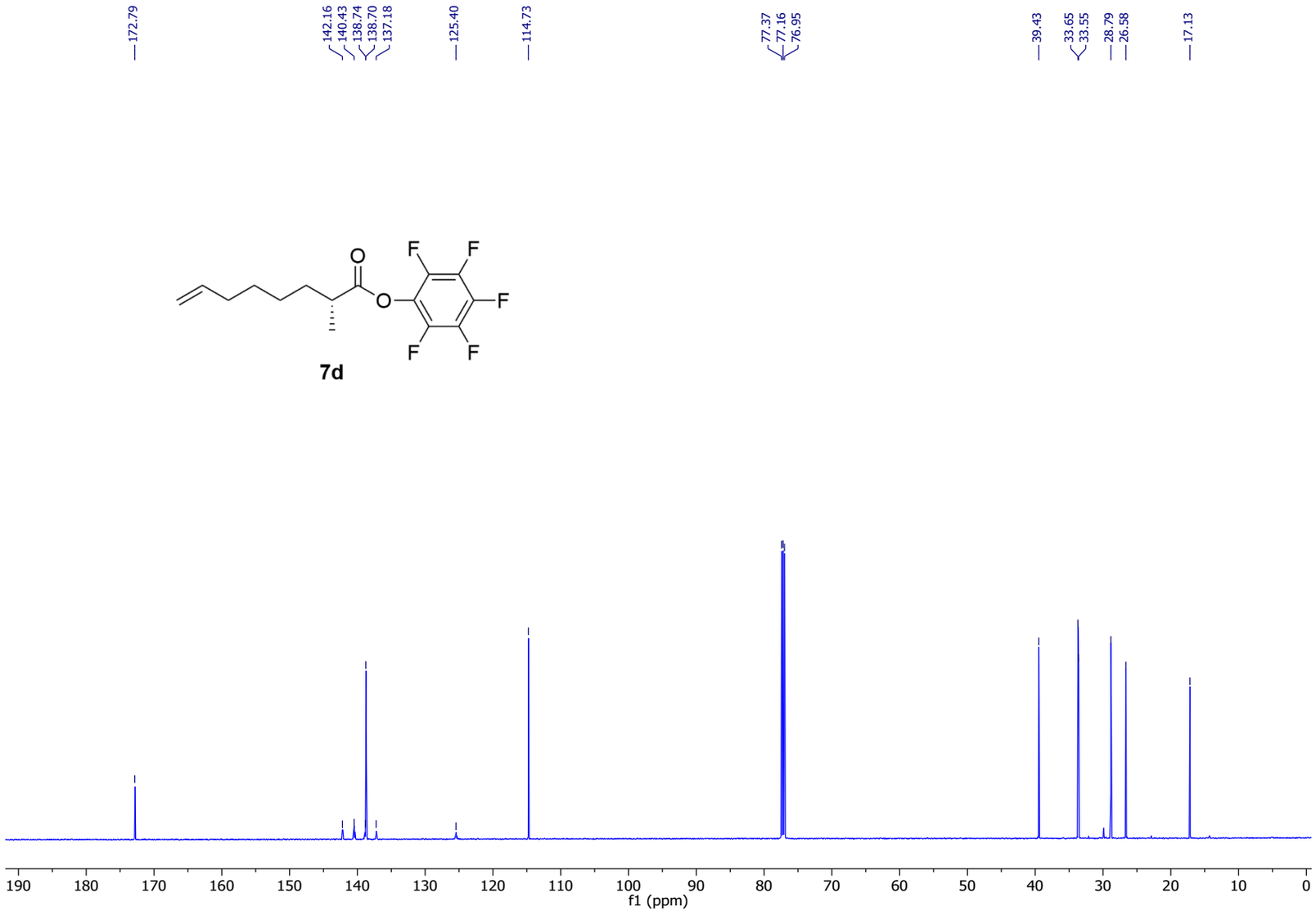


Figure S65. ^{13}C NMR spectrum of **7d** in $CDCl_3$ (150 MHz) at 27 °C.

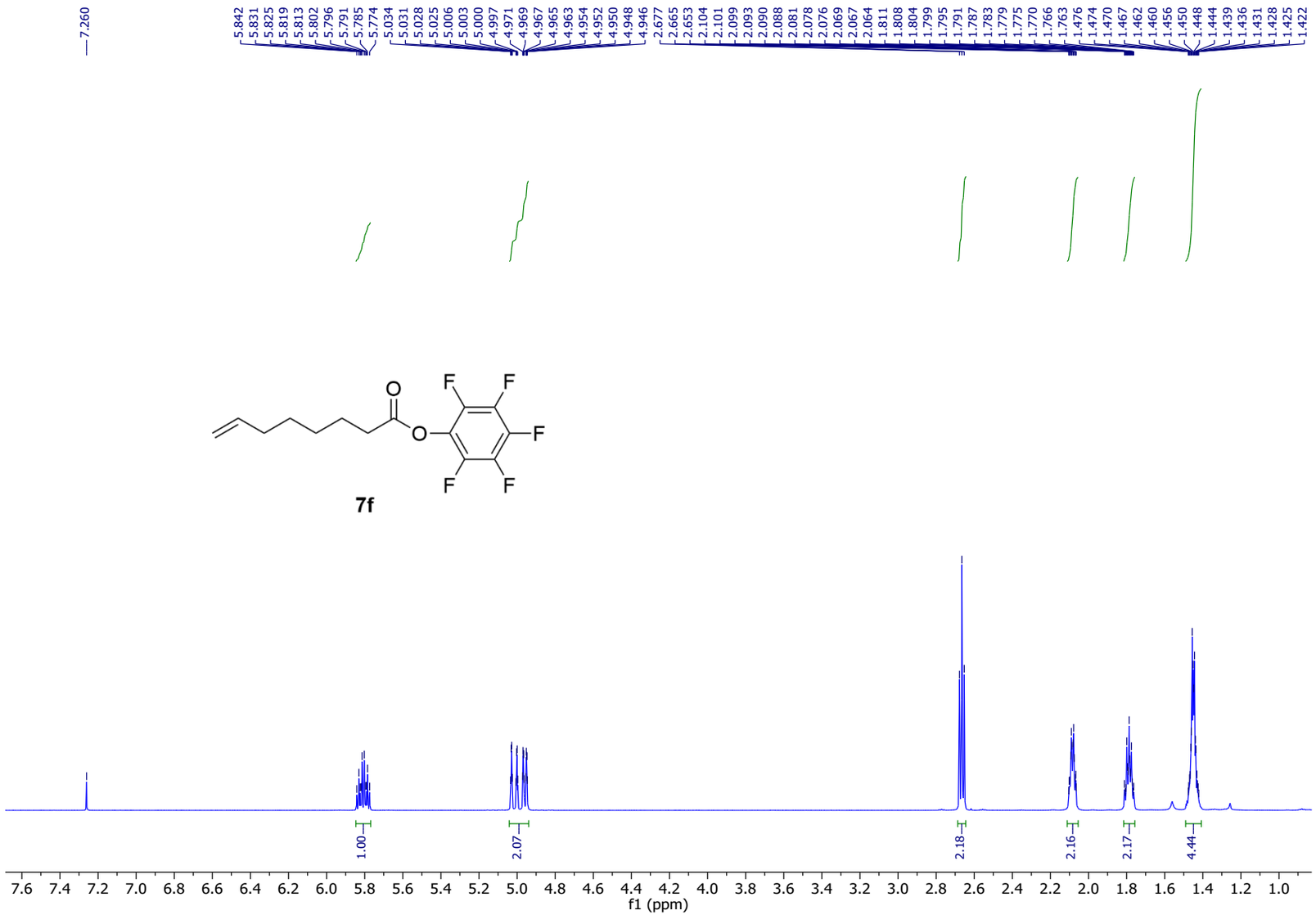


Figure S66. ^{1}H NMR spectrum of **7f** in $CDCl_3$ (600 MHz) at 27 °C.

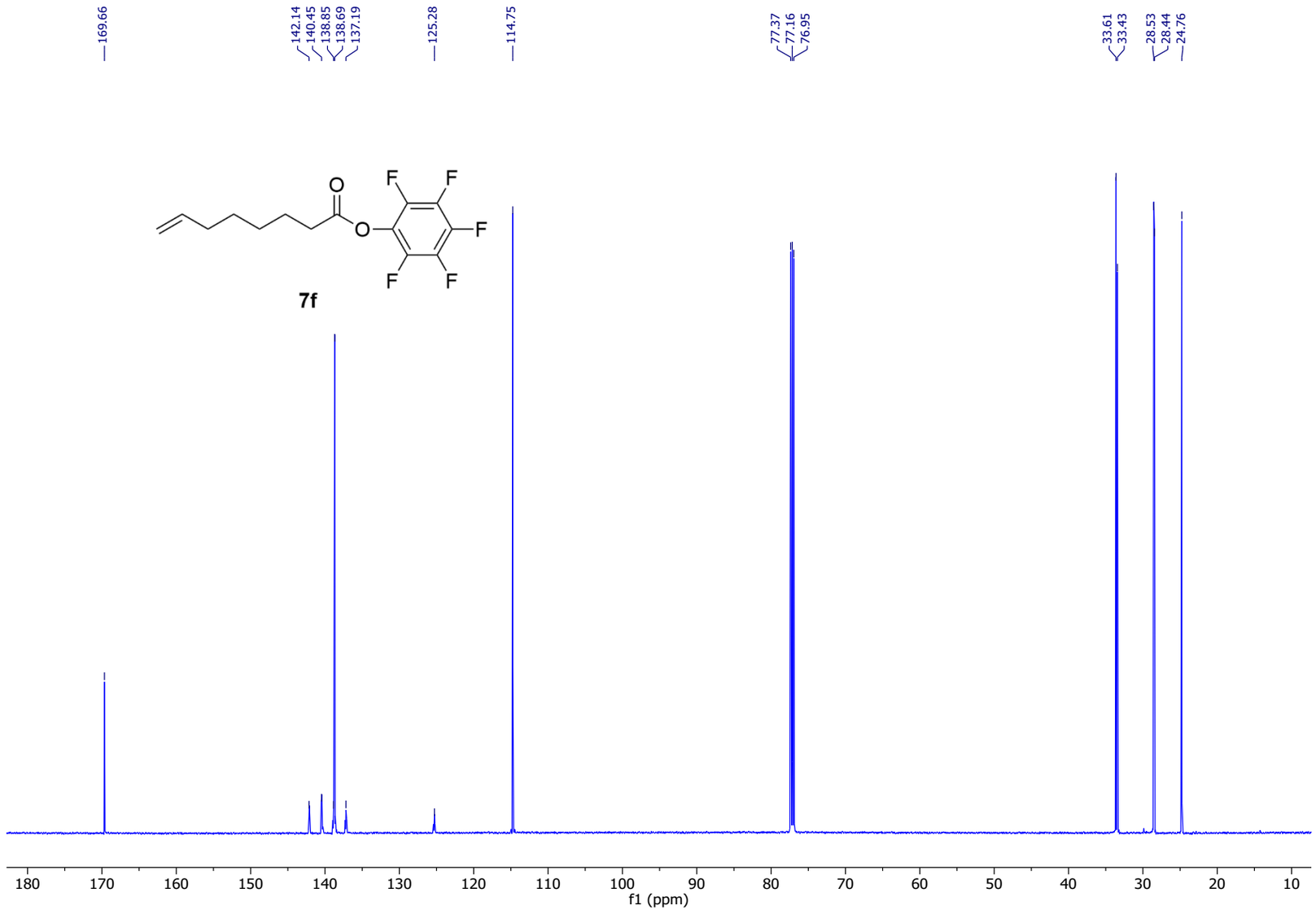


Figure S67. ^{13}C NMR spectrum of **7f** in $CDCl_3$ (150 MHz) at 27 °C.

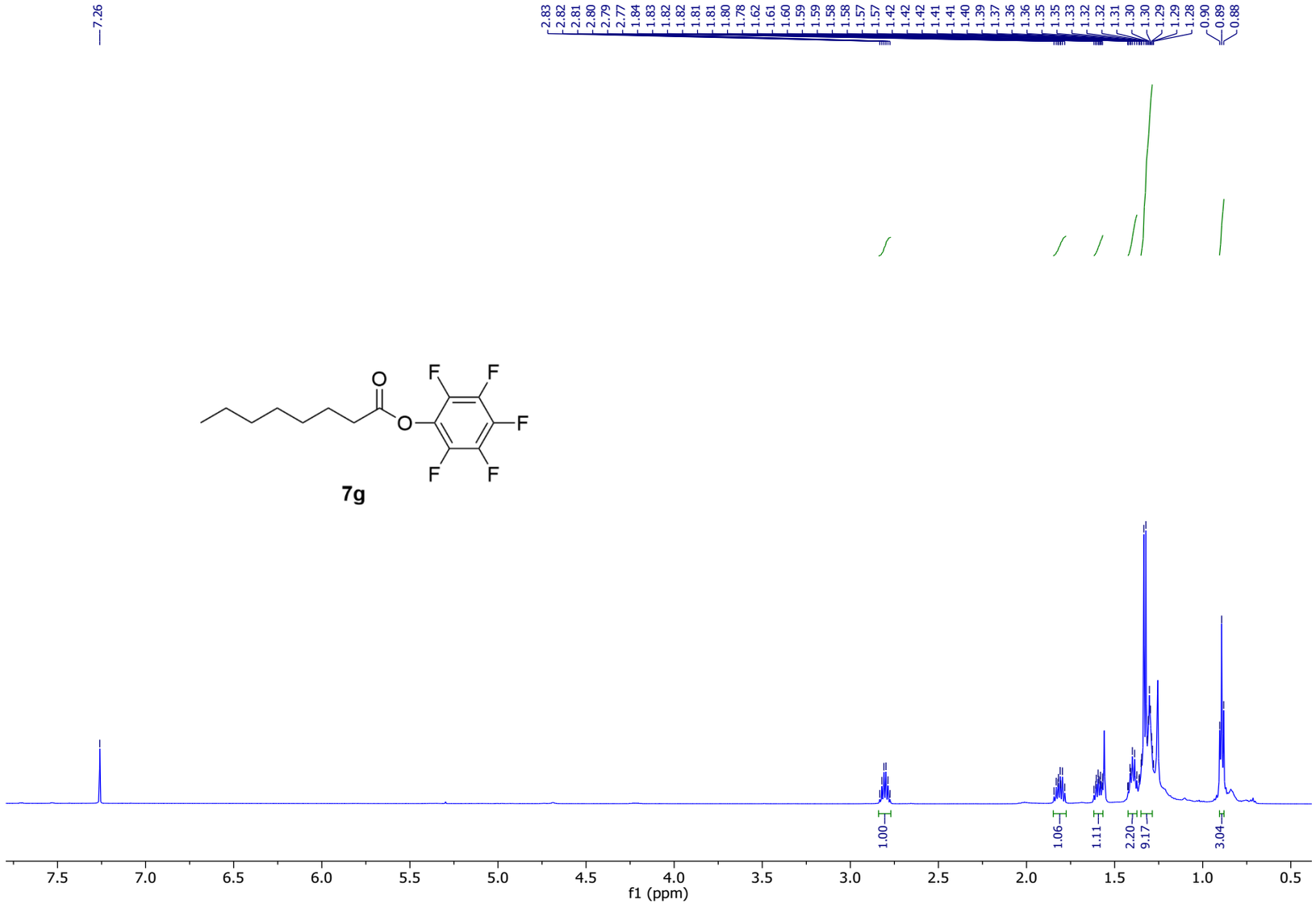


Figure S68. ^{1}H NMR spectrum of **7g** in $CDCl_3$ (600 MHz) at 27 °C.

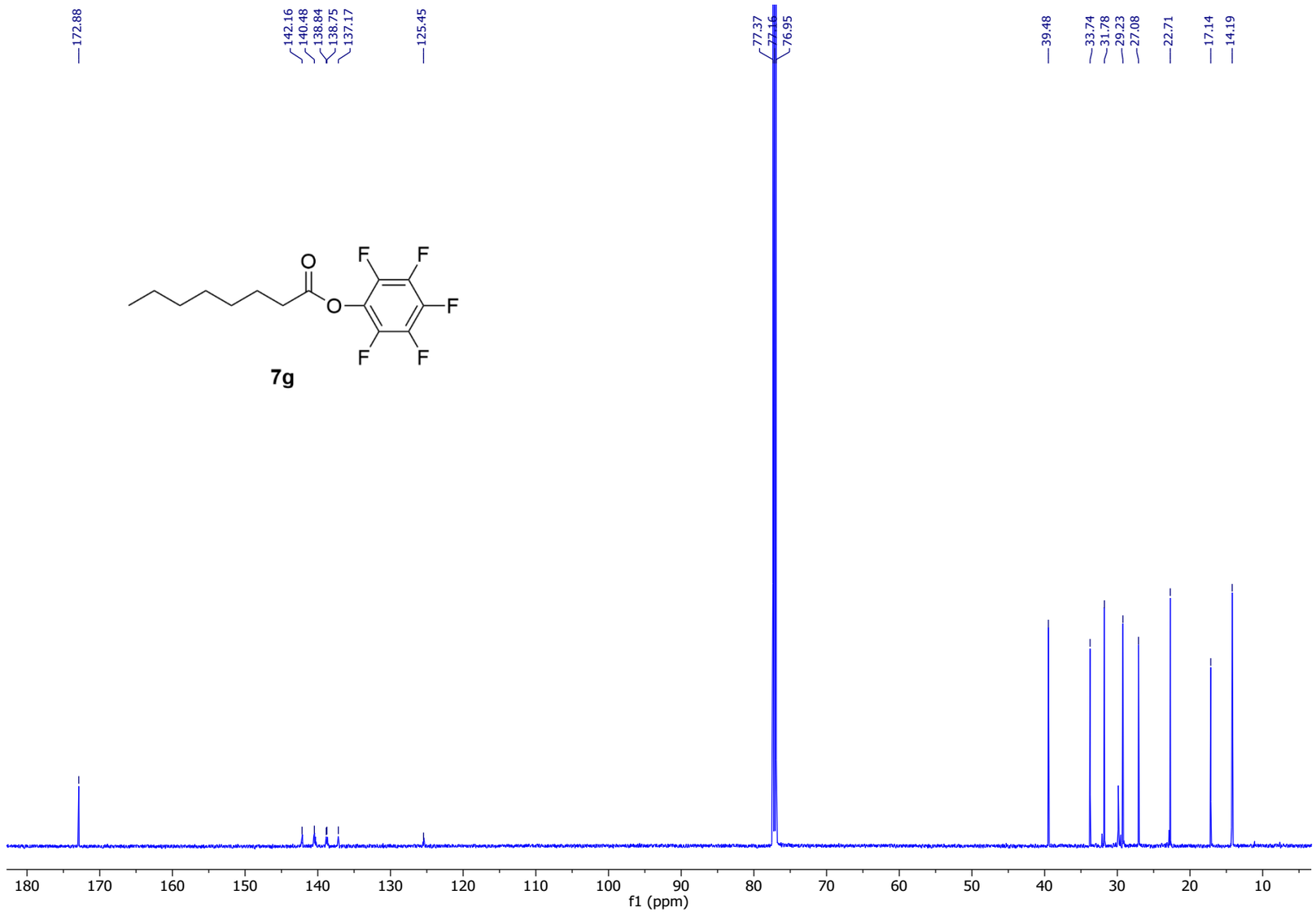


Figure S69. ^{13}C NMR spectrum of **7g** in $CDCl_3$ (150 MHz) at 27 °C.

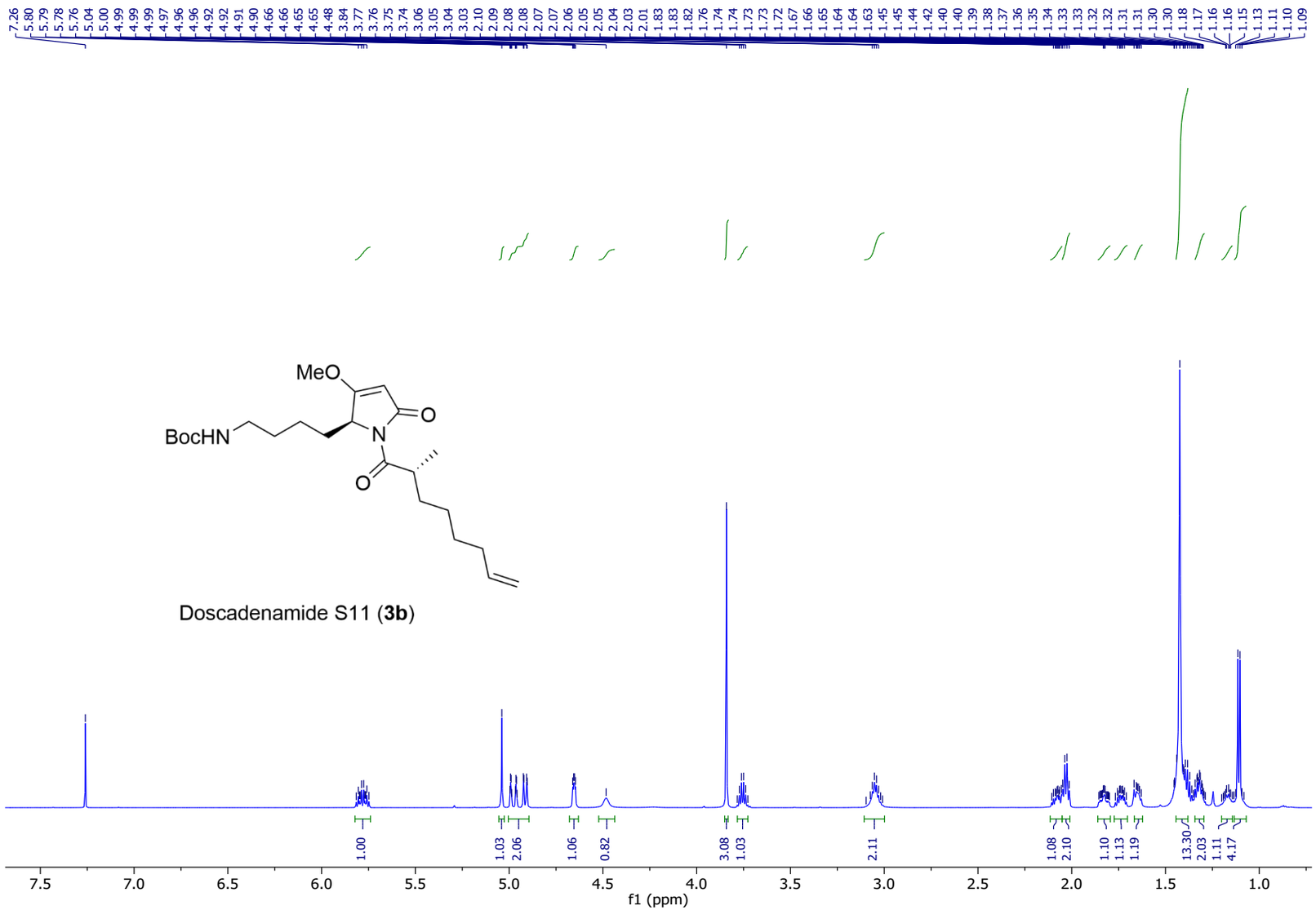


Figure S70. ^{1}H NMR spectrum of doscadenamide S11 (**3b**) in $CDCl_3$ (600 MHz) at 27 °C.

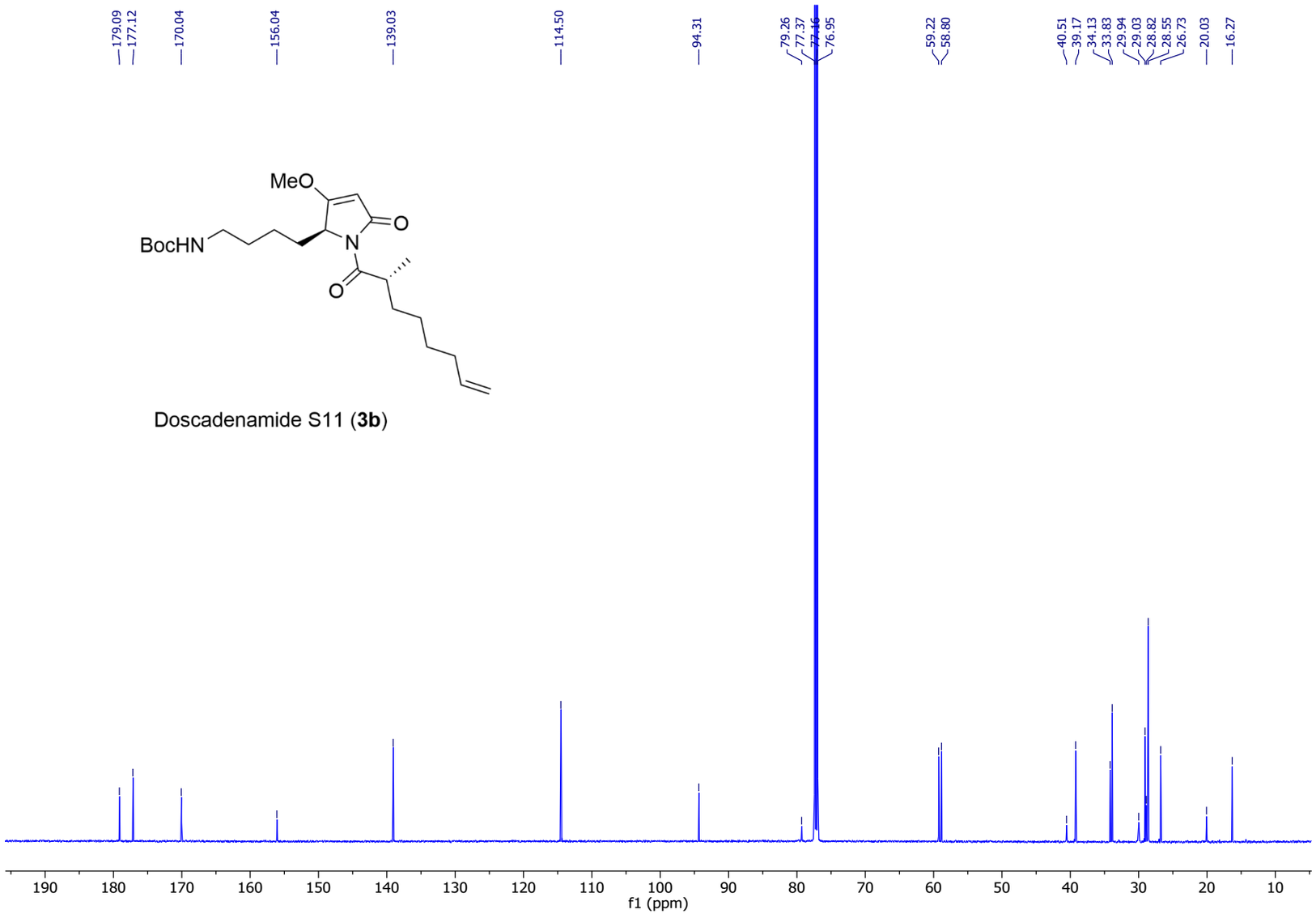


Figure S71. ^{13}C NMR spectrum of doscadenamide S11 (**3b**) in $CDCl_3$ (150 MHz) at 27 °C.

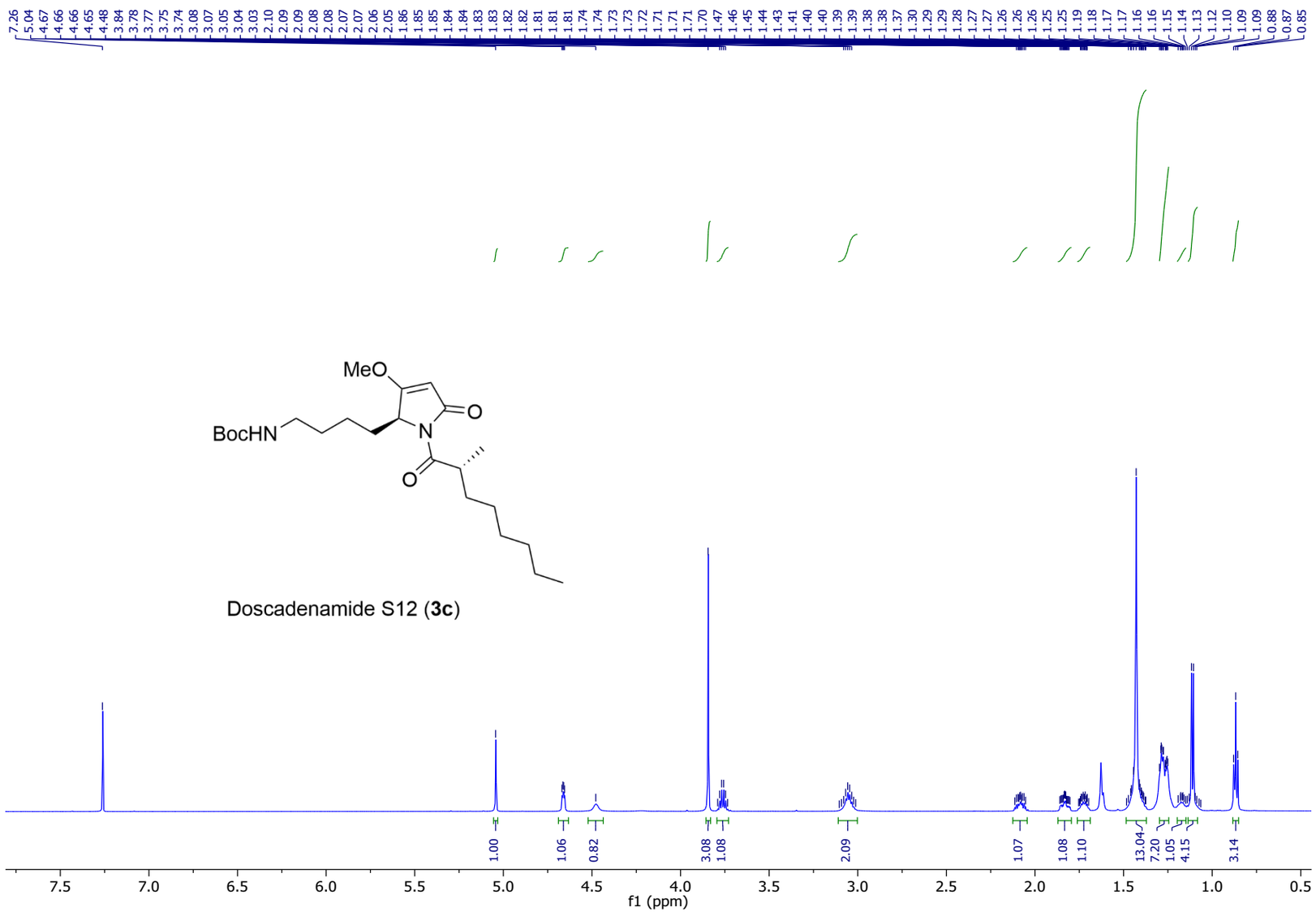


Figure S72. ^{1}H NMR spectrum of doscadenamide S12 (**3c**) in $CDCl_3$ (600 MHz) at 27 °C.

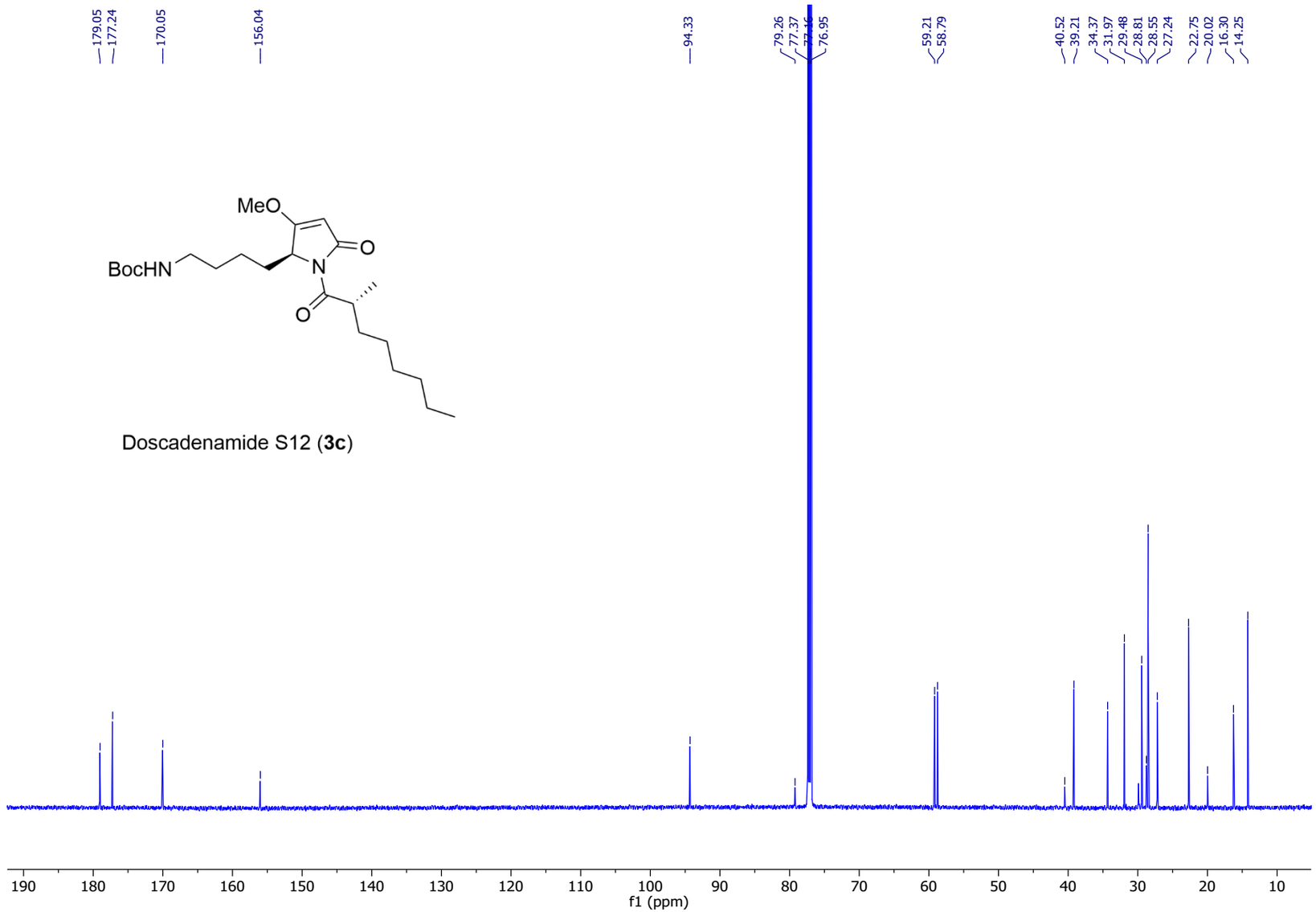


Figure S73. ^{13}C NMR spectrum of doscadenamide S12 (**3c**) in $CDCl_3$ (150 MHz) at 27 °C.

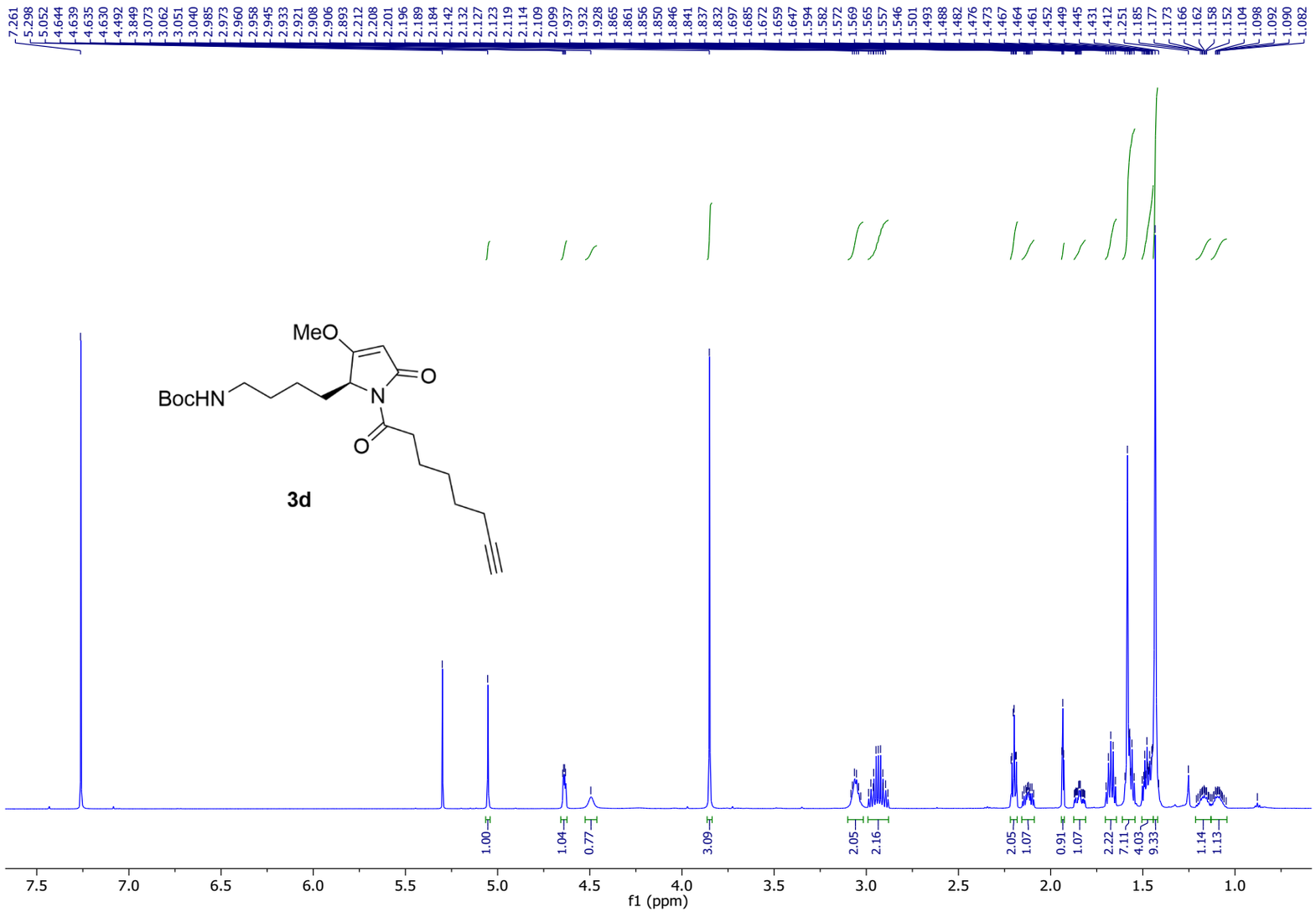


Figure S74. ^{1}H NMR spectrum of **3d** in $CDCl_3$ (600 MHz) at 27 °C.

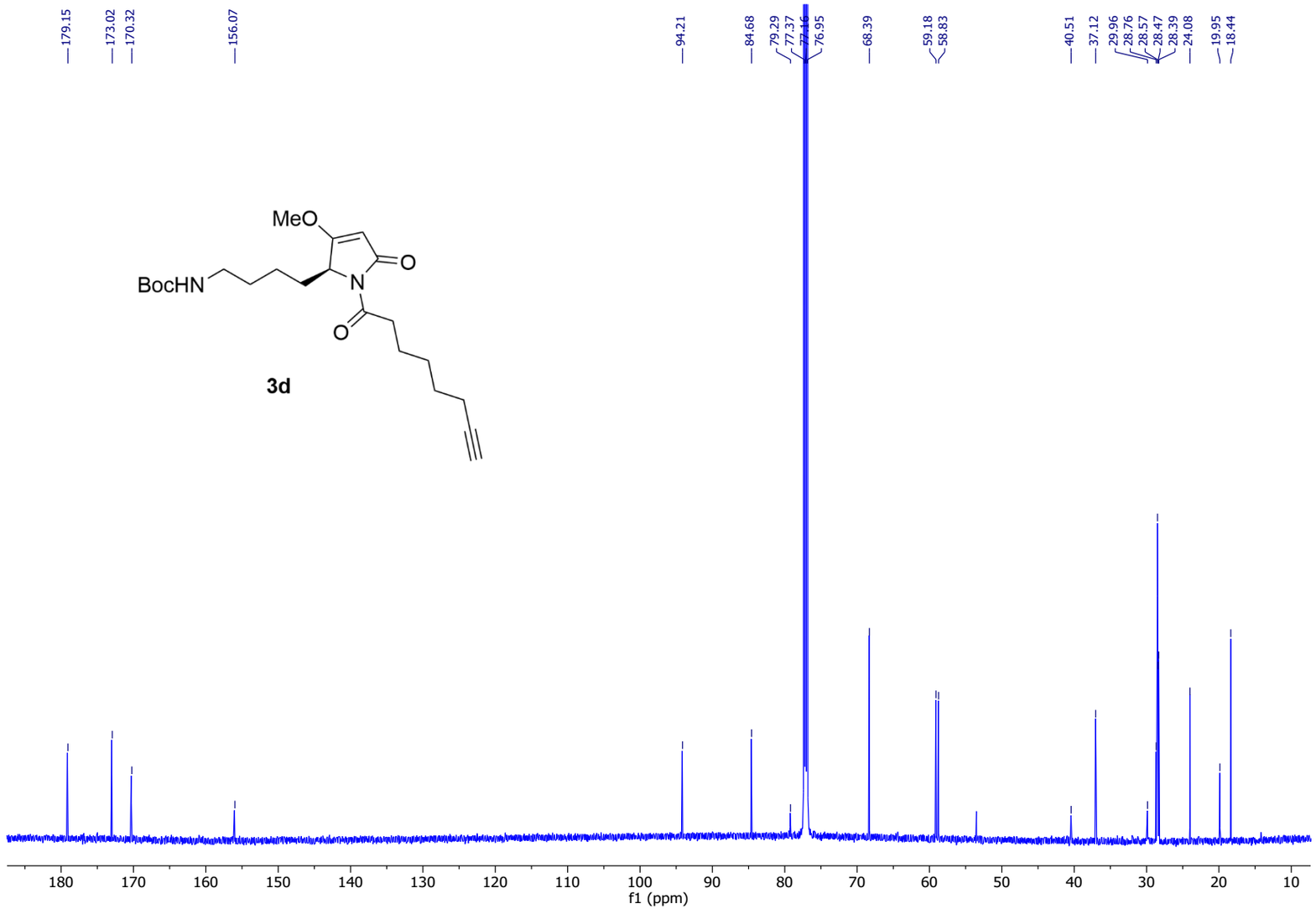


Figure S75. ^{13}C NMR spectrum of **3d** in $CDCl_3$ (150 MHz) at 27 °C.

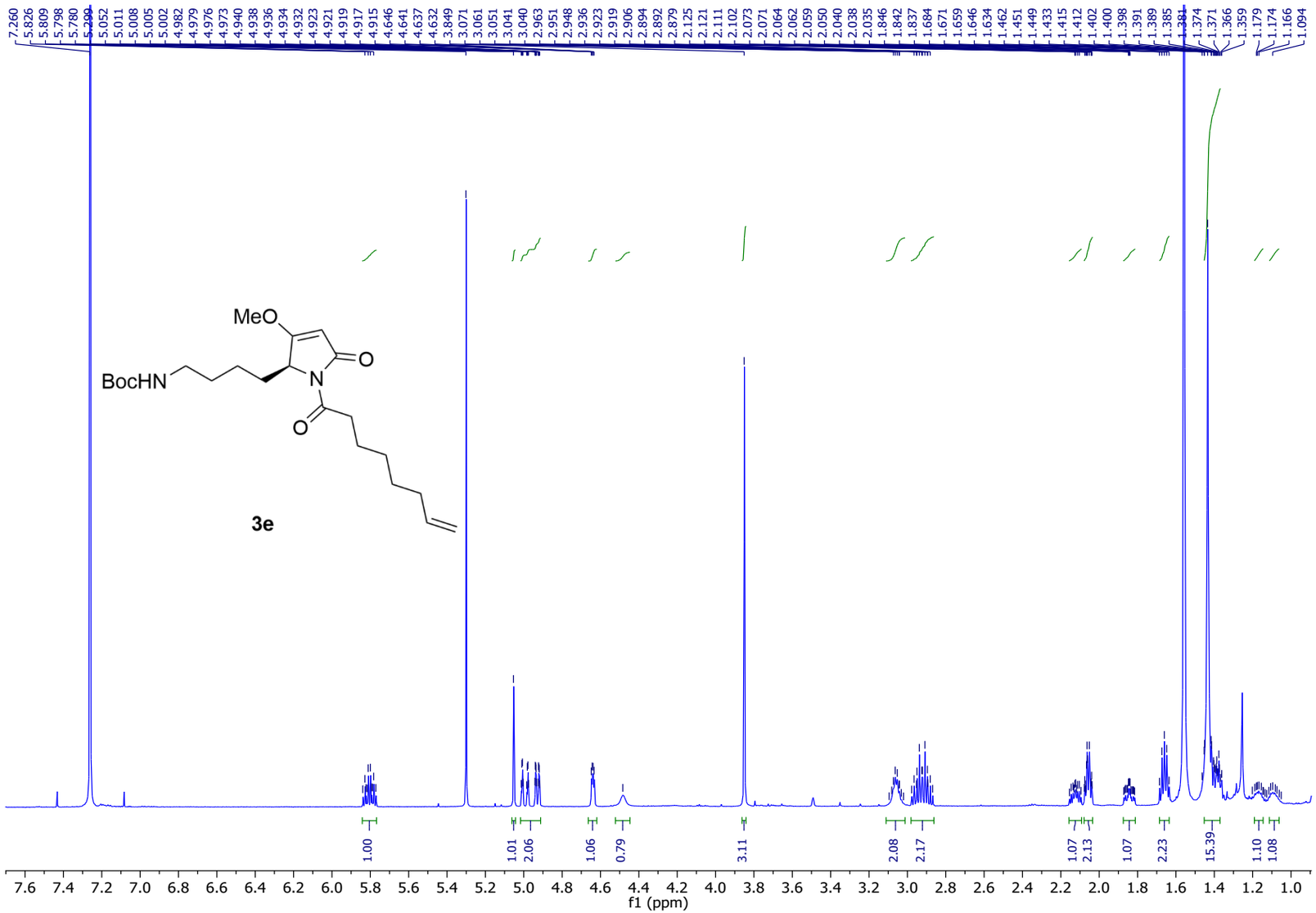


Figure S76. ^{1}H NMR spectrum of **3e** in $CDCl_3$ (600 MHz) at 27 °C.

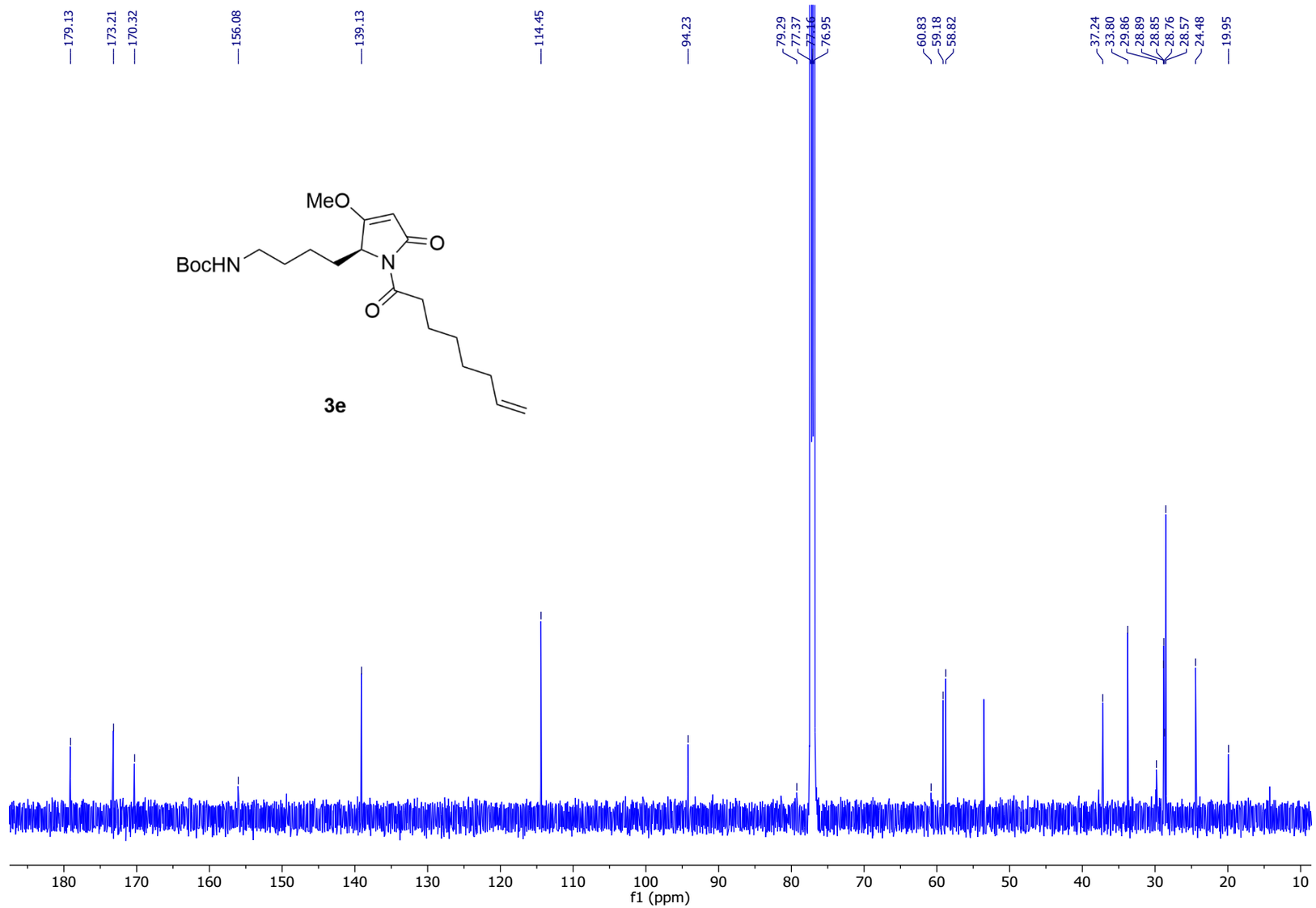


Figure S77. ^{13}C NMR spectrum of **3e** in $CDCl_3$ (150 MHz) at 27 °C.

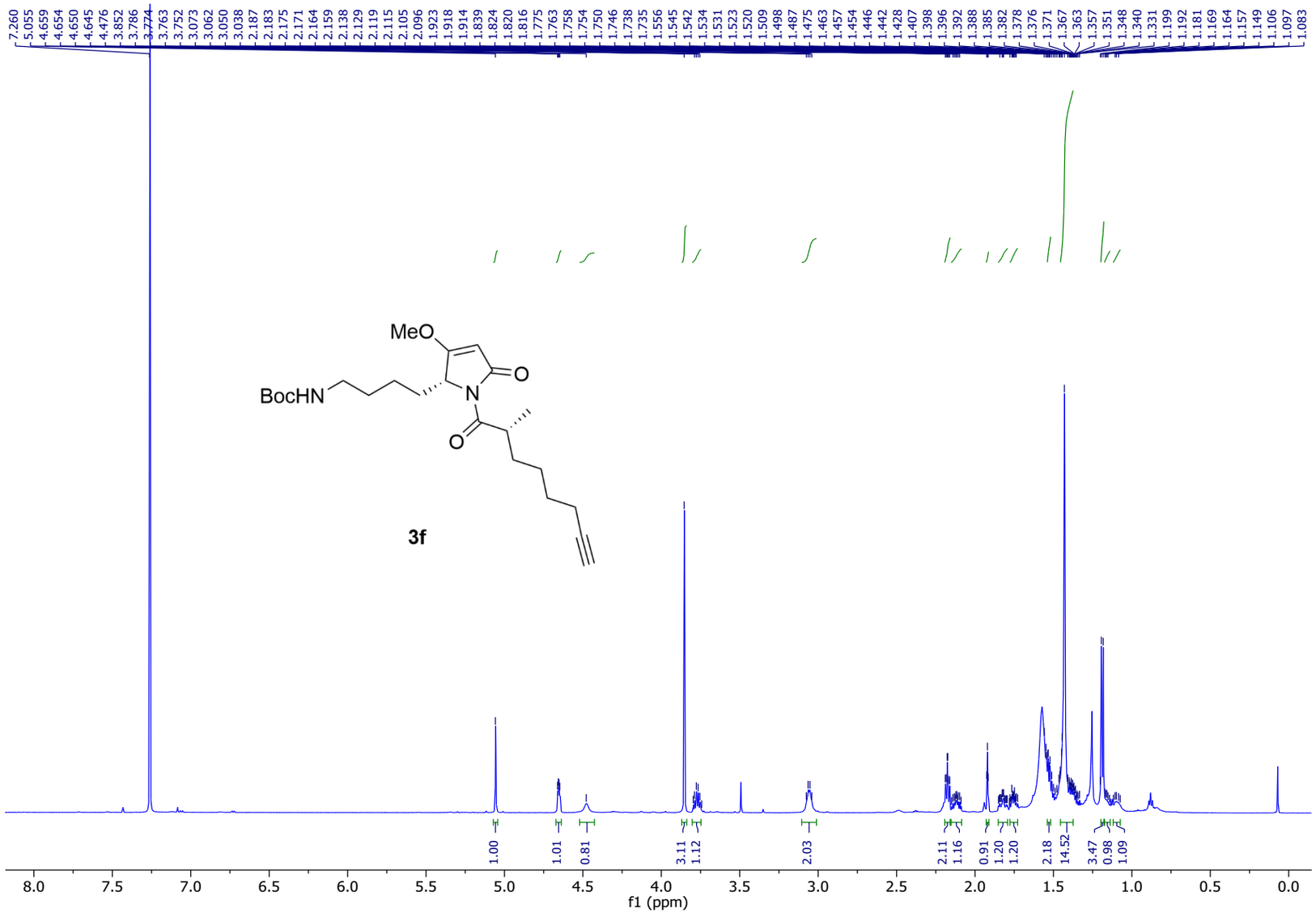


Figure S78. ^{1}H NMR spectrum of **3f** in $CDCl_3$ (600 MHz) at 27 °C.

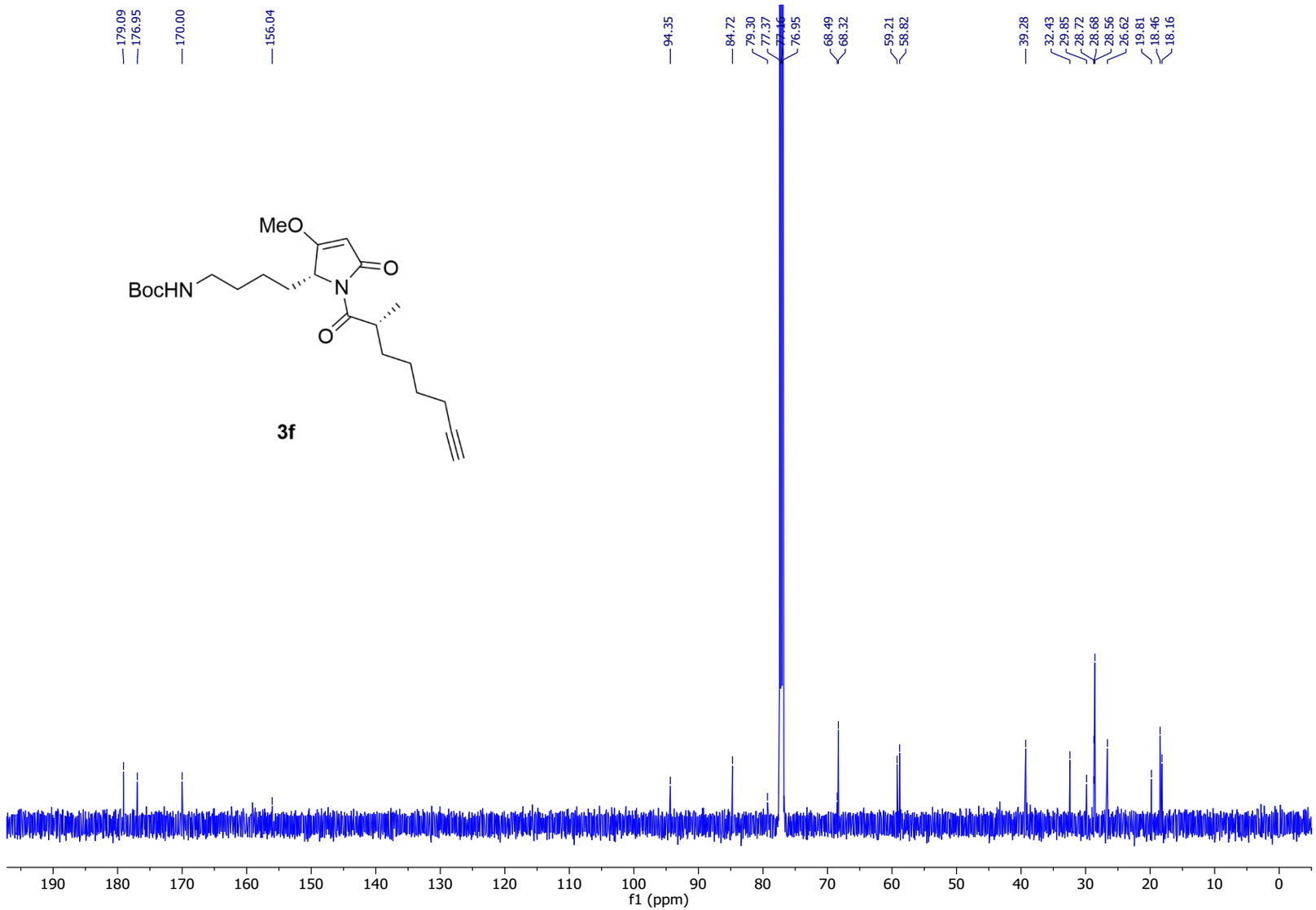


Figure S79. ^{13}C NMR spectrum of **3f** in $CDCl_3$ (150 MHz) at 27 °C.

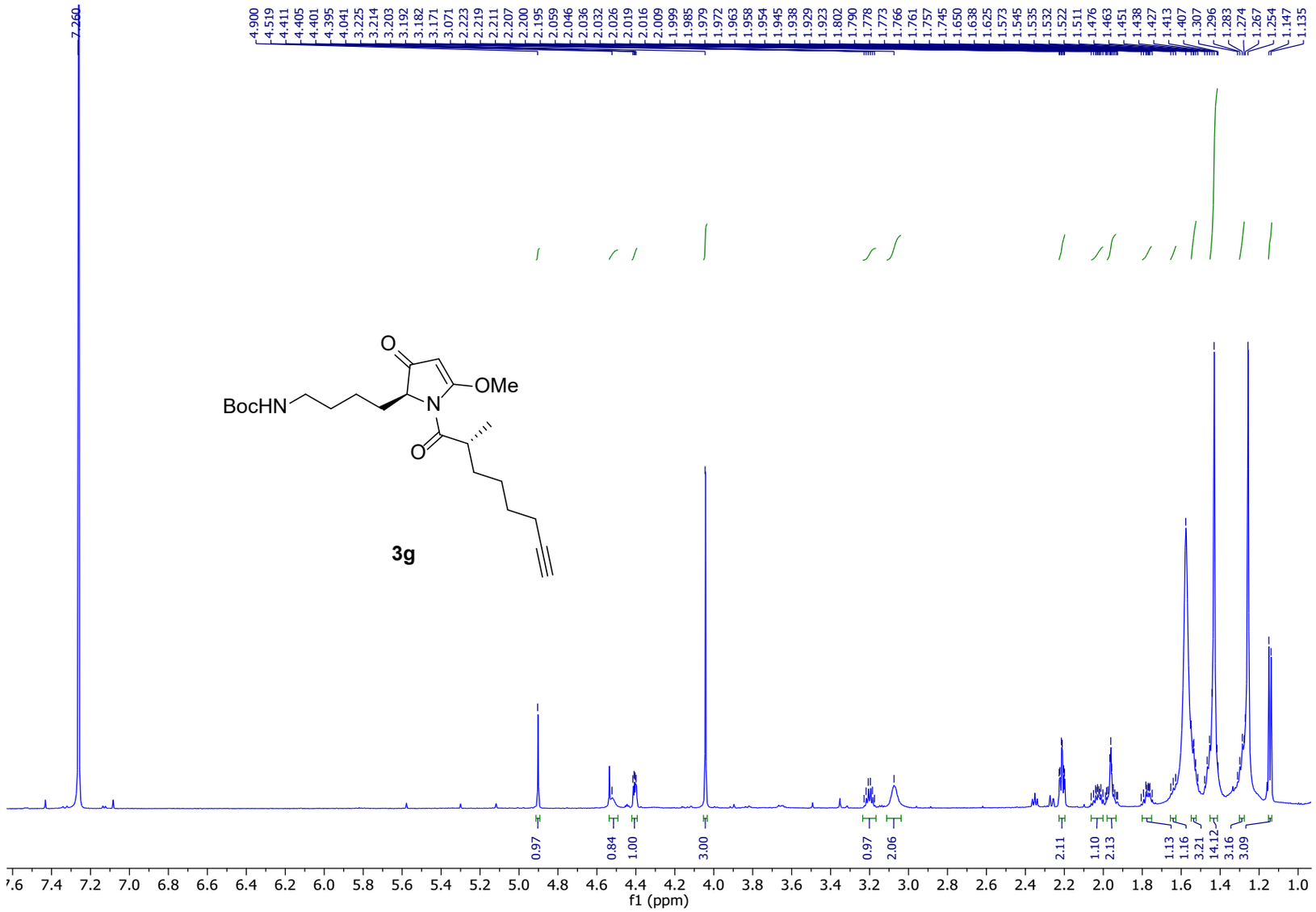


Figure S80. ^{1}H NMR spectrum of **3g** in $CDCl_3$ (600 MHz) at 27 °C.

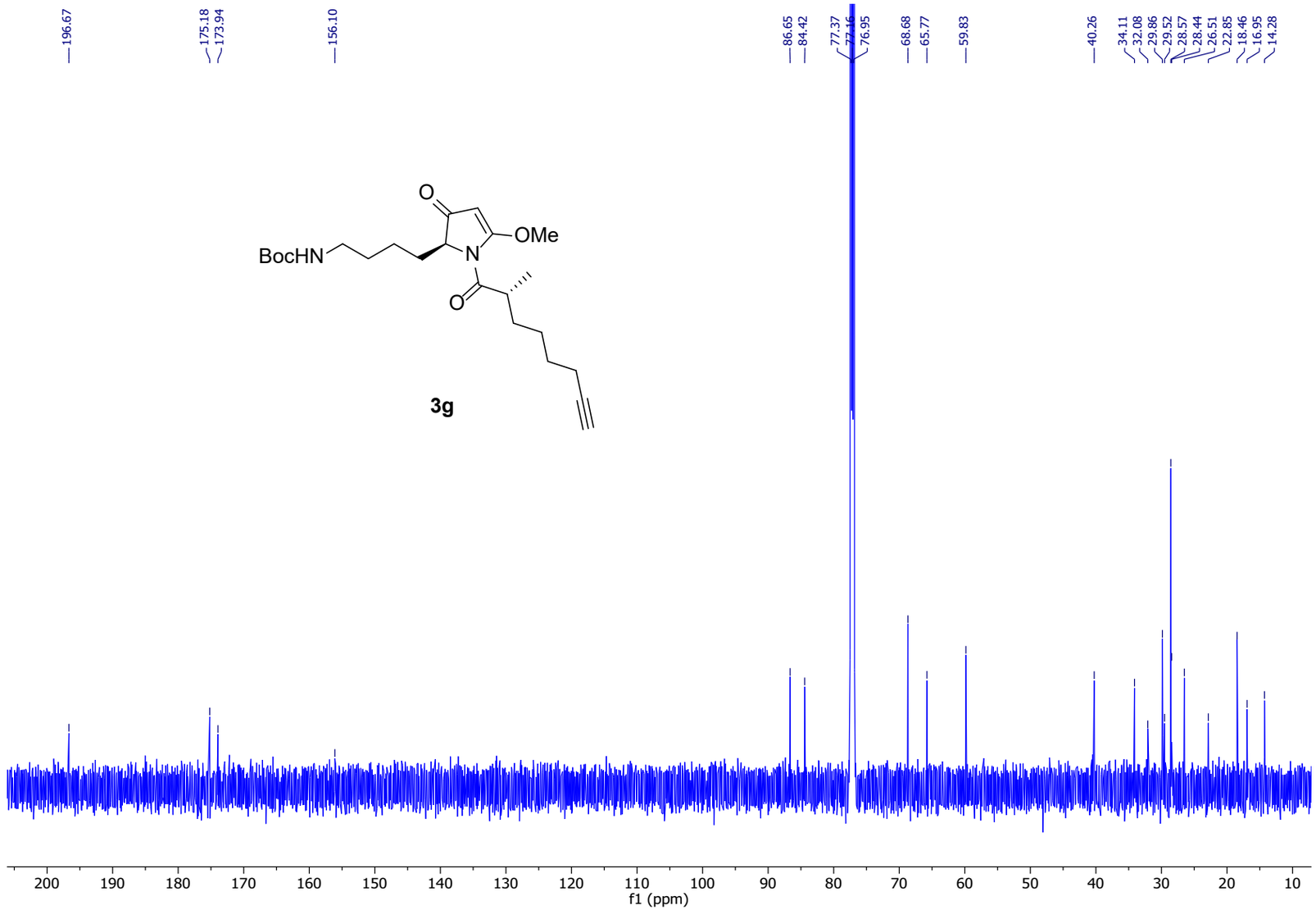


Figure S81. ^{13}C NMR spectrum of **3g** in $CDCl_3$ (150 MHz) at 27 °C.

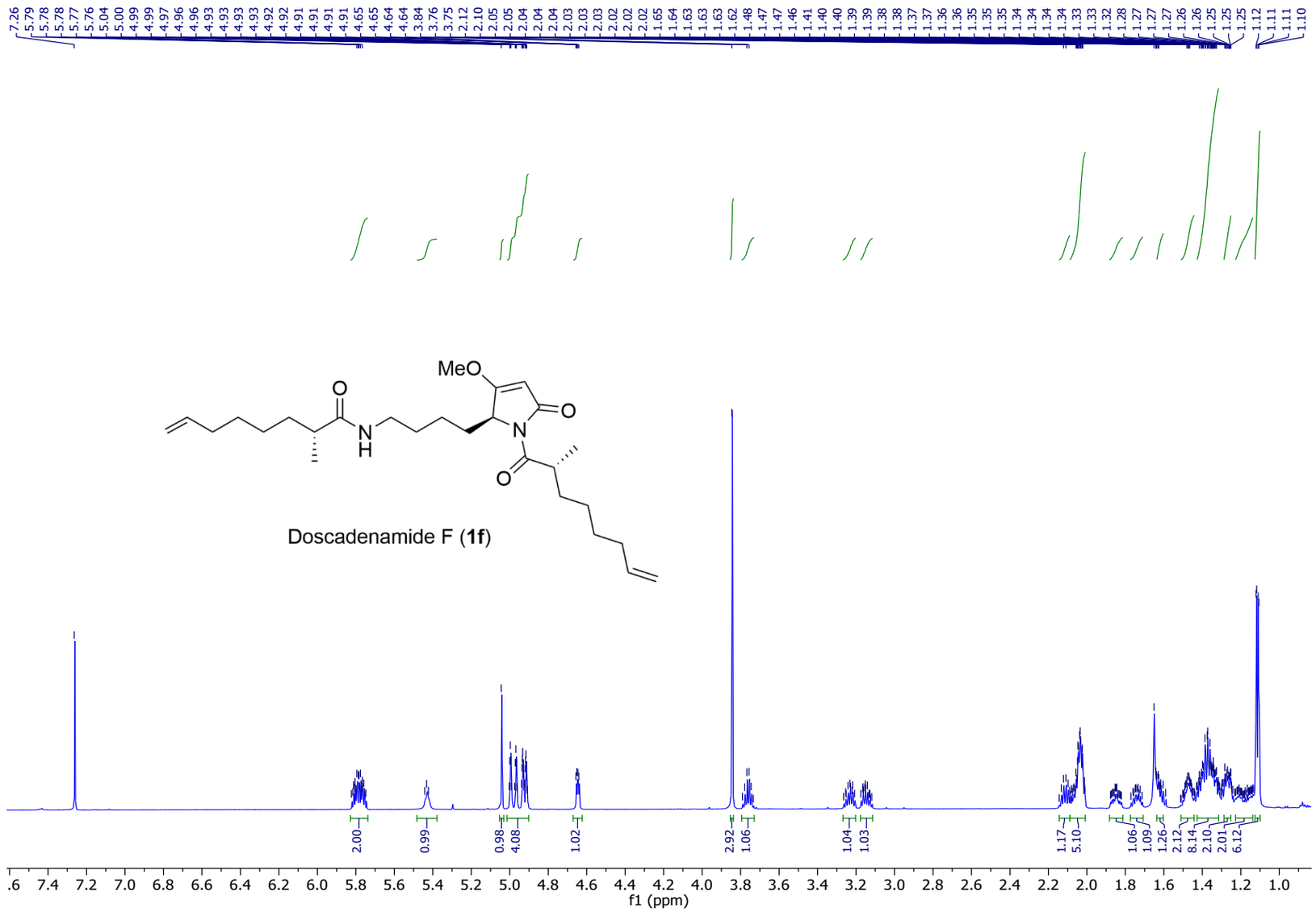


Figure S82. ^{1}H NMR spectrum of synthetic doscadenamide F (**1f**) in $CDCl_3$ (600 MHz) at 27 °C.

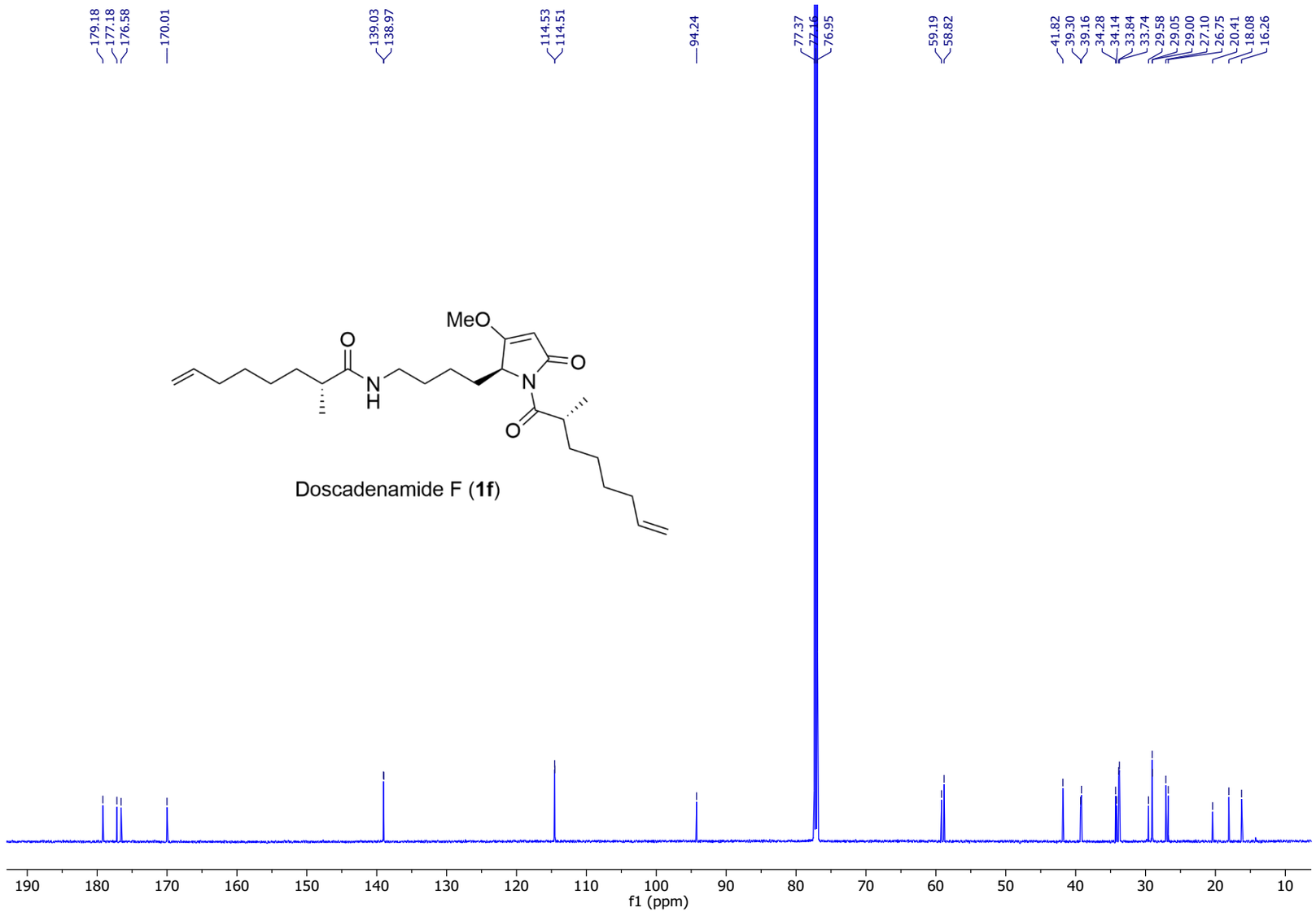


Figure S83. ^{13}C NMR spectrum of synthetic doscadenamide F (**1f**) in $CDCl_3$ (150 MHz) at 27 °C.

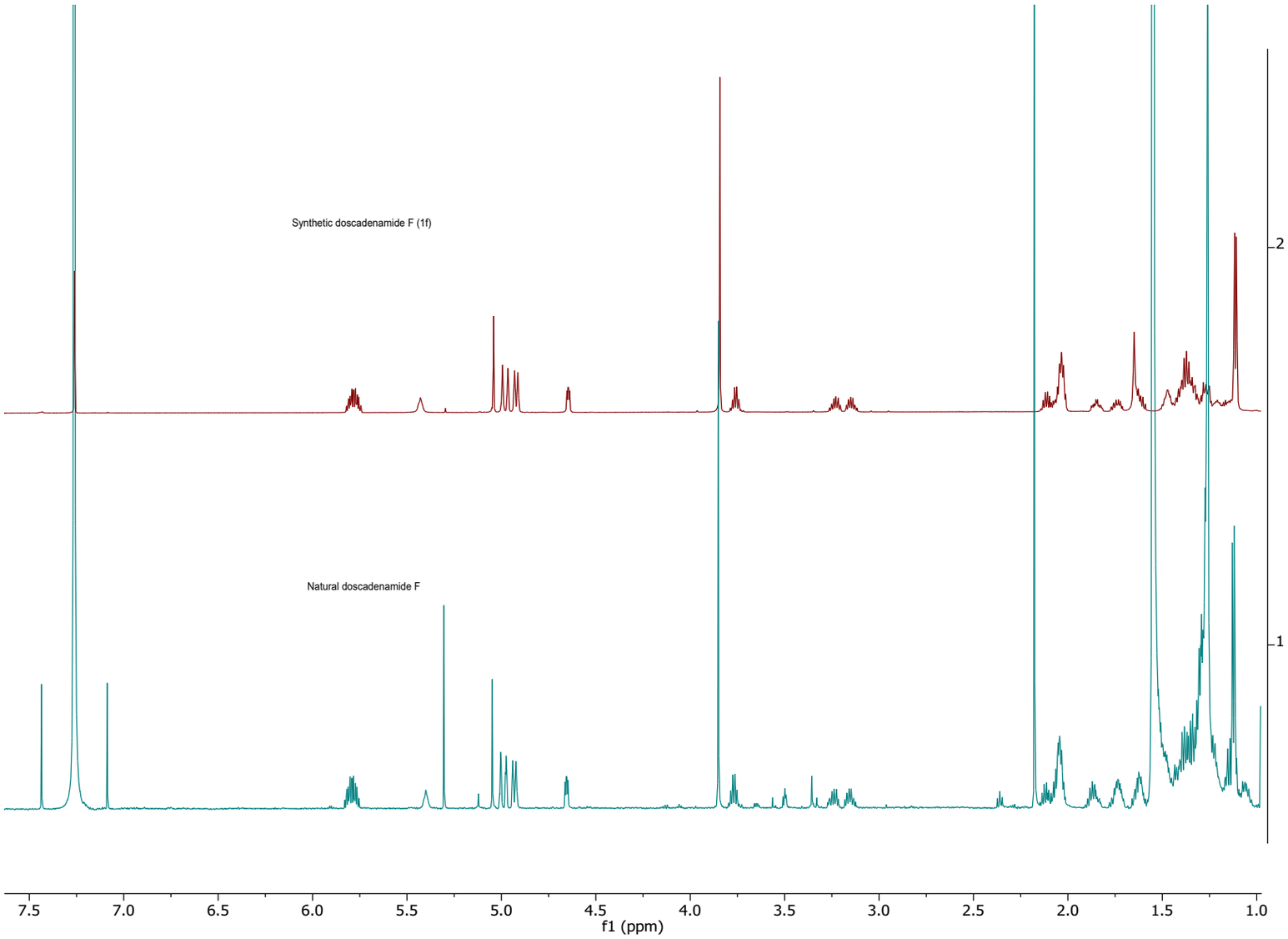


Figure S84. Comparison of ^{1}H NMR spectrum of synthetic doscadenamide F (**1f**) and natural doscadenamide F in $CDCl_3$ (600 MHz) at 27 °C.

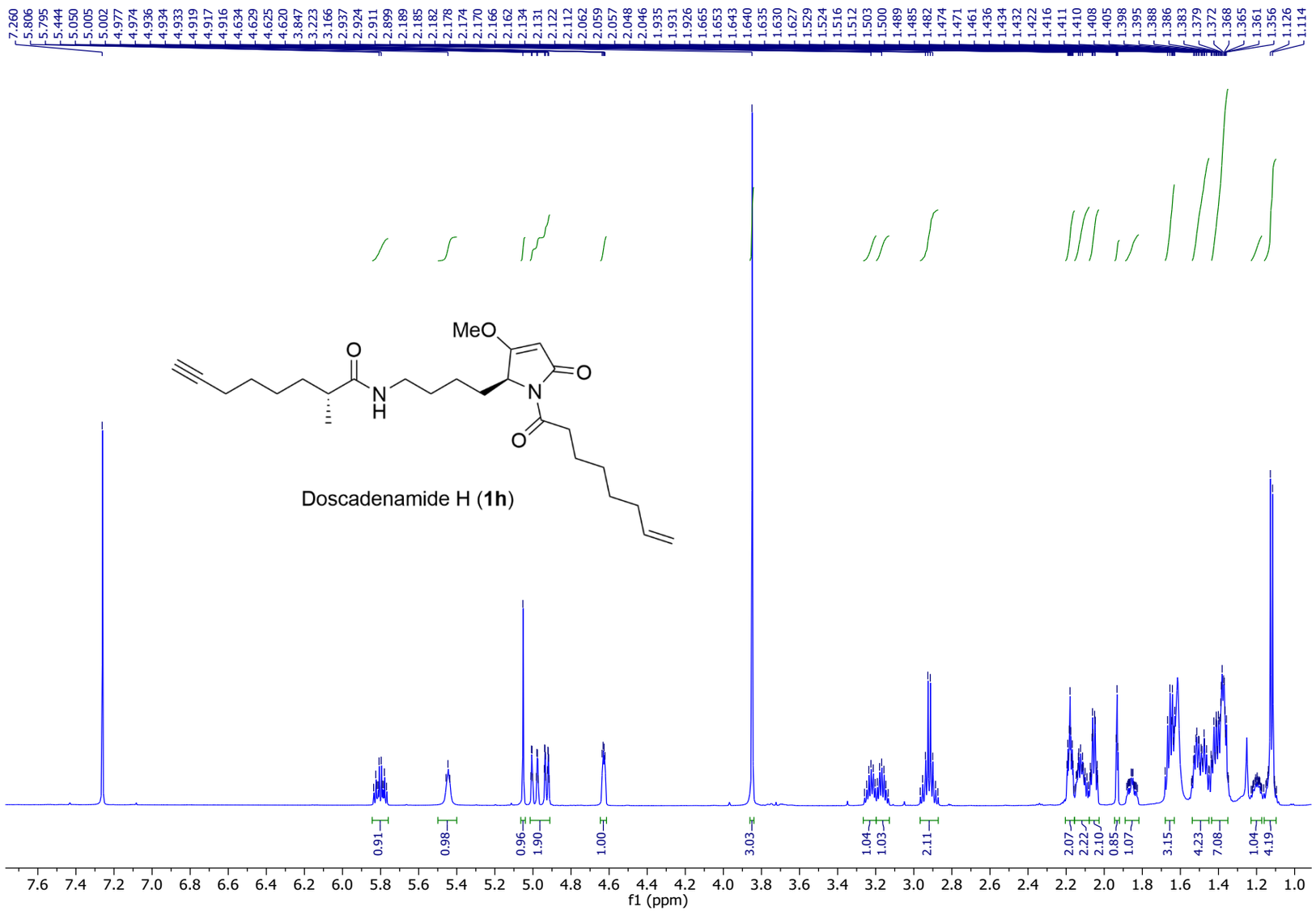


Figure S85. ^{1}H NMR spectrum of synthetic doscadenamide H (**1h**) in $CDCl_3$ (600 MHz) at 27 °C.

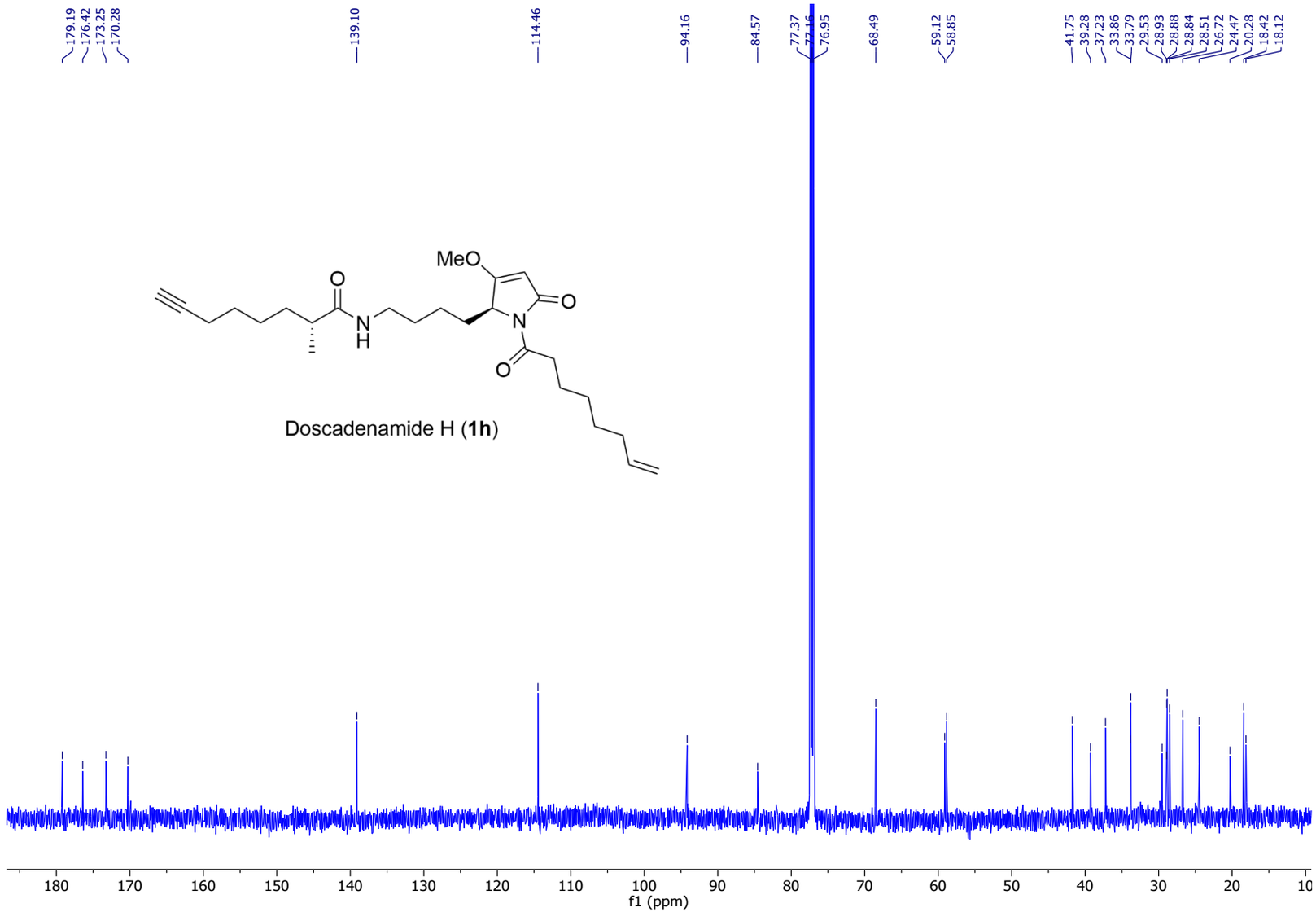


Figure S86. ^{13}C NMR spectrum of synthetic doscadenamide H (**1h**) in $CDCl_3$ (150 MHz) at 27 °C.

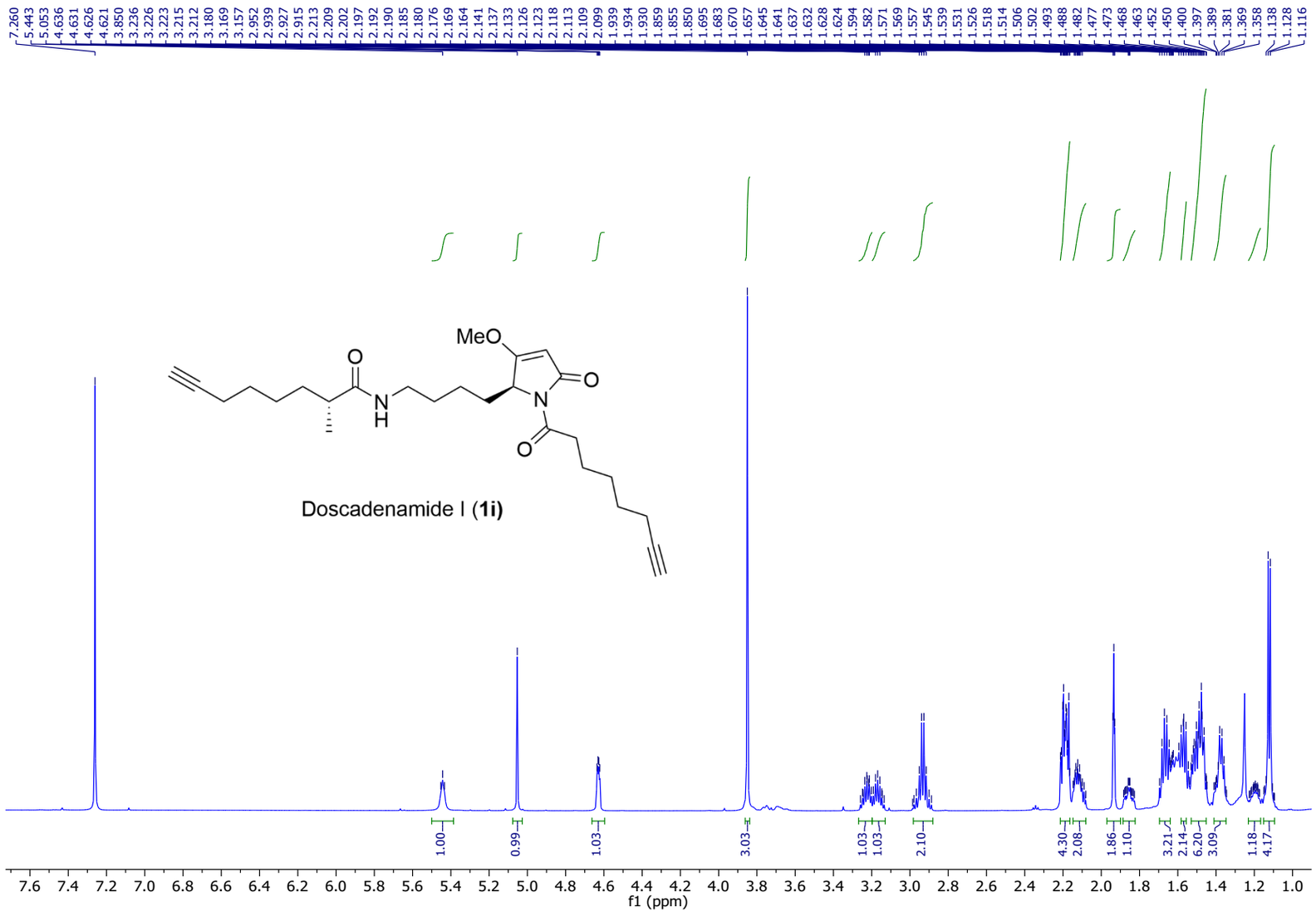


Figure S87. ^{1}H NMR spectrum of synthetic doscadenamide I (**1i**) in $CDCl_3$ (600 MHz) at 27 °C.

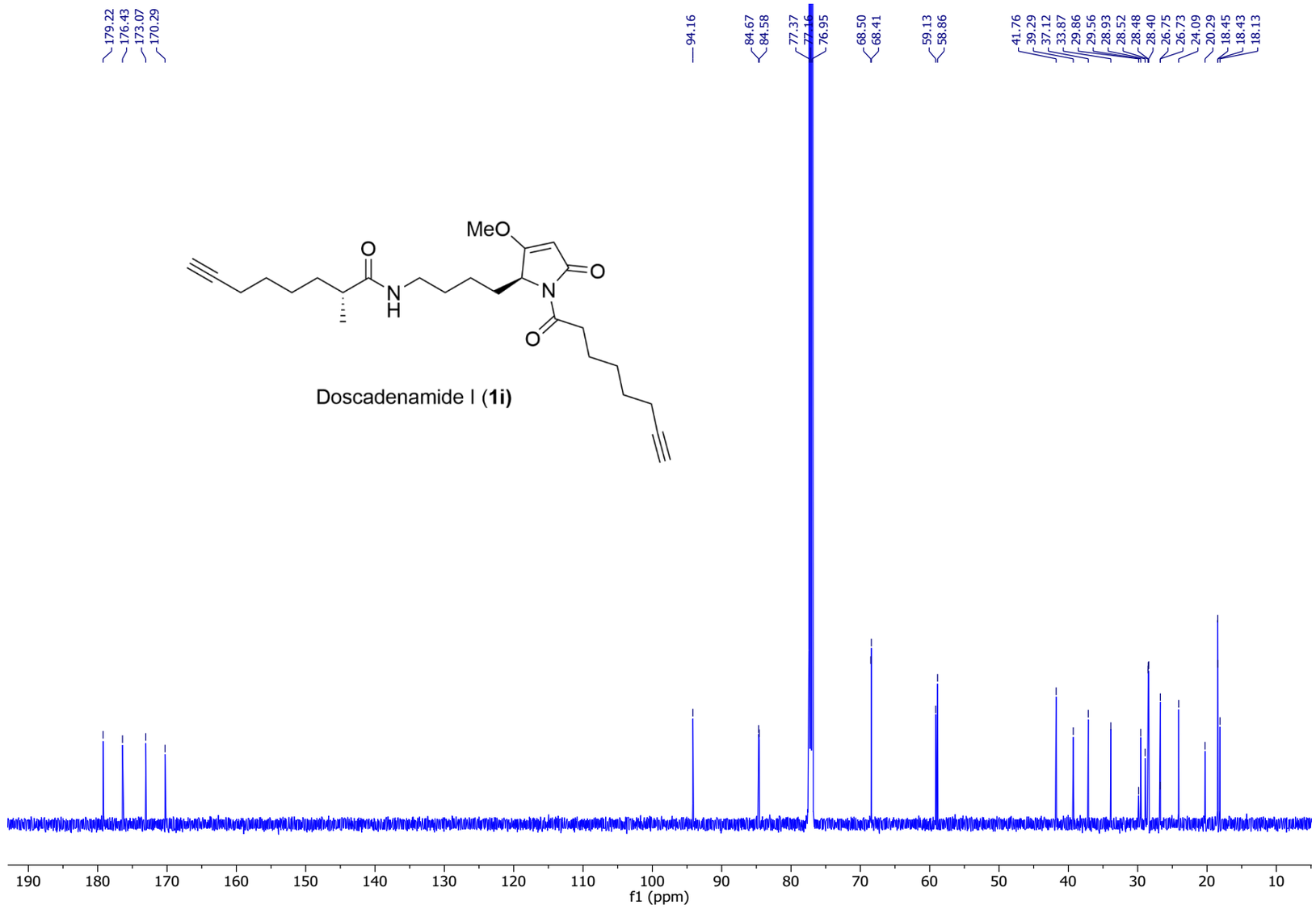


Figure S88. ^{13}C NMR spectrum of synthetic doscadenamide I (**1i**) in $CDCl_3$ (150 MHz) at 27 °C.

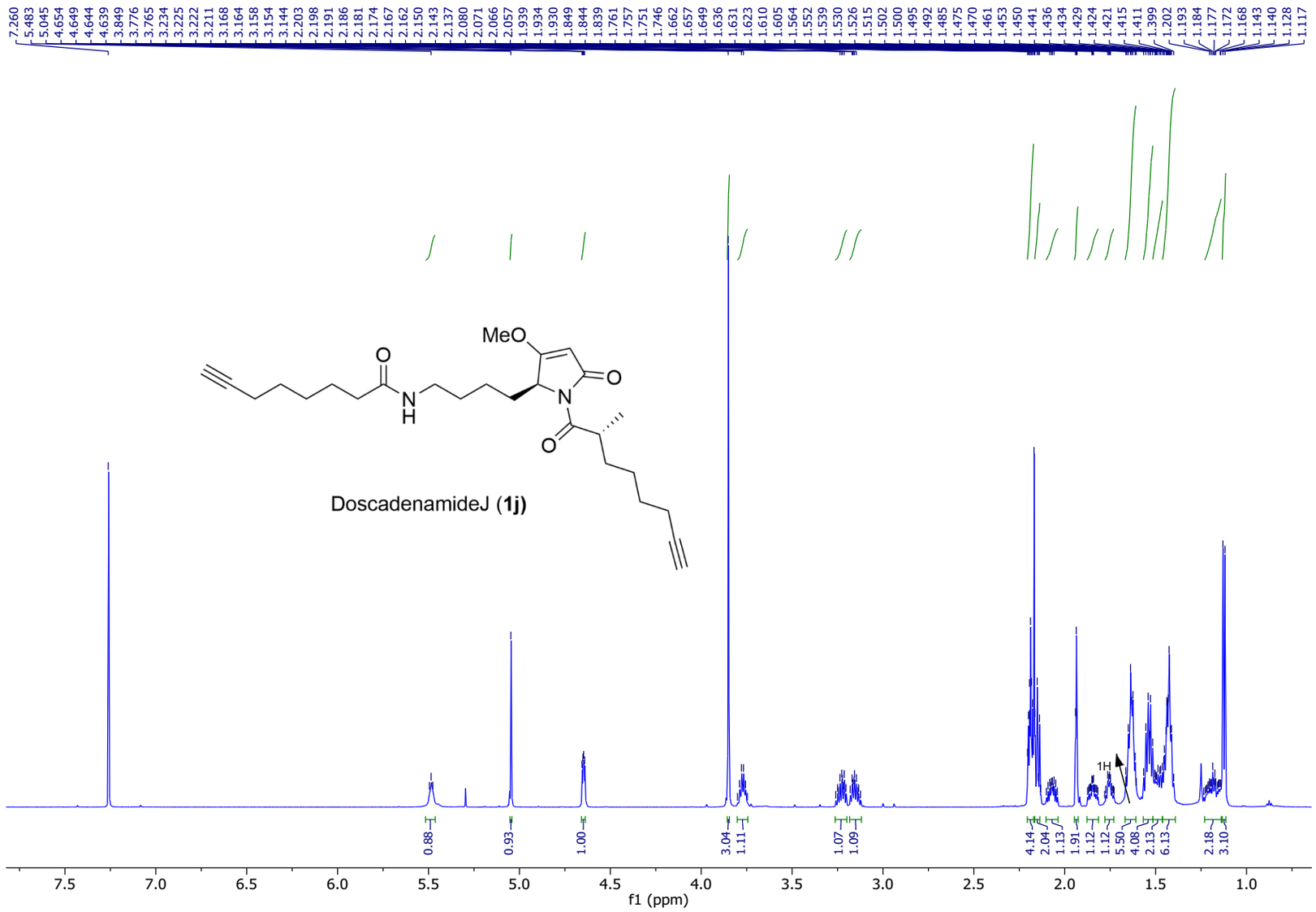


Figure S89. ^{1}H NMR spectrum of synthetic doscadenamide J (**1j**) in $CDCl_3$ (600 MHz) at 27 °C.

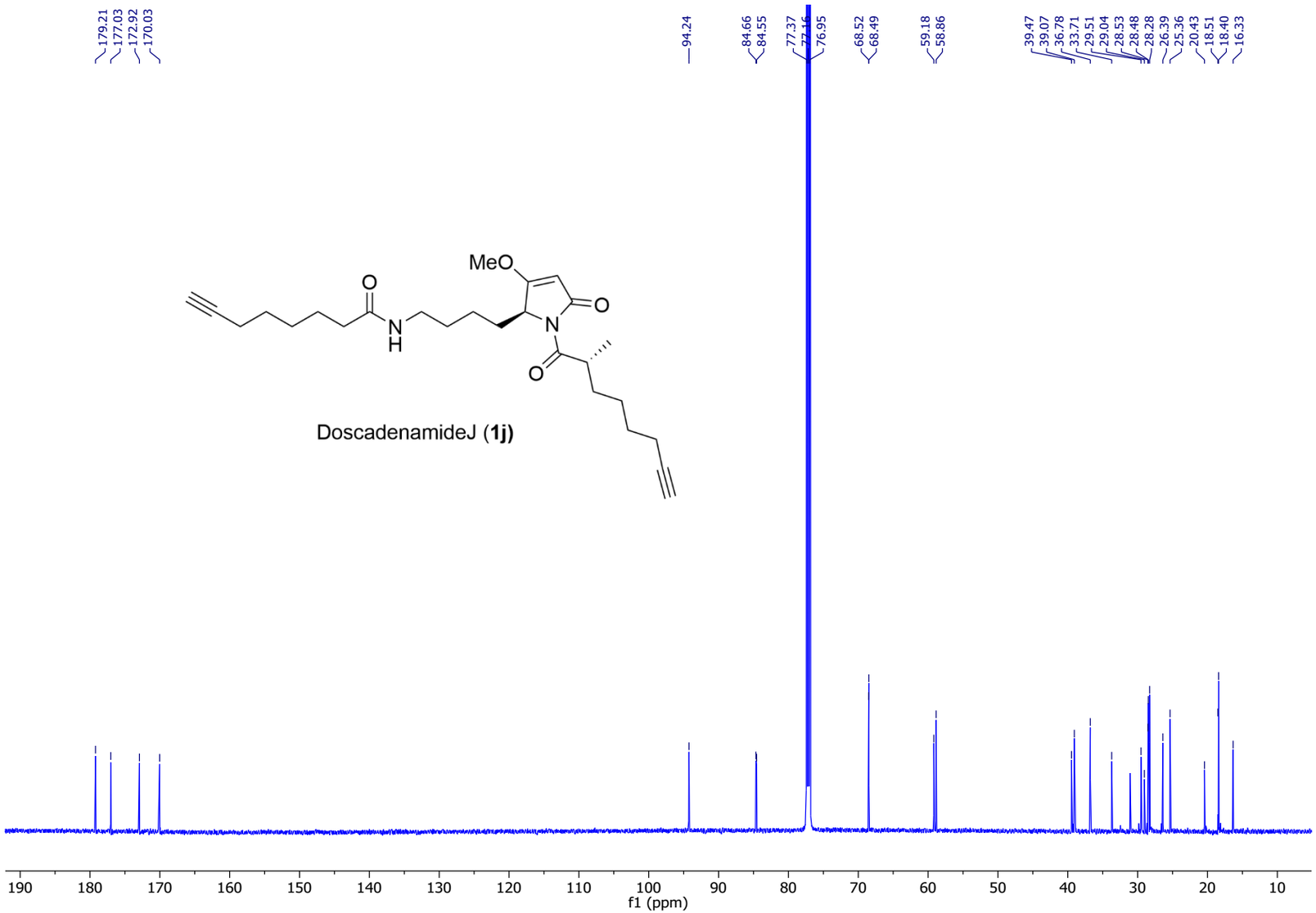


Figure S90. ^{13}C NMR spectrum of synthetic doscadenamide J (**1j**) in $CDCl_3$ (150 MHz) at 27 °C.

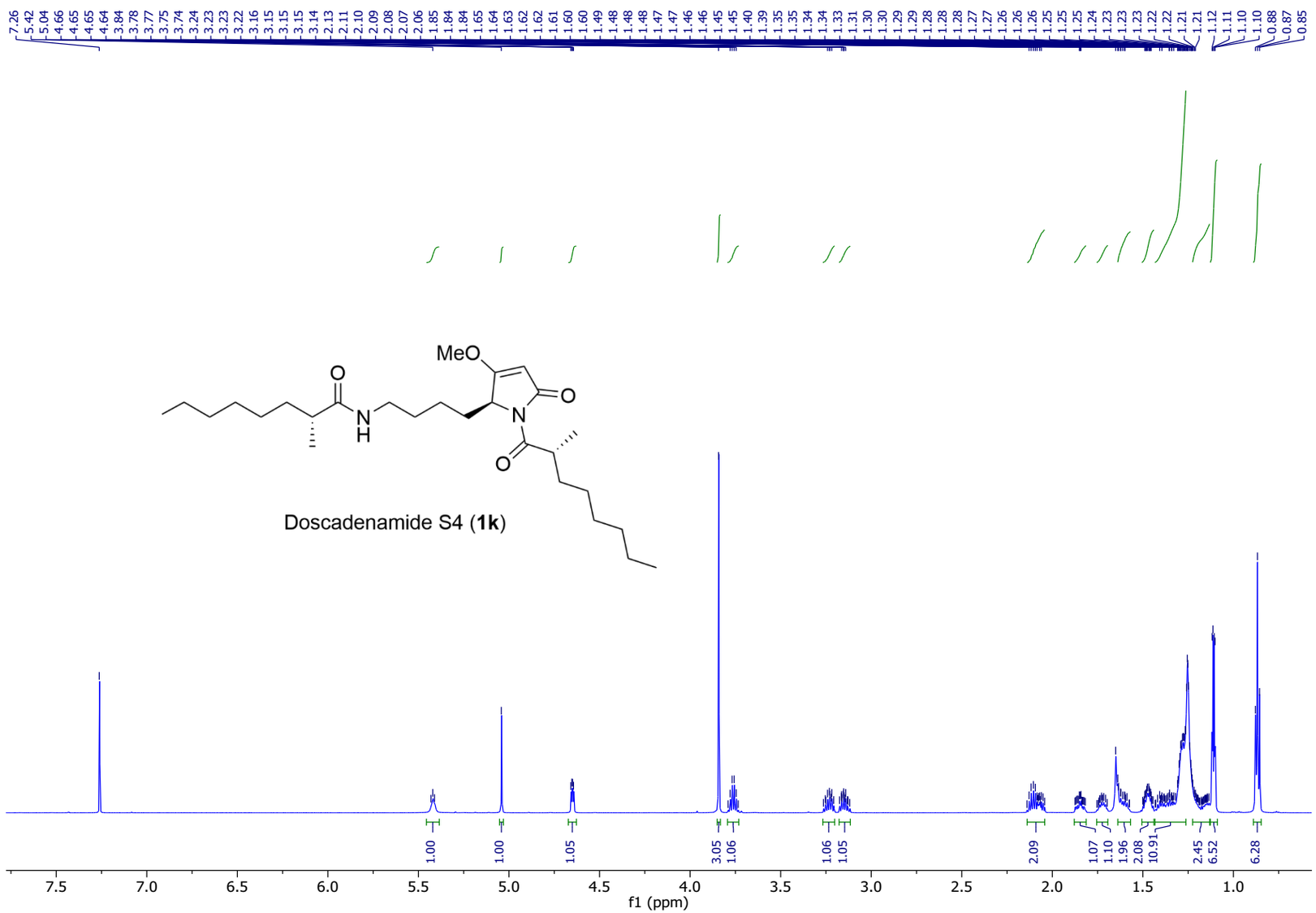


Figure S91. ^{1}H NMR spectrum of synthetic doscadenamide S4 (**1k**) in $CDCl_3$ (600 MHz) at 27 °C.

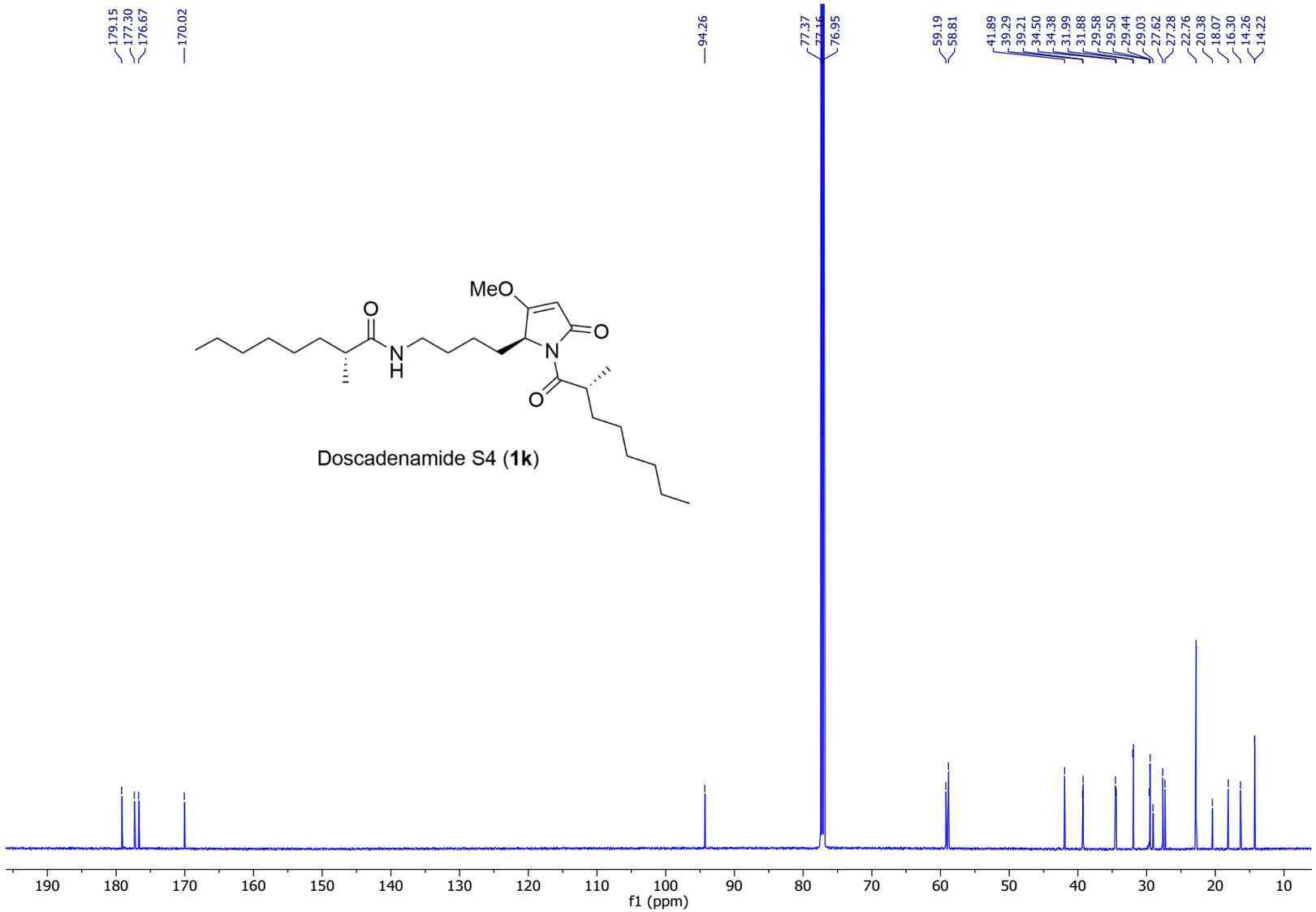


Figure S92. ^{13}C NMR spectrum of synthetic doscadenamide S4 (**1k**) in $CDCl_3$ (150 MHz) at 27 °C.

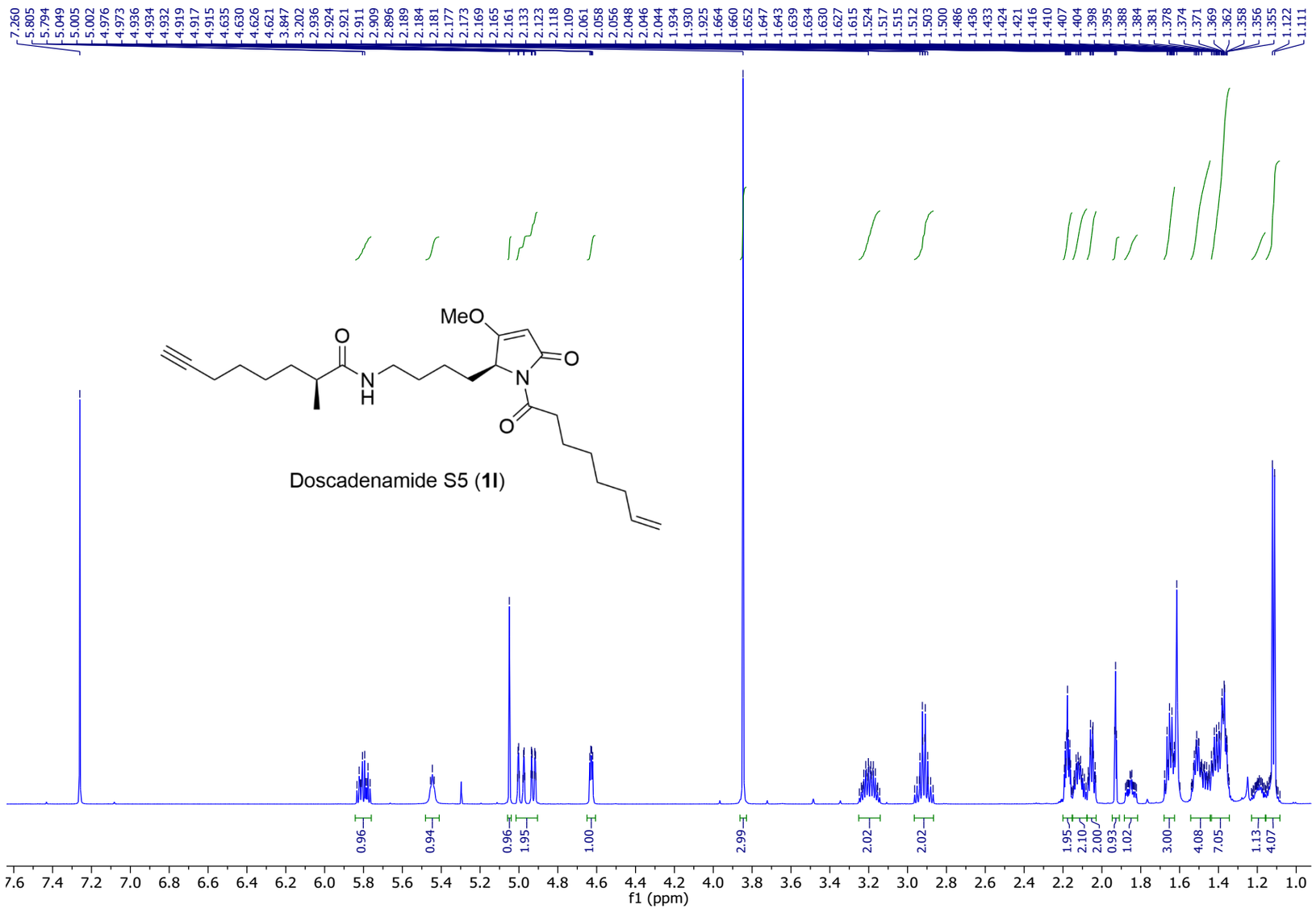


Figure S93. ^{1}H NMR spectrum of synthetic doscadenamide S5 (**1l**) in $CDCl_3$ (600 MHz) at 27 °C.

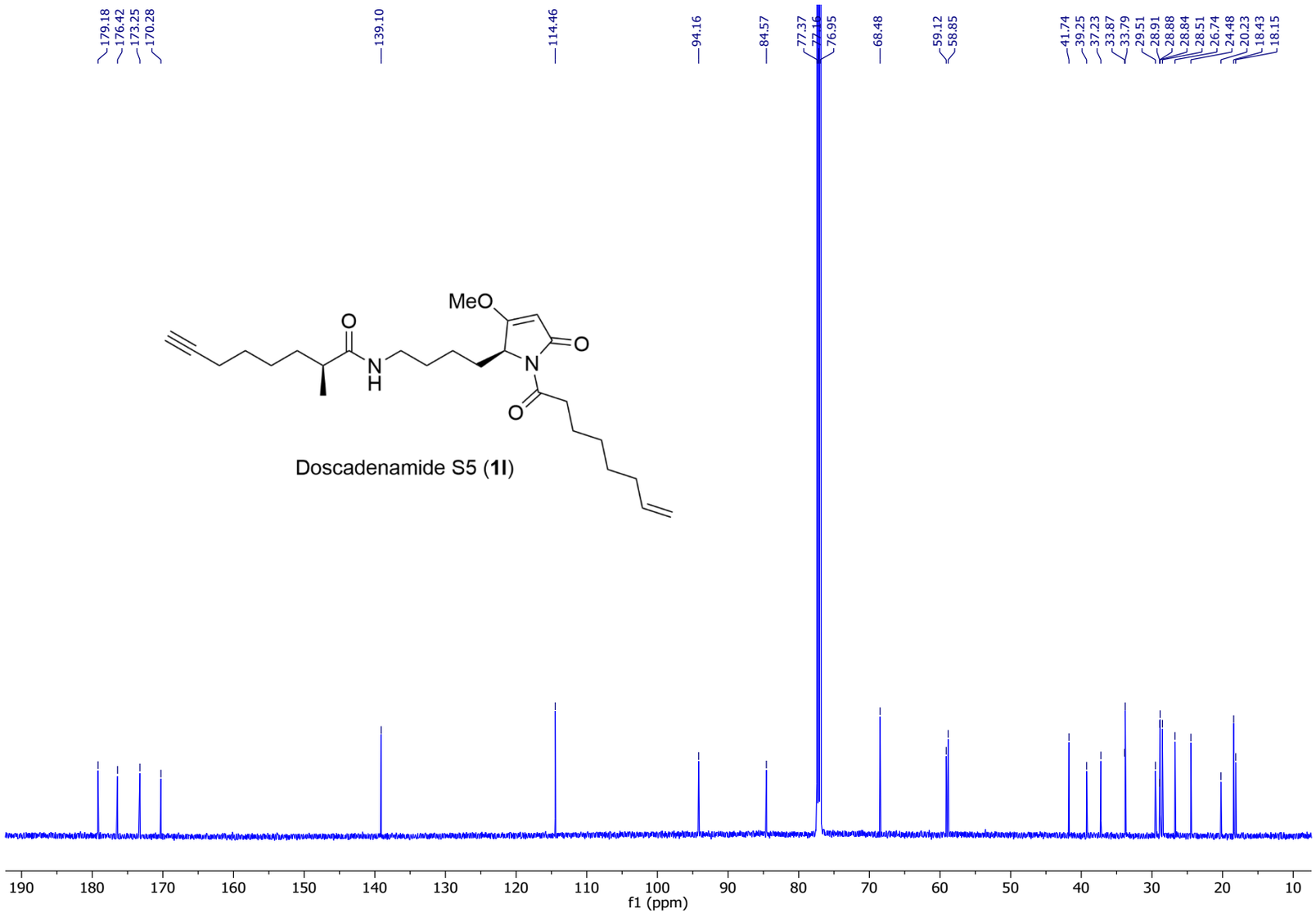


Figure S94. ^{13}C NMR spectrum of synthetic doscadenamide S5 (**1l**) in $CDCl_3$ (150 MHz) at 27 °C.

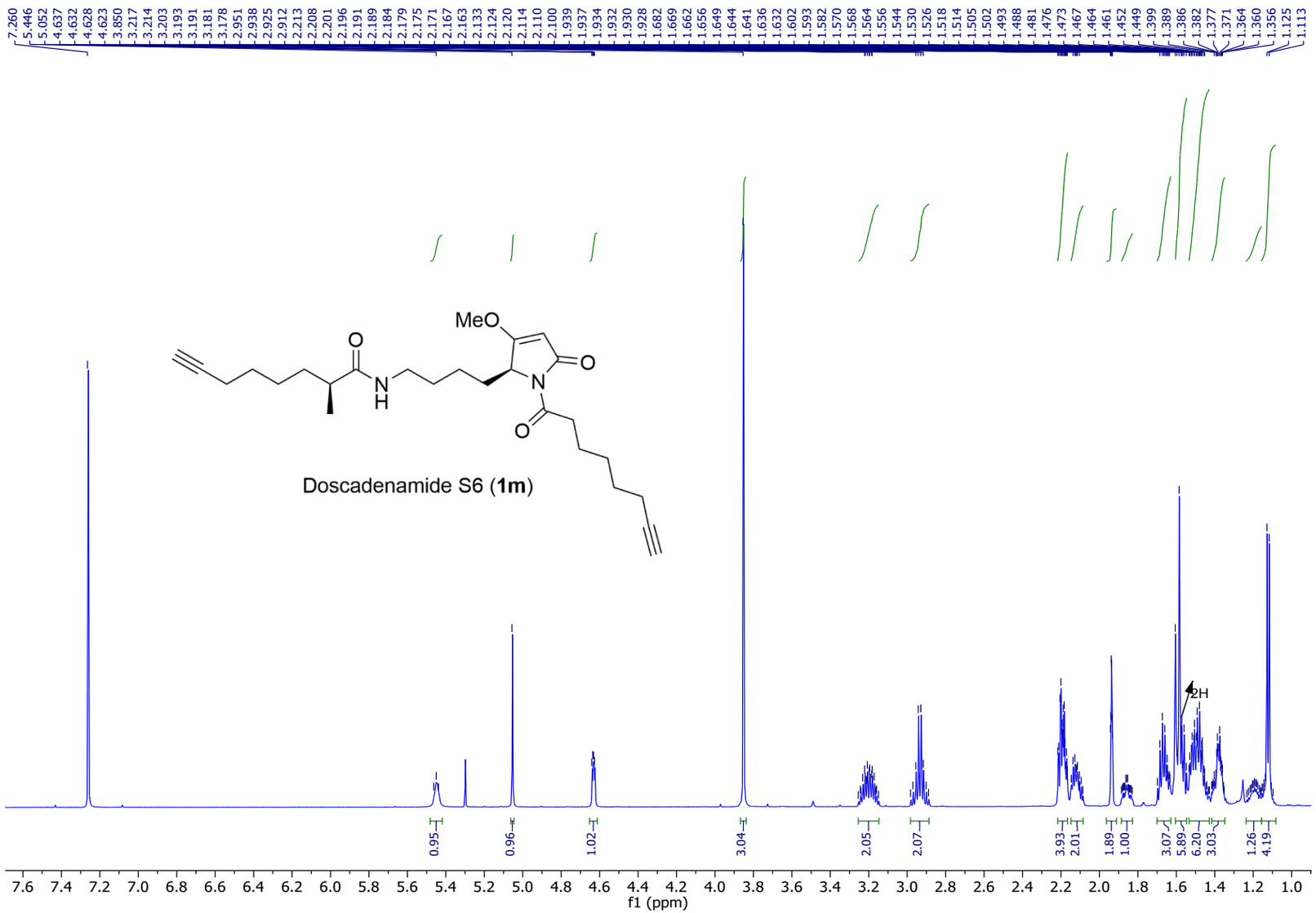


Figure S95. ^{1}H NMR spectrum of synthetic doscadenamide S6 (**1m**) in $CDCl_3$ (600 MHz) at 27 °C.

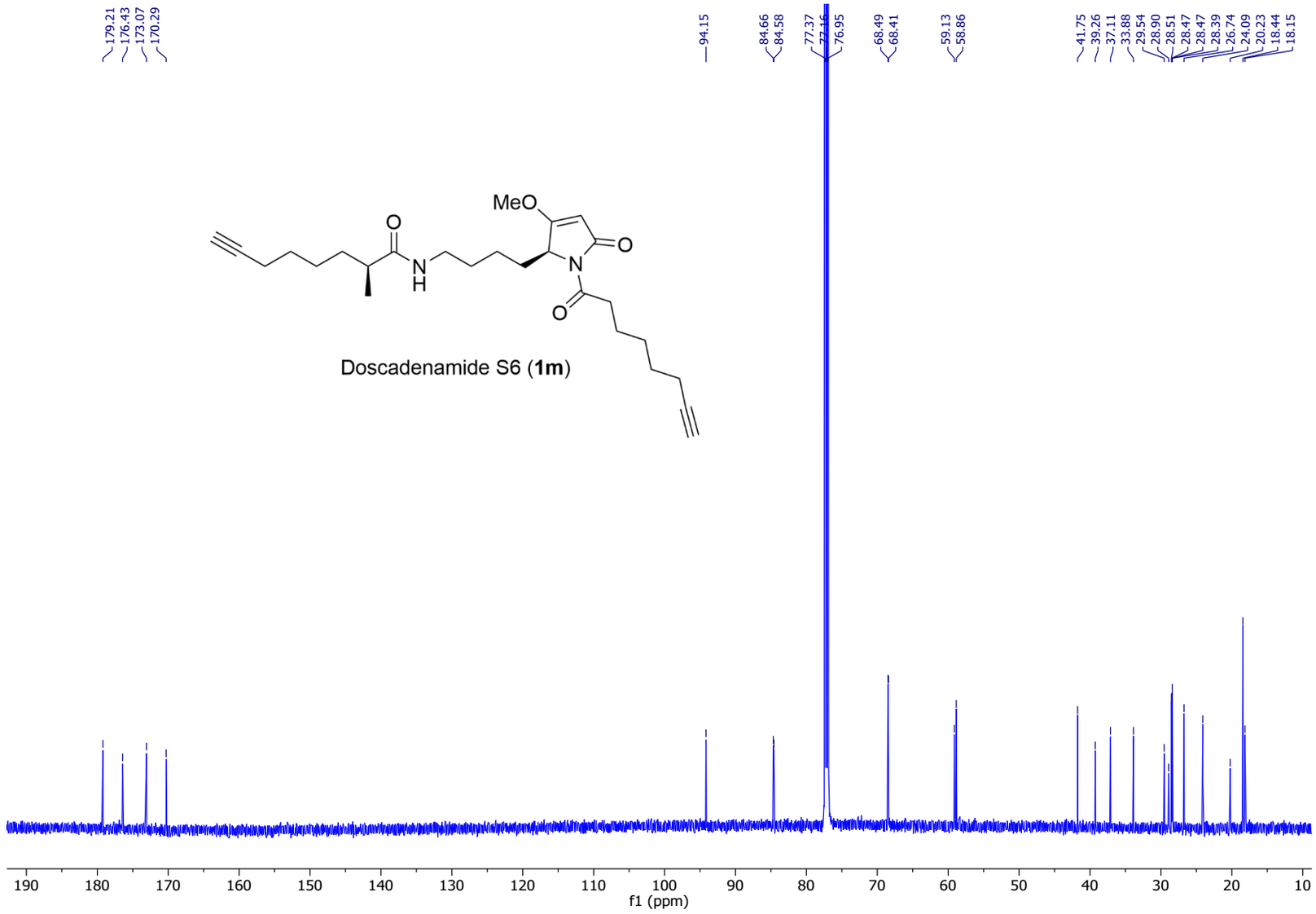


Figure S96. ^{13}C NMR spectrum of synthetic doscadenamide S6 (**1m**) in $CDCl_3$ (600 MHz) at 27 °C.

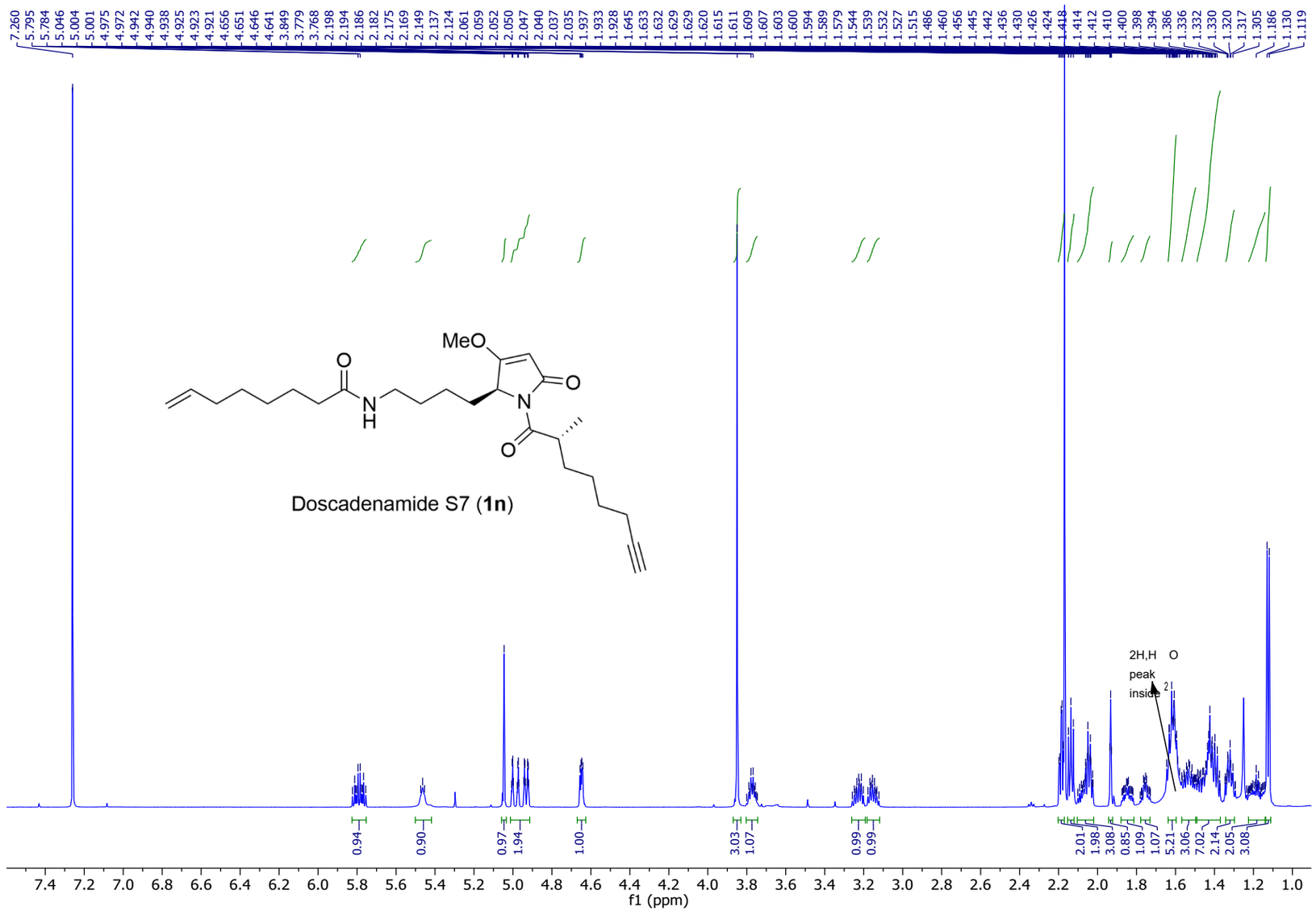


Figure S97. ^{1}H NMR spectrum of synthetic doscadenamide S7 (**1n**) in $CDCl_3$ (600 MHz) at 27 °C.

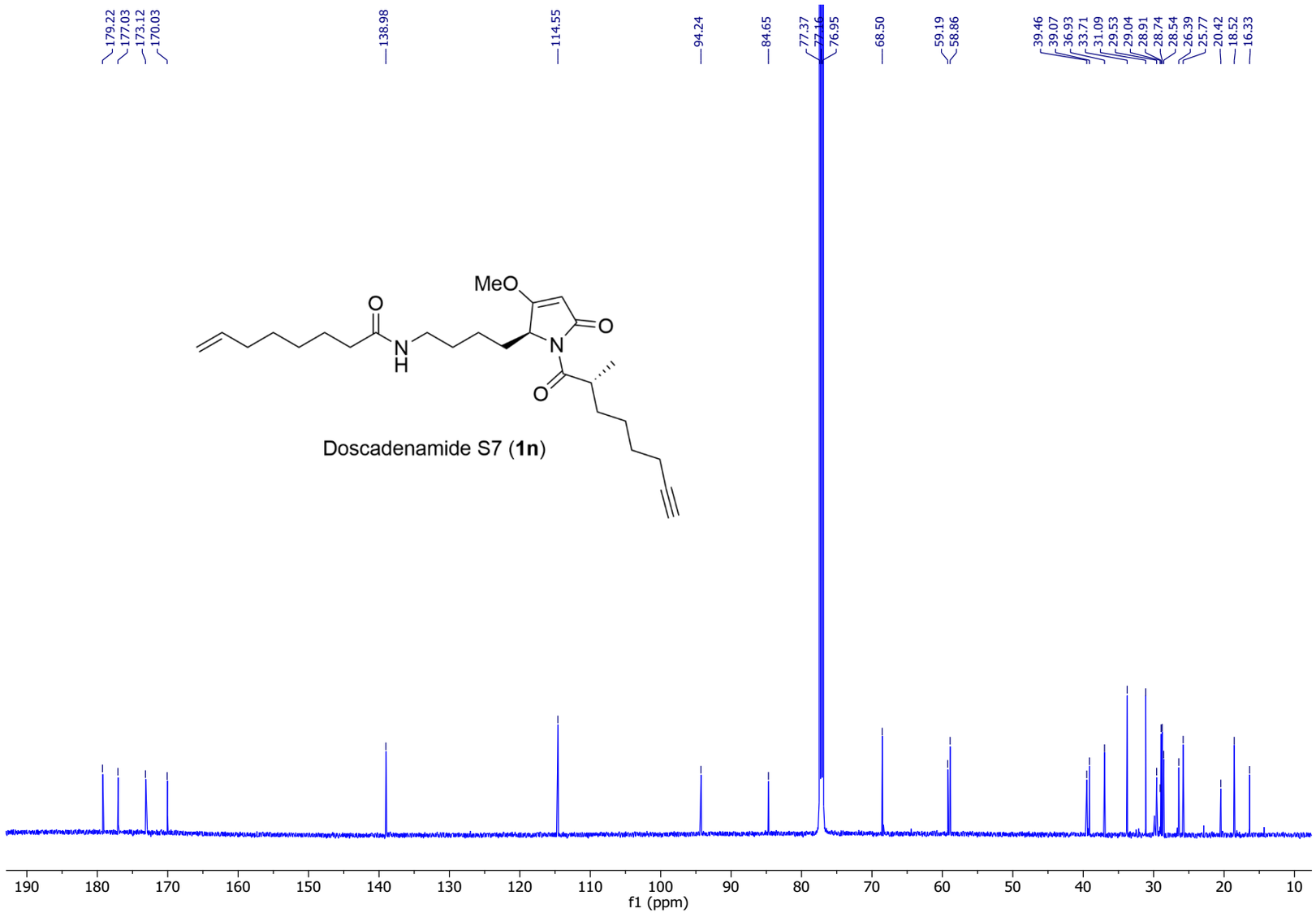


Figure S98. ^{13}C NMR spectrum of synthetic doscadenamide S7 (**1n**) in $CDCl_3$ (600 MHz) at 27 °C.

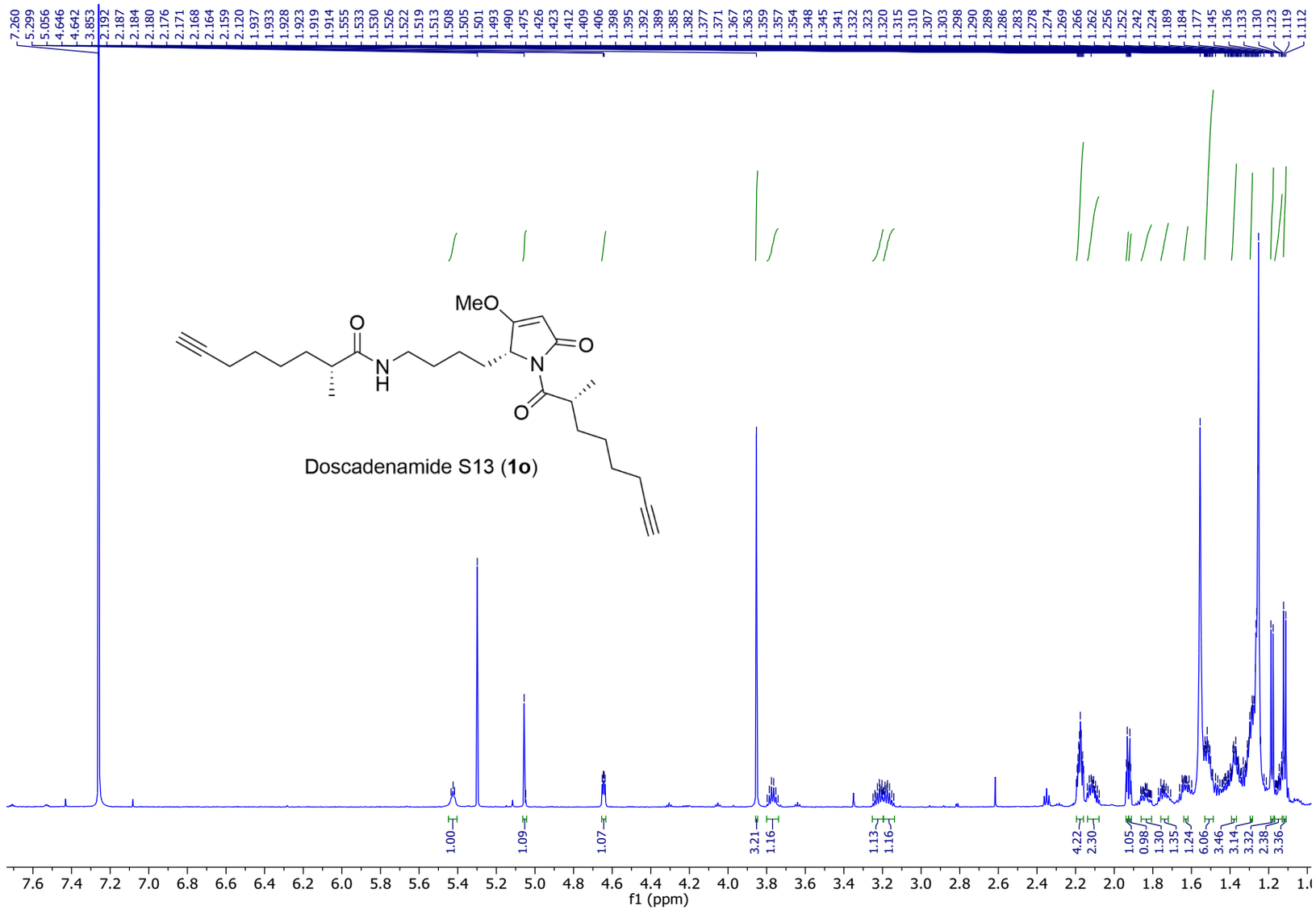


Figure S99. ^{1}H NMR spectrum of synthetic doscadenamide S13 (**1o**) in $CDCl_3$ (600 MHz) at 27 °C.

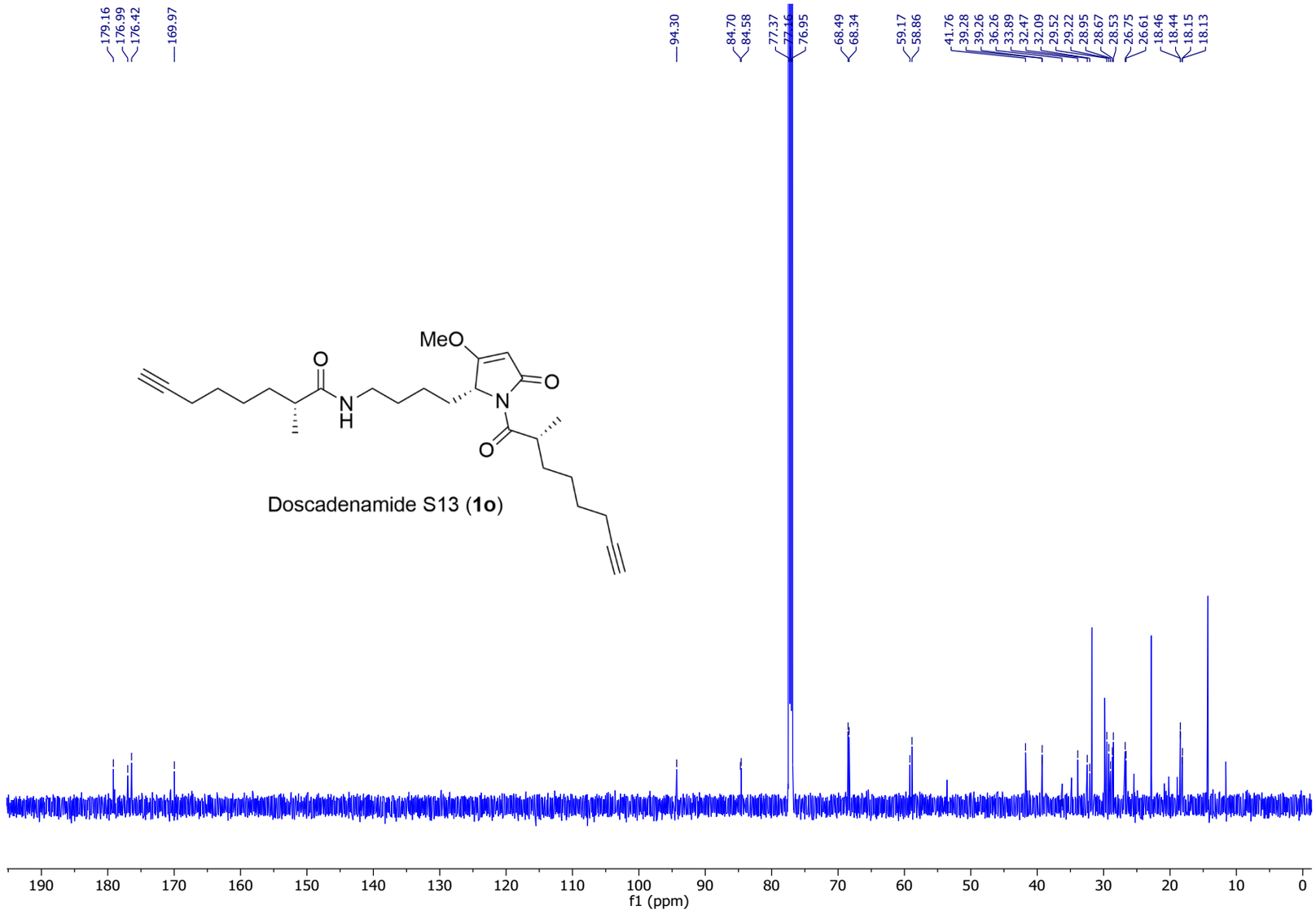


Figure S100. ^{13}C NMR spectrum of synthetic doscadenamide S13 (**1o**) in $CDCl_3$ (600 MHz) at 27 °C.

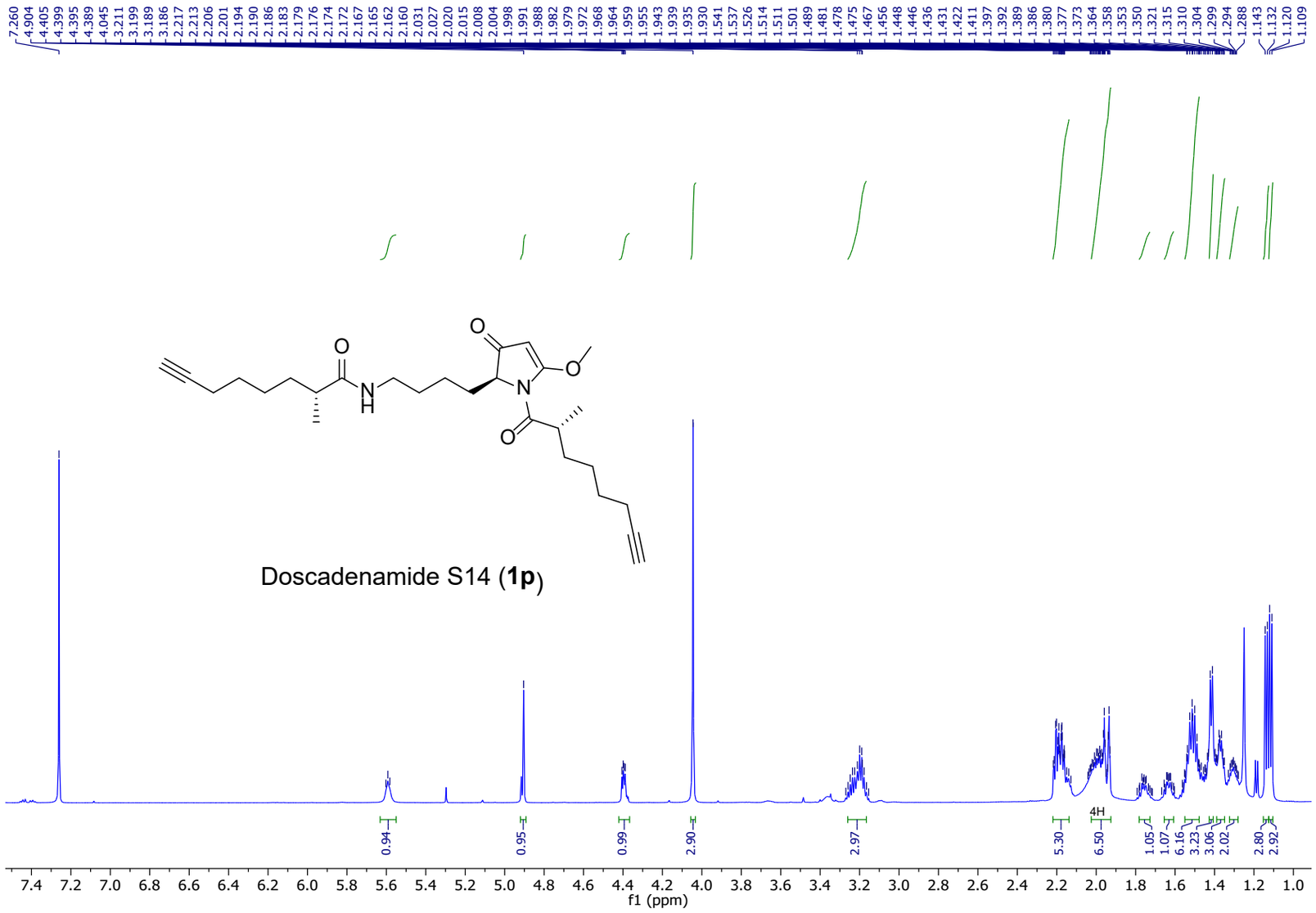


Figure S101. ^{1}H NMR spectrum of synthetic doscadenamide S14 (**1p**) in $CDCl_3$ (600 MHz) at 27 °C.

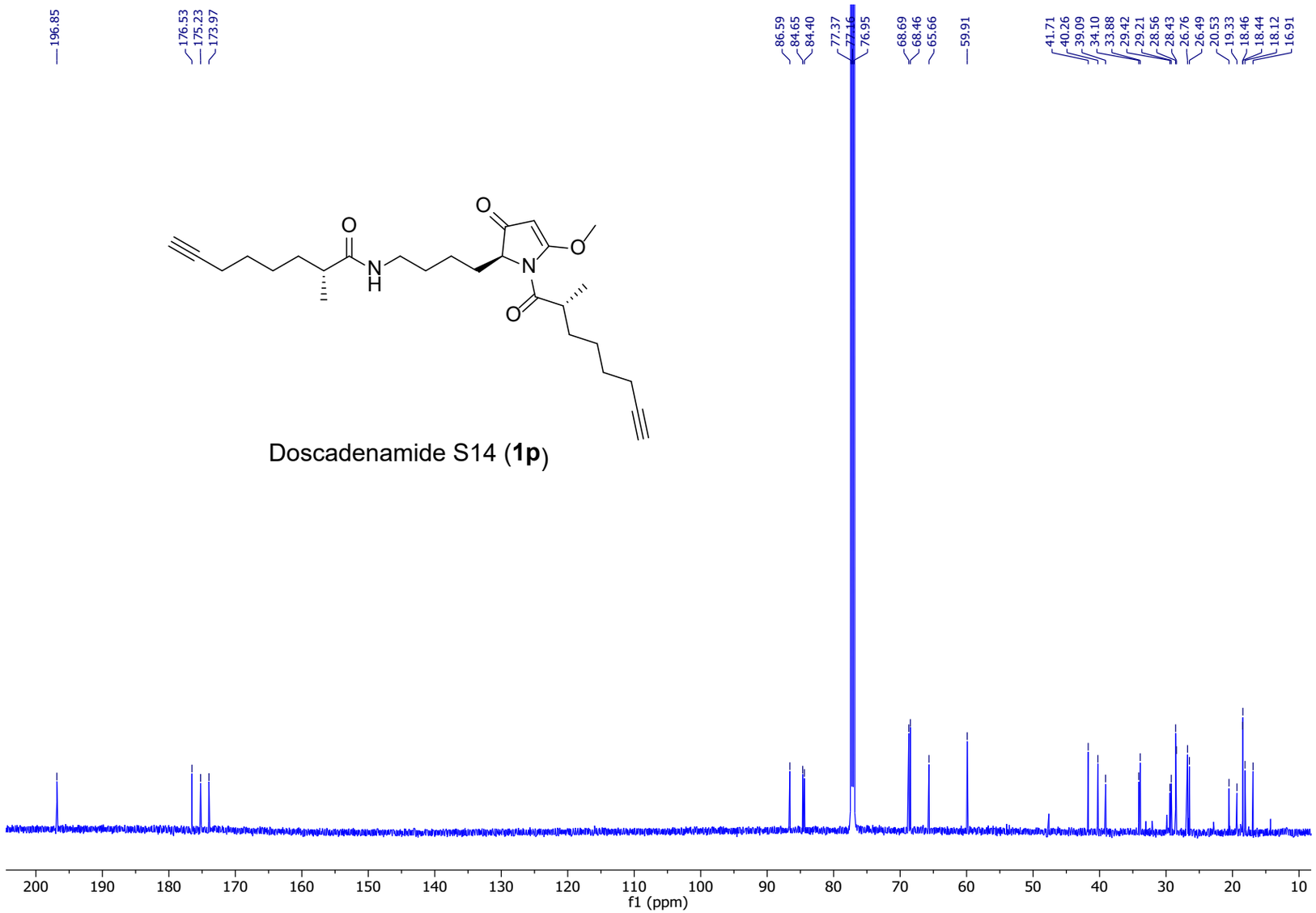


Figure S102. ^{13}C NMR spectrum of synthetic doscadenamide S14 (**1p**) in $CDCl_3$ (600 MHz) at 27 °C.

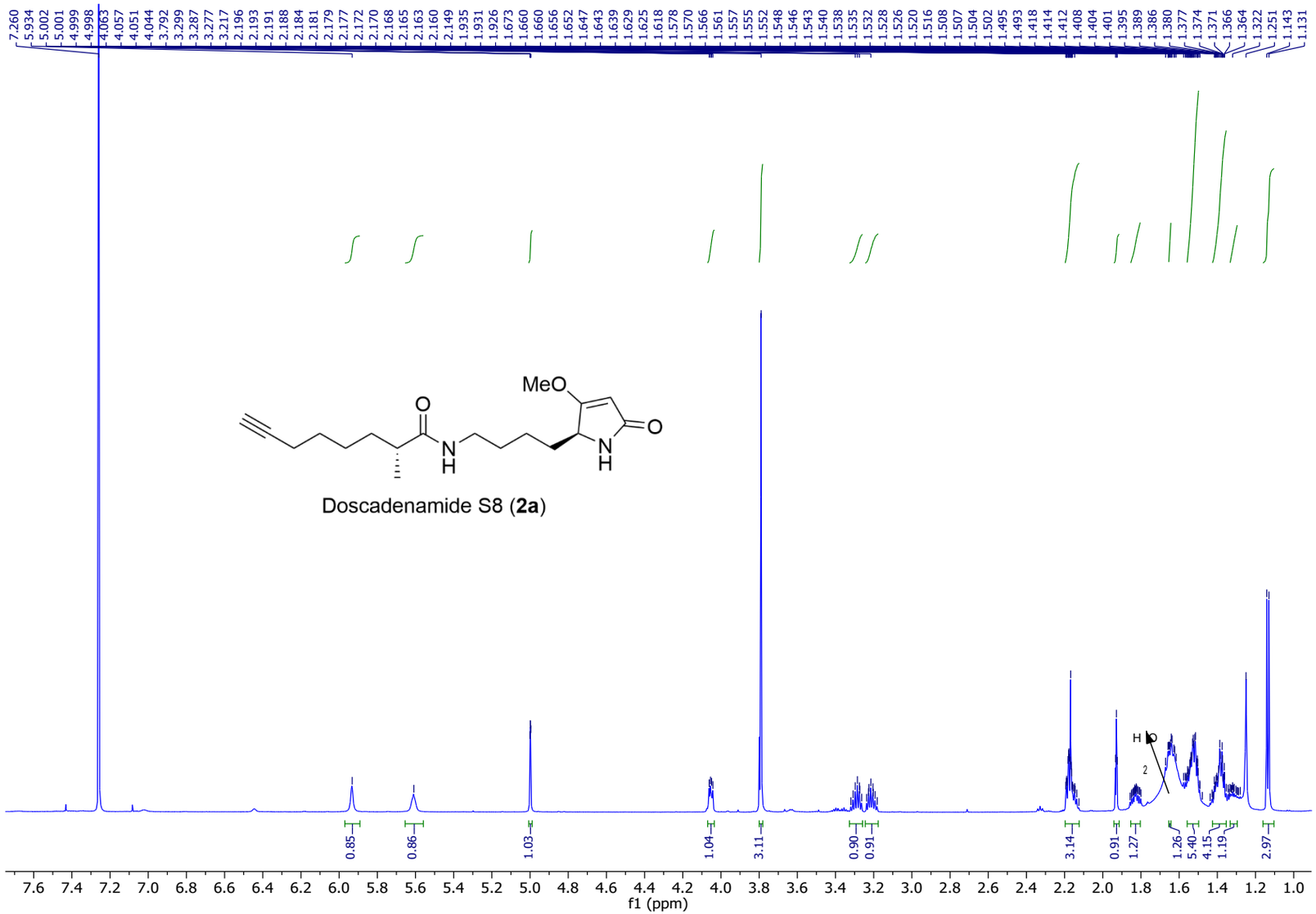


Figure S103. ^{1}H NMR spectrum of synthetic doscadenamide S8 (**2a**) in $CDCl_3$ (600 MHz) at 27 °C.

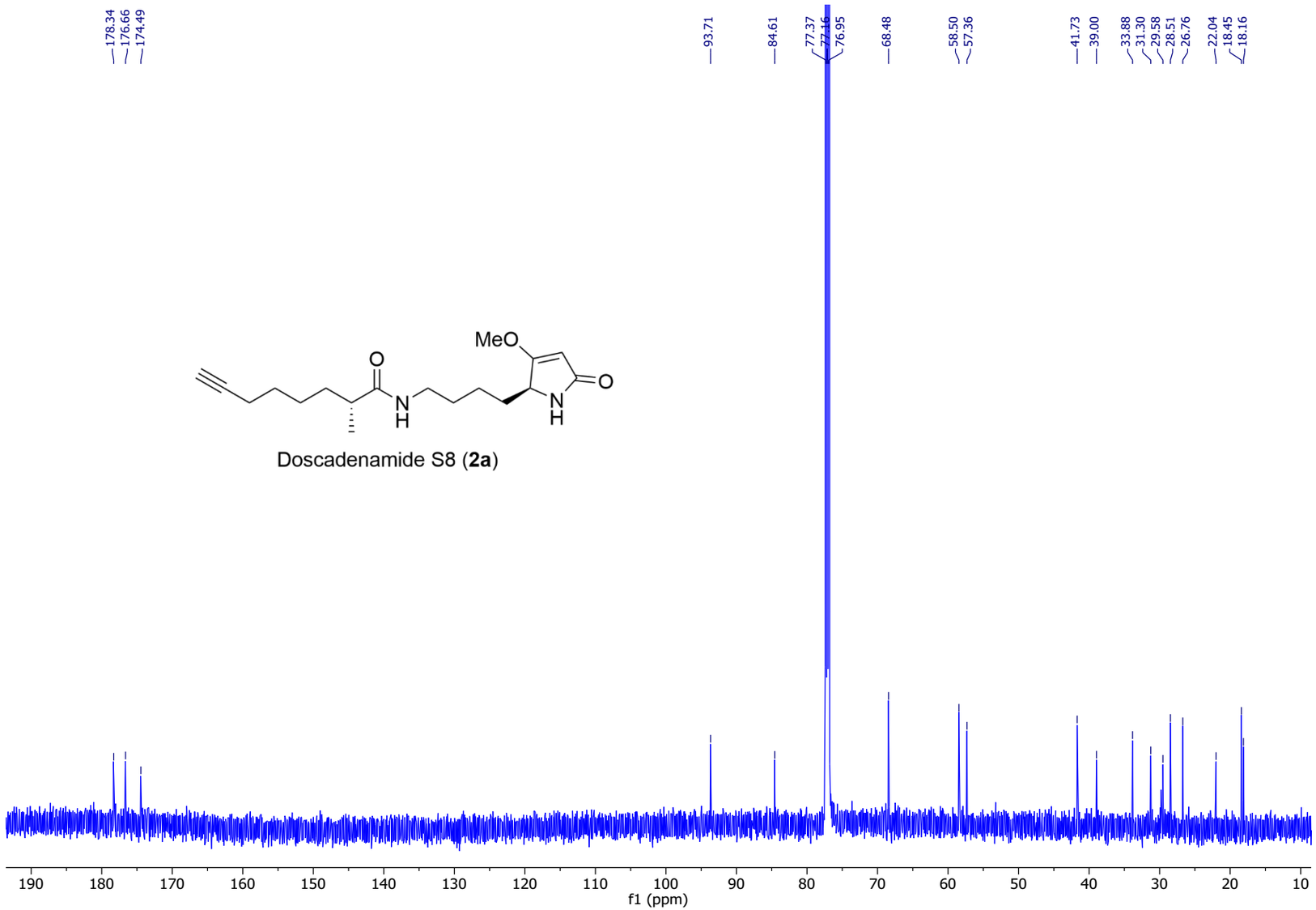


Figure S104. ^{13}C NMR spectrum of synthetic doscadenamide S8 (**2a**) in $CDCl_3$ (600 MHz) at 27 °C.

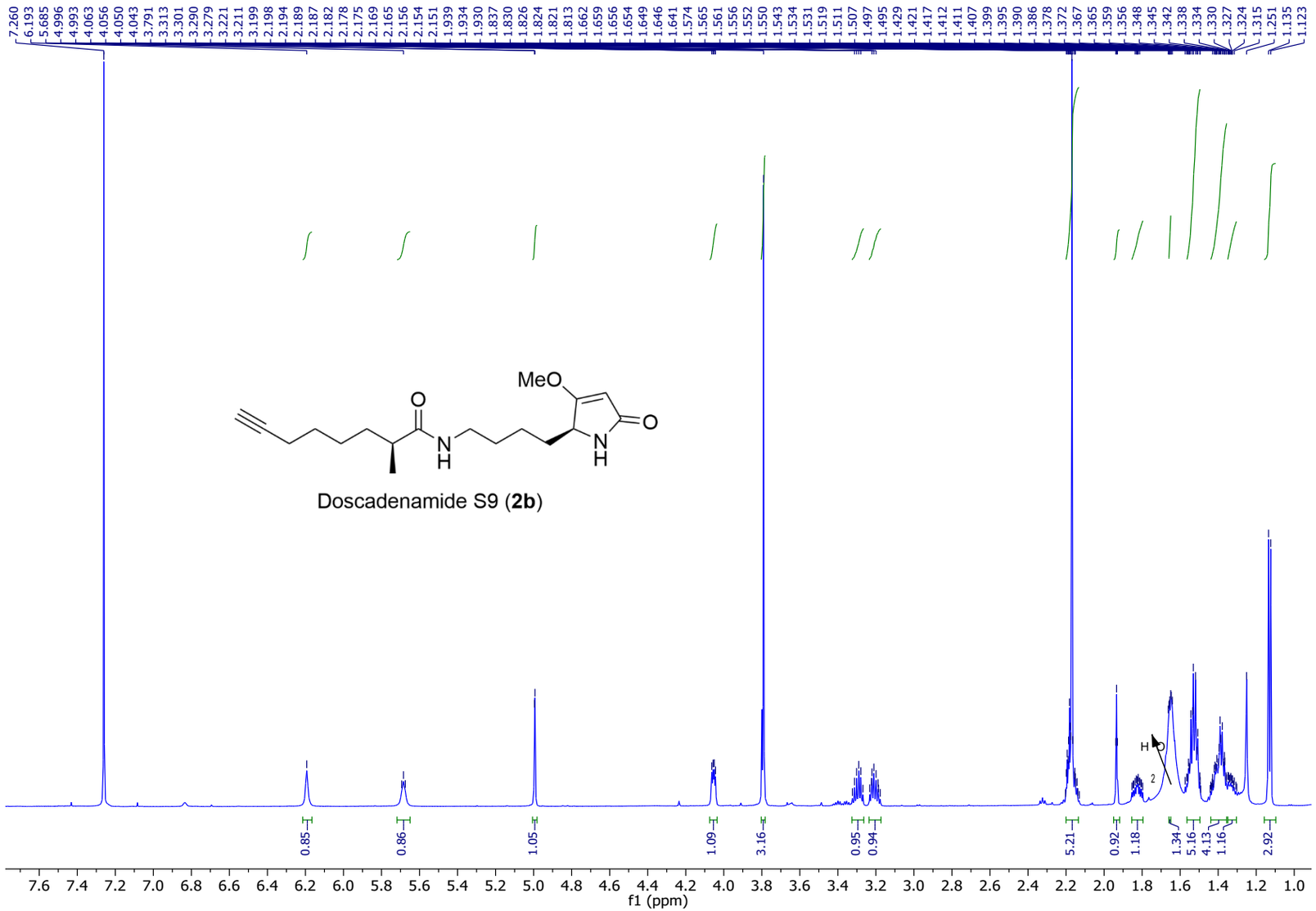


Figure S105. ^{1}H NMR spectrum of synthetic doscadenamide S9 (**2b**) in $CDCl_3$ (600 MHz) at 27 °C.

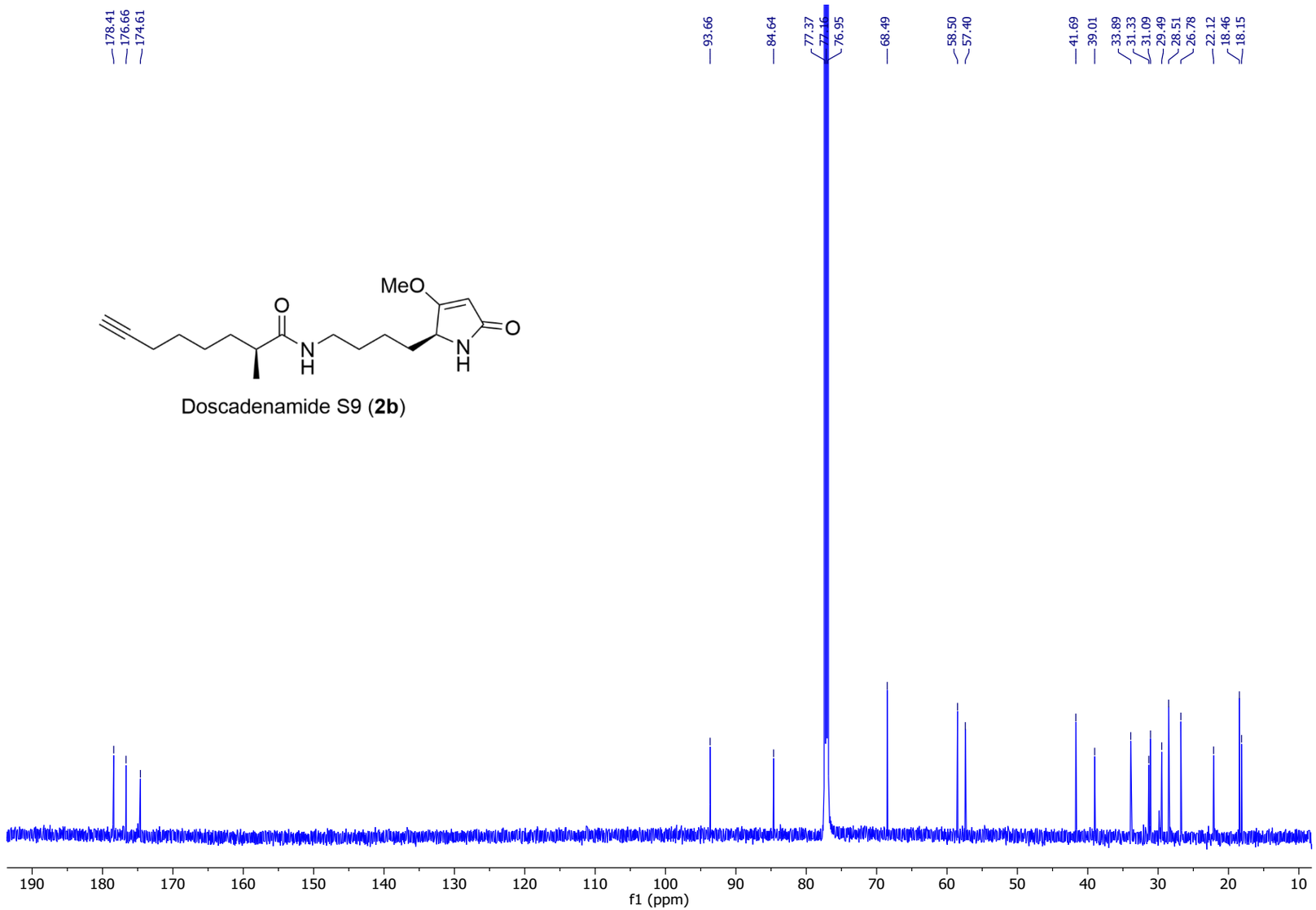


Figure S106. ^{13}C NMR spectrum of synthetic doscadenamide S9 (**2b**) in $CDCl_3$ (600 MHz) at 27 °C.

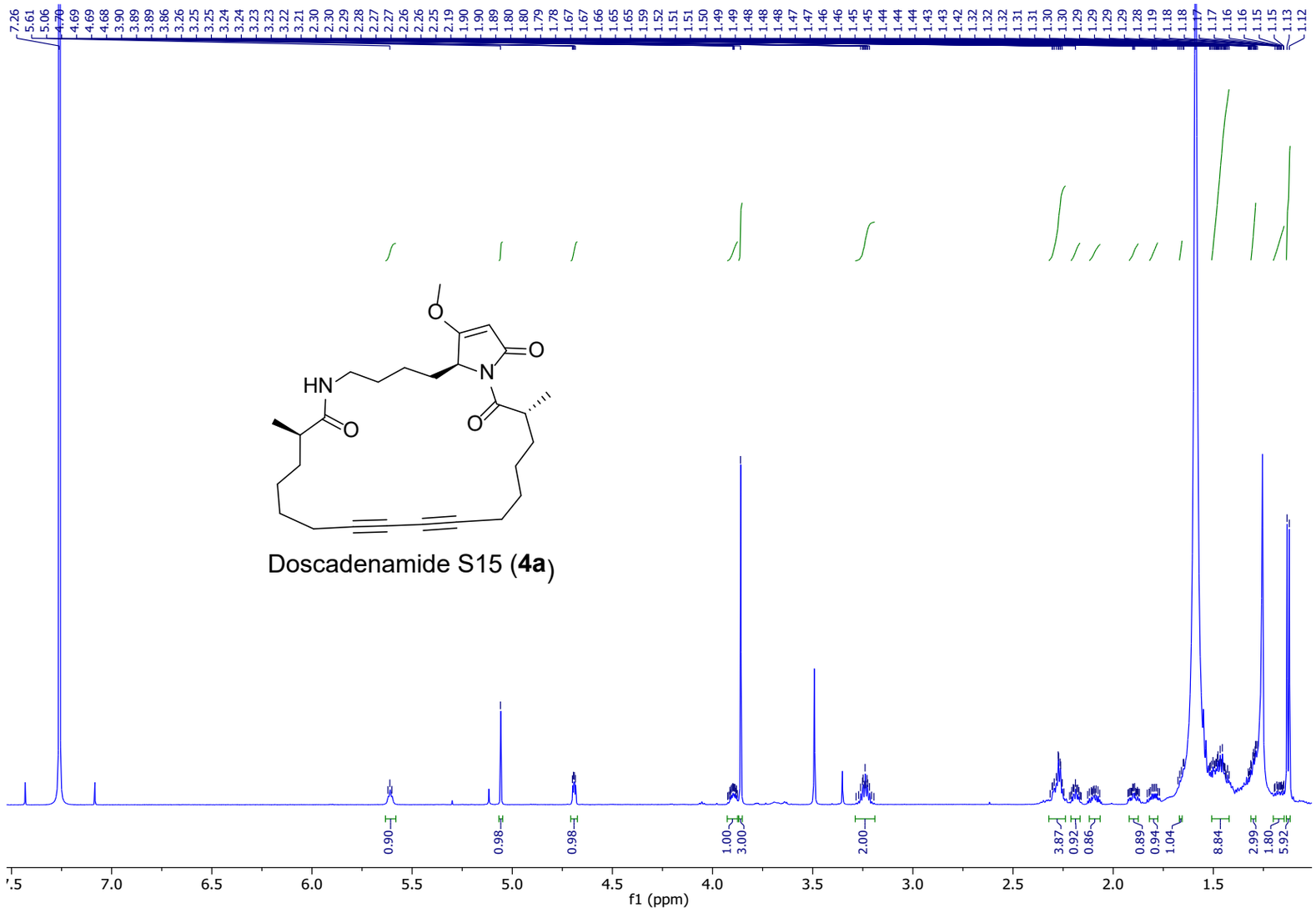


Figure S107. ^{1}H NMR spectrum of synthetic doscadenamide S15 (**4a**) in $CDCl_3$ (600 MHz) at 27 °C.

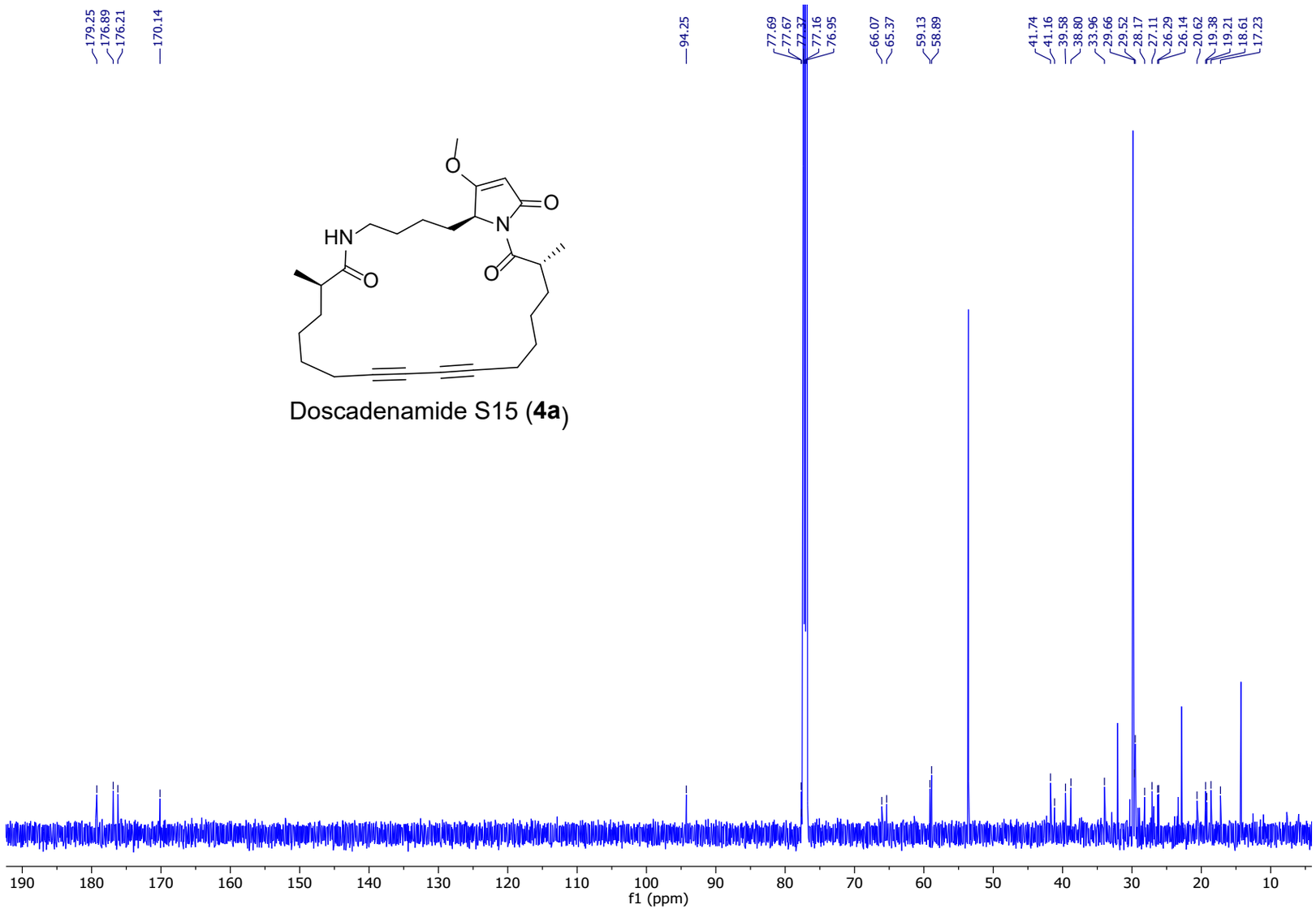


Figure S108. ^{13}C NMR spectrum of synthetic doscadenamide S15 (**4a**) in $CDCl_3$ (600 MHz) at 27 °C.