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Supporting Information

69451 Weinheim, Germany

Total Synthesis of Spirastrellolide A Methyl Ester. Part 2: Subunit Union and Completion of the Synthesis

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The following data is included as supporting information:

Characterisation data for compound **12**, **25**, and **2**

^{1}H NMR data for macrocyclic pentaol **12** (C_6D_6)

^{13}C NMR data for macrocyclic pentaol **12** (C_6D_6)

^{1}H NMR data for *bis*-acetonide of spirastrellolide A methyl ester **25** (C_6D_6)

^{13}C NMR data for *bis*-acetonide of spirastrellolide A methyl ester **25** (C_6D_6)

^{1}H NMR data for natural and synthetic spirastrellolide A methyl ester **2** (C_6D_6)

HPLC chromatograms of natural and synthetic spirastrellolide A methyl ester **2**

CD spectra for natural and synthetic spirastrellolide A methyl ester **2** (CH_2Cl_2)

NMR spectra were recorded in deuterated benzene (C_6D_6). Signal positions (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of the solvent in which the sample was analyzed (C_6D_6: δ 7.15, ^{1}H NMR; δ 128.0, ^{13}C NMR). Coupling constants (*J* values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ^{1}H NMR spectral data are tabulated in the order: multiplicity (br, broad; s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet), coupling constant. Infra-red spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer fitted with a universal ATR sampling accessory. Wavelengths of maximum absorbance (ν_{max}) are quoted in cm^{-1}. High and low resolution mass spectra were recorded by the EPSRC Mass Spectrometry service, Swansea, UK and by the Departmental Mass Spectrometry Service (Cambridge University Chemical Laboratories), using chemical ionization (CI), electron impact (EI) or electron spray ionization (ESI) techniques. The parent ion $[M]^+$ or $[M+H]^+$, $[M+NH_4]^+$, $[M+Na]^+$ is quoted. Optical rotations were measured on a Perkin Elmer 241 polarimeter at the sodium D-line (589 nm) and are reported as follows: $[\alpha]_D^{20}$ concentration (c in g / 100 mL) and

solvent. Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F254 plates with visualization by ultraviolet light (254 nm) and potassium permanganate or phosphomolybdic acid / cerium sulphate dips. Flash chromatography was carried out on Merck Kieselgel 60 (230-400 mesh) under a positive pressure using distilled solvents; the procedure includes the subsequent evaporation of solvents *in vacuo*. High performance liquid chromatography (HPLC) was carried out using a Waters Spherisorb S5 ODS2 column® (4.6 x 250 mm), equipped with a Gilson UV detector (Model 118) at a wavelength of 200 nm. 25 % water in methanol was used as a solvent and the flow rate was 1.0 mL/min. CD spectra were recorded on an Applied Photophysics Chirascan circular dichroism spectropolarimeter using a 1-mm path length quartz cuvette. Scans were performed at 20°C over a wavelength range of 190-320 nm with response time of 1.0 s, 1 nm pitch and 1 nm bandwidth. Blank spectra of samples (CH_2Cl_2) were subtracted from collected data. The CD spectra represent an average of three scans and are zero-corrected at 320 nm (θ quoted in mdeg).

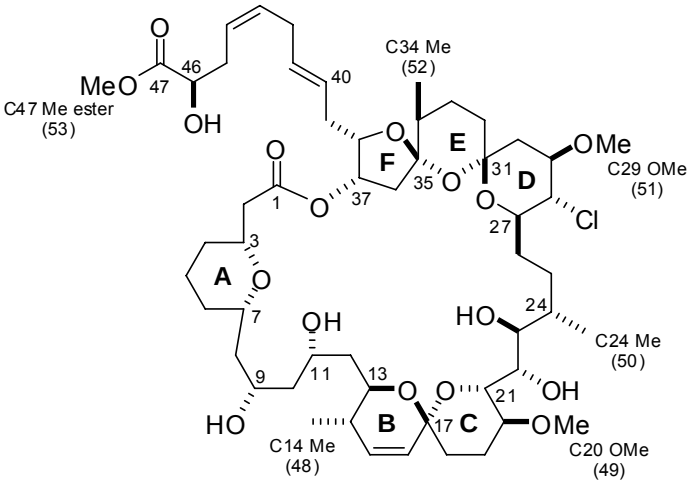
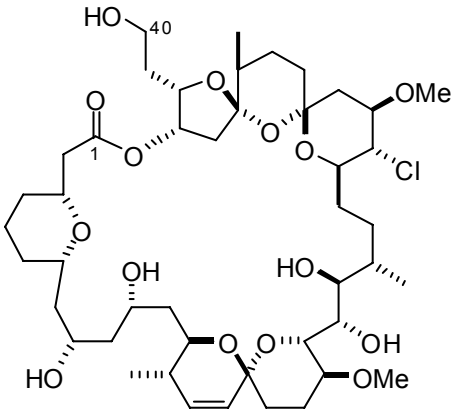


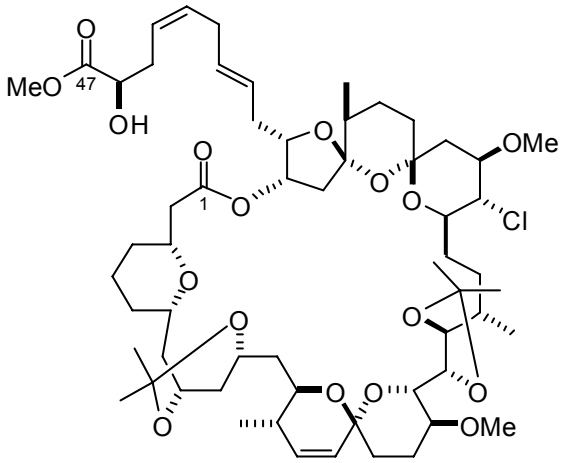
Figure 1: Numbering system for spirastrellolide A methyl ester (**2**)

Macrocyclic pentaol 12



m.p. 174 °C; $\mathbf{R_f}$ 0.27 (EtOAc / PE 40-60, 2:1); $\mathbf{[\alpha]_D^{20}}$ = +14.1 (*c* 0.49, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3481 (br), 2933, 1747, 1380, 1251, 1092, 978; **^{1}H NMR**, see Table 1; **^{13}C NMR**, see Table 1; **HRMS** (ES^+) calcd for $C_{45}H_{73}O_{15}ClNa$ $[M+Na]^+$ 911.4541, found 911.4512.

***Bis*-acetonide of spirastrellolide A methyl ester (25)**

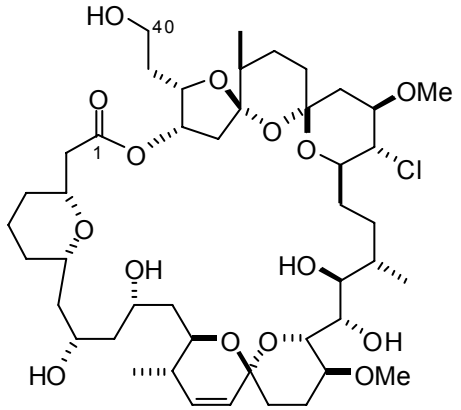


$\mathbf{R_f}$ 0.38 (EtOAc / PE 40-60, 1:1); $\mathbf{[\alpha]_D^{20}}$ = +7.7 (*c* 0.08, CH_2Cl_2), cf. $\mathbf{[\alpha]_D^{25}}$ = +5 (*c* 0.96, CH_2Cl_2) as reported by Andersen and co-workers; ν_{max} (thin film)/cm^{-1} 2924, 2854, 1736, 1669, 1633, 1465, 1378, 1260, 1217, 1096, 1022, 799; **^{1}H NMR**, see Table 2; **^{13}C NMR**, see Table 2; **HRMS** (ES^+) calcd for $C_{59}H_{91}O_{17}ClNa$ $[M+Na]^+$ 1129.5837, found 1129.5880.

Synthetic spirastrellolide A methyl ester (2)

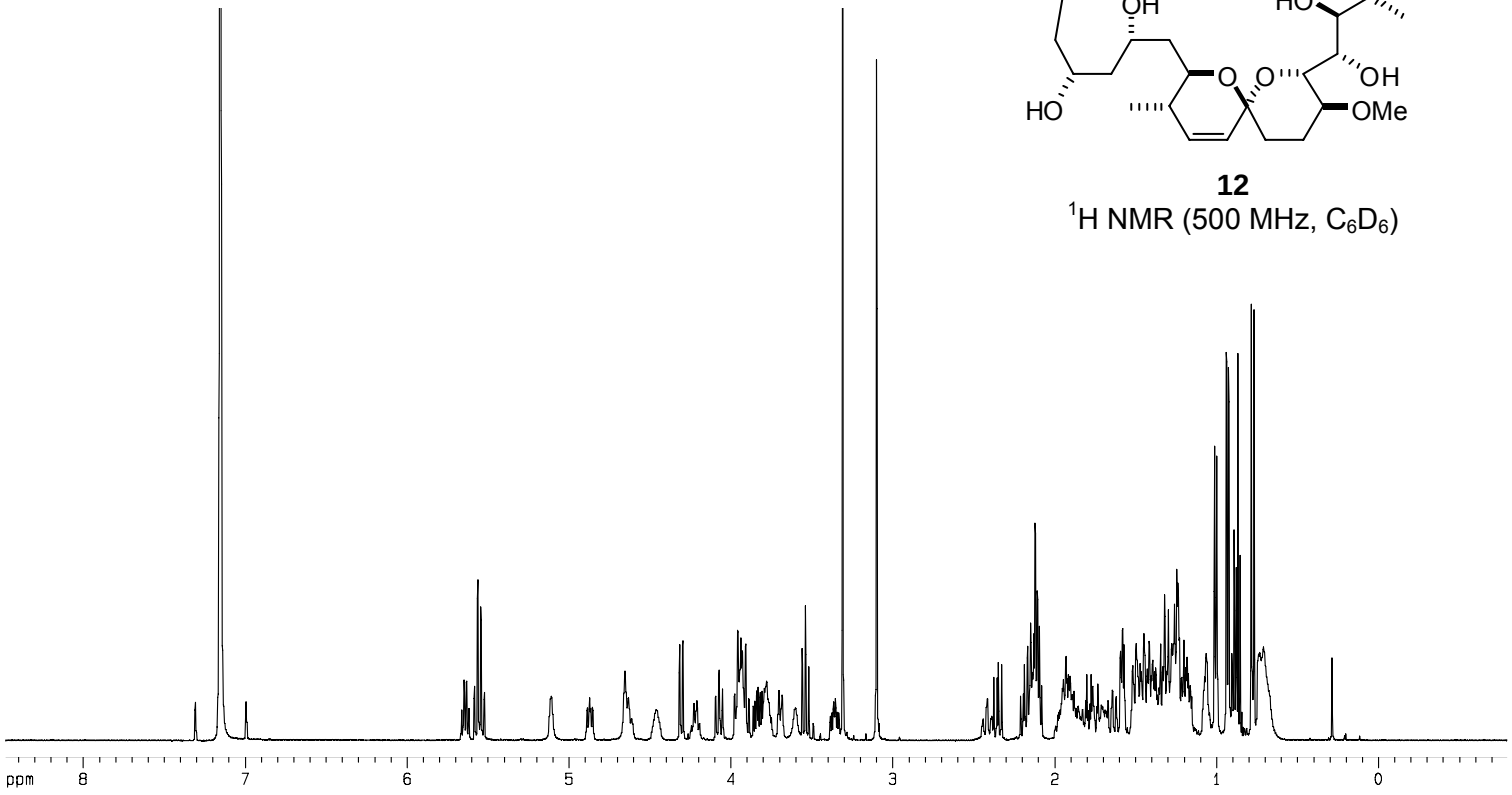
$\mathbf{R_f}$ 0.10 (EtOAc / PE 40-60, 2:1); $\mathbf{[\alpha]_D^{20}}$ = +28.6 (*c* 0.007, CH_2Cl_2), cf. $\mathbf{[\alpha]_D^{25}}$ = +27 (*c* 0.16, CH_2Cl_2) as reported by Andersen and co-workers; ν_{max} (thin film)/cm^{-1} 3352 (br), 2923, 2853, 1740, 1556, 1464, 1261, 1096, 804; **^{1}H NMR**, see Table 3; **HRMS** (ES^+) calcd for $C_{53}H_{83}O_{17}ClNa$ $[M+Na]^+$ 1049.5211, found 1049.5234.

^{1}H NMR Spectrum for macrocyclic pentaol 12

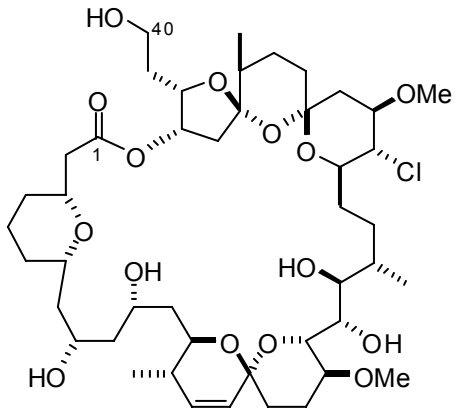


12

^{1}H NMR (500 MHz, C_6D_6)



^{13}C NMR Spectrum for macrocyclic pentaol 12



12

^{13}C NMR (127.5 MHz, C_6D_6)

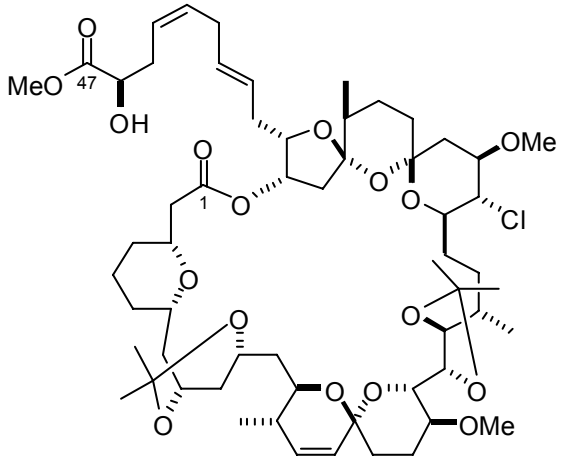
Table 1. ^{1}H NMR and ^{13}C NMR data for macrocyclic pentaol 12

Hydrogen Number	^{1}H NMR (500 MHz, C_6D_6)[a]	Carbon Number	^{13}C NMR (127.5 MHz, C_6D_6)[b]
		1	170.1
2a	2.35 dd (14.3, 9.9)	2	42.8
2b	2.14		
3	3.78 m	3	74.2
4a	1.08 m	4	31.9
4b	1.08 m		
5a	1.24	5	23.9
5b	1.50		
6a	1.25	6	32.2
6b	1.19		
7	3.94	7	74.6
8a	1.58	8	45.1
8b	1.58		
9	4.48 m	9	62.8
10a	1.44	10	47.2
10b	1.37		
11	4.62 br t (10.6)	11	63.3
12a	1.64	12	42.8
12b	1.45		
13	3.91	13	70.6
14	1.92	14	34.9
15	5.57 dd (9.9, 1.3)	15	135.3
16	5.53 dd (10.0, 2.3)	16	128.4
		17	93.8
18a	1.74 dt (13.2, 3.6)	18	34.5
18b	1.37		
19a	1.90	19	24.2
19b	1.67		
20	3.37 ddd (11.2, 10.4, 5.0)	20	74.5
21	4.31 d (9.8)	21	71.1
22	4.07 br t (10.8)	22	69.0
23	3.68 br d (9.7)	23	76.1
24	2.12	24	33.9
25a	2.14	25	25.5

25b	1.42		
26a	2.42 br td (13.2, 3.2)	26	31.0
26b	1.30		
27	3.96	27	75.5
28	3.54 t (9.9)	28	66.0
29	3.83 ddd (11.4, 9.7, 5.0)	29	79.3
30a	2.12	30	43.6
30b	1.33		
		31	97.8
32a	1.34 bt (13.6, 4.0)	32	35.7
32b	1.76		
33a	1.17	33	23.8
33b	1.89		
34	1.49	34	36.0
		35	107.4
36a	2.19 dd (13.2, 9.2)	36	40.4
36b	2.10		
37	5.64 dt (8.4, 7.3)	37	73.8
38	4.87 ddd (10.8, 6.9, 2.7)	38	77.2
39a	1.96	39	31.5
39b	1.85		
40a	4.22 br dd (17.1, 8.6)	40	60.4
40b	3.94		
48 (C14 Me)	0.77 d (7.1)	48	16.6
49 (C20 OMe)	3.08 s	49	56.6
50 (C24 Me)	0.99 d (7.0)	50	17.9
51 (C29 OMe)	3.31 s	51	57.5
52 (C34 Me)	0.92 d (6.7)	52	17.2

[a] ^{1}H NMR recorded in order: chemical shift (δ_H in ppm), multiplicity, (coupling constant in Hz). [b] ^{13}C NMR recorded: chemical shift (δ_C in ppm).

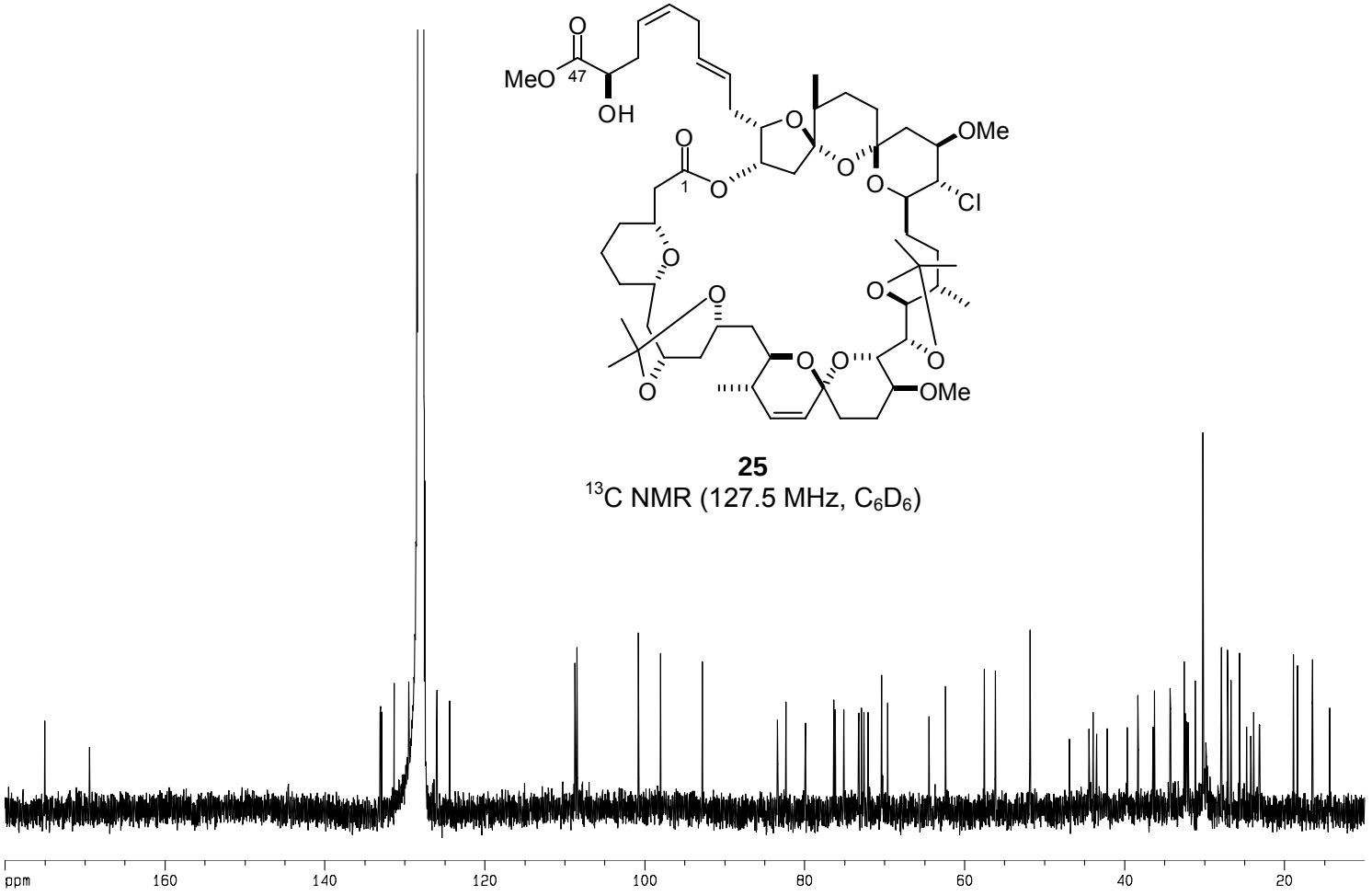
^{1}H NMR Spectrum for *bis*-acetonide of spirastrellolide A methyl ester (25)



25

^{1}H NMR (500 MHz, C_6D_6)

^{13}C NMR Spectrum for *bis*-acetonide of spirastrellolide A methyl ester (25)



25

^{13}C NMR (127.5 MHz, C_6D_6)

Table 2. ^{1}H NMR and ^{13}C NMR data for *bis*-acetonide 25

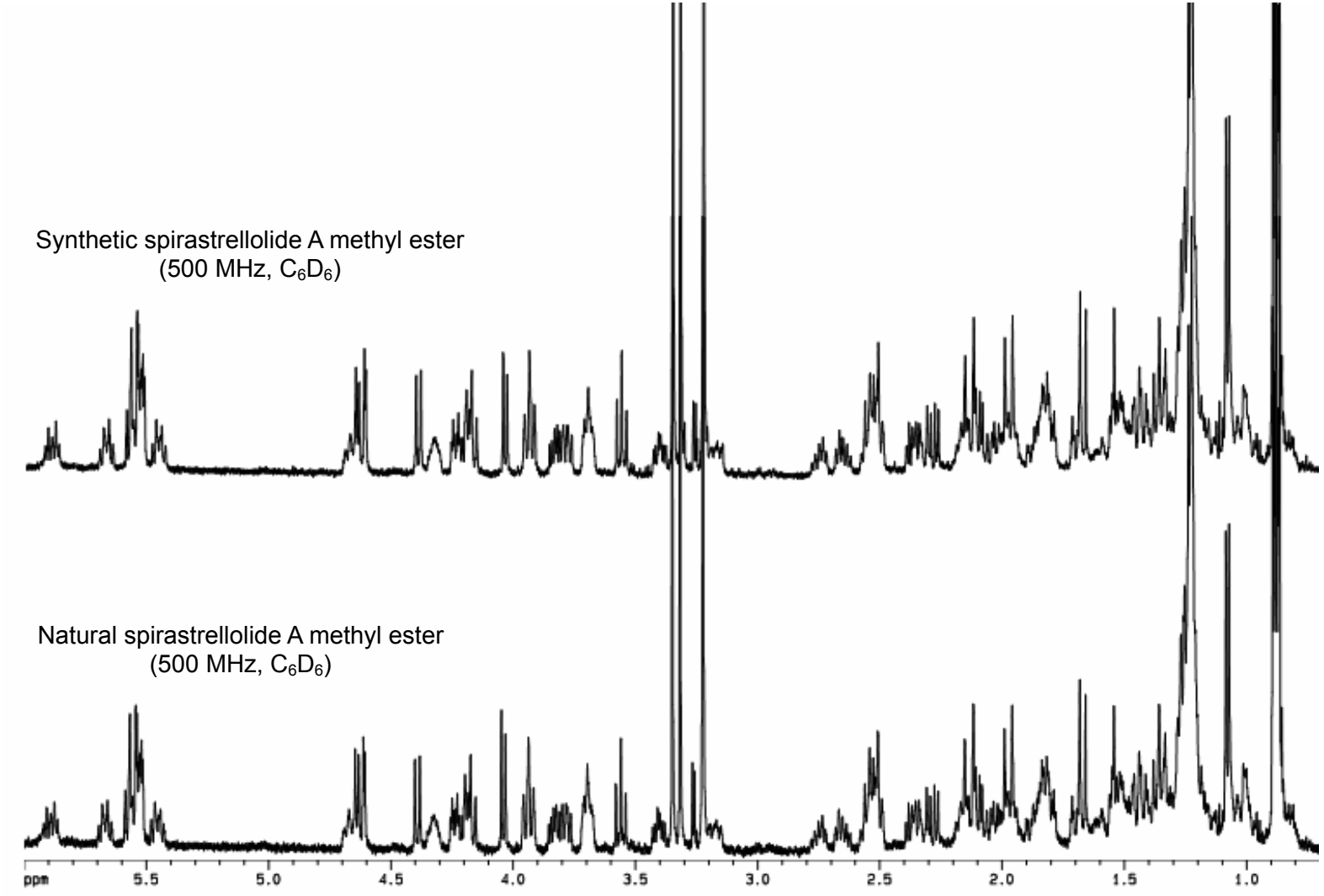
Hydrogen Number	^{1}H NMR (800 MHz, C_6D_6), literature data[a,b]	^{1}H NMR (500 MHz, C_6D_6), synthetic sample[b]	Carbon Number	^{13}C NMR (100 MHz, C_6D_6), literature data[a,c]	^{13}C NMR (127.5 MHz, C_6D_6), synthetic sample[c]
			1	169.4	169.4
2a	2.62 dd (16.3, 10.0)	2.63 dd (16.4, 10.3)	2	43.9	43.9
2b	2.22 dd (16.3, 1.6)	2.21 dd (16.2, 1.5)			
3	3.82 m	3.83 m	3	73.3	73.3
4a	1.06	1.07	4	32.1	32.0
4b	1.06	1.07			
5a	1.48	1.49	5	24.2	24.2
5b	1.27	1.27			
6a	1.30 br d (11.2)	1.31	6	32.2	32.2
6b	1.13	1.14			
7	3.59 br t (10.0)	3.59 br t (9.4)	7	76.2	76.2
8a	1.66	1.66	8	42.2	42.2
8b	1.46 m	1.47 m			
9	4.30 td (10.8, 3.2)	4.30 br t (10.0)	9	64.5	64.5
10a	1.69	1.69	10	39.7	39.6
10b	1.34	1.34			
11	4.55 m	4.55 m	11	62.4	62.4
12a	2.17 ddd (12.0, 10.4, 3.2)	2.18 m	12	44.4	44.5
12b	1.58 ddd (12.0, 10.4, 3.2)	1.58 m			
13	4.07 td (9.6, 3.2)	4.07 td (9.5, 3.0)	13	69.6	69.6
14	1.92	1.91	14	36.3	36.3
15	5.56 dd (9.9, 2.4)	5.56 dd (9.9, 2.6)	15	132.9	132.9
16	5.66 dd (9.9, 2.8)	5.65 dd (9.9, 2.6)	16	129.6	129.5
			17	92.8	92.8
18a	1.95	1.94	18	34.3	34.3
18b	1.49	1.51			
19a	1.94	1.94	19	23.2	23.2
19b	1.85 m	1.86 m			
20	3.50 td (10.0, 4.8)	3.51 td (10.9, 4.2)	20	75.1	75.0
21	3.89 d (9.6)	3.89 d (9.4)	21	72.1	72.1
22	4.66 d (6.4)	4.65 d (6.2)	22	76.4	76.4
23	4.00 dd (10.4, 6.4)	4.01 dd (10.2, 5.9)	23	82.3	82.3

24	2.26 m	2.26 m	24	34.2	34.2
25a	2.44 m	2.44 m	25	24.8	24.8
25b	1.18	1.18			
26a	2.57 m	2.56 m	26	28.0	28.0
26b	1.91	1.92			
27	4.11	4.11	27	72.6	72.6
28	3.75 t (9.6)	3.75 t (10.1)	28	62.4	62.4
29	3.78 ddd (9.6, 9.6, 4.8)	3.78 m	29	79.9	79.9
30a	2.14 dd (12.8, 4.8)	2.14 dd (12.9, 4.8)	30	43.5	43.5
30b	1.34 dd (12.8, 10.4)	1.35			
			31	98.1	98.1
32a	1.63 dt (13.6, 3.2)	1.63	32	36.5	36.4
32b	1.37 td (13.6, 4.0)	1.36			
33a	2.01 dddd (13.1, 13.1, 13.1, 3.8)	2.01 m	33	23.9	23.9
33b	1.18 m	1.17 m			
34	1.50	1.50	34	38.3	38.3
			35	108.5	108.5
36a	2.23 dd (15.2, 6.4)	2.22 dd (15.6, 6.5)	36	46.9	46.9
36b	1.95 d (15.2)	1.95 d (15.7)			
37	5.53	5.52	37	72.9	72.9
38	4.18 dt (11.2, 2.8)	4.18 dt (11.0, 3.1)	38	83.4	83.4
39a	2.88 m	2.88 m	39	32.4	32.4
39b	2.78 m	2.78 m			
40	5.52	5.52	40	126.0	126.0
41	5.78 dt (16.0, 6.4)	5.77 dt (15.0, 6.5)	41	133.1	133.1
42a	2.82 m	2.82 m	42	31.2	31.2
42b	2.82 m	2.82 m			
43	5.69 m	5.69 m	43	131.3	131.4
44	5.51	5.51	44	124.4	124.4
45a	2.51 m	2.50 m	45	32.6	32.5
45b	2.40 m	2.41 m			
46	4.12	4.12	46	70.4	70.3
			47	175.0	175.0
48 (C14 Me)	1.08 d (7.2)	1.07 d (7.1)	48	18.3	18.3
49 (C20 OMe)	3.16 s	3.16 s	49	56.2	56.2
50 (C24 Me)	1.20 d (6.4)	1.19 d (6.2)	50	18.8	18.8
51 (C29 OMe)	3.31 s	3.31 s	51	57.6	57.6

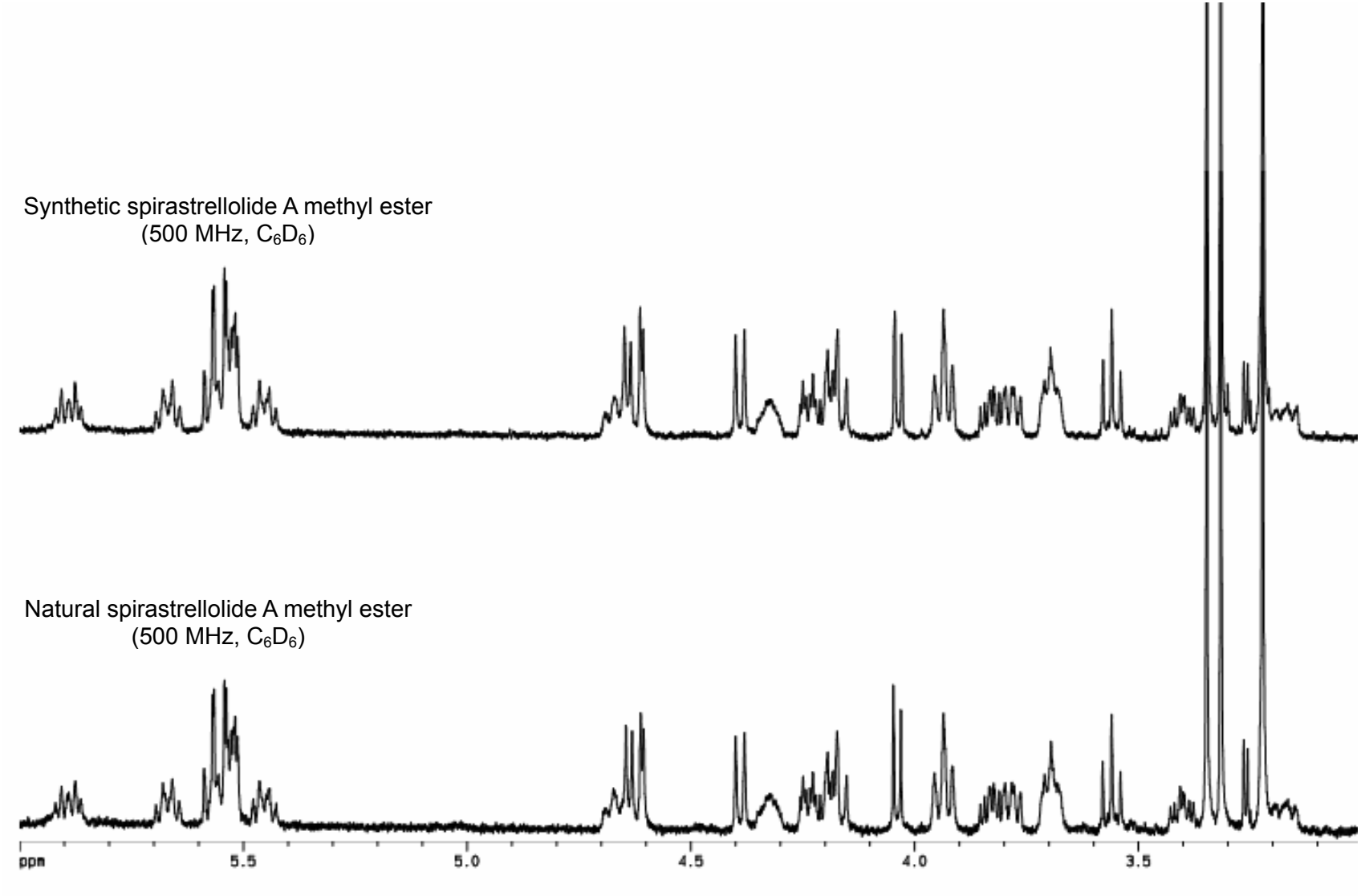
52 (C34 Me)	1.04 d (7.2)	1.04 d (7.0)	52	16.5	16.5
53 (C47 Me ester)	3.28 s	3.27 s	53	51.8	51.8
C9/11 acetonide Me	1.71 br s	1.71 br s	C9/11 acetonide Me	27.9, 25.6	27.9, 25.6
	1.65 s	1.65 s	C9/11 acetonide C	100.8	100.8
C22/23 acetonide Me	1.71 br s	1.71 br s	C22/23 acetonide Me	27.1, 26.6	27.1, 26.6
	1.50 s	1.50 s	C22/23 acetonide C	108.7	108.7

[a] D.E. Williams, M. Lapawa, X. Feng, T. Tarling, M. Roberg, R. J. Andersen, *Org. Lett*. **2004**, *6*, 2607. [b] ^{1}H NMR recorded in order: chemical shift (δ_H in ppm), multiplicity, (coupling constant in Hz). [c] ^{13}C NMR recorded: chemical shift (δ_C in ppm).

^{1}H NMR Spectrum for natural and synthetic spirastrellolide A methyl ester (2)



^{1}H NMR Spectrum for natural and synthetic spirastrellolide A methyl ester (2)



^{1}H NMR Spectrum for natural and synthetic spirastrellolide A methyl ester (2)

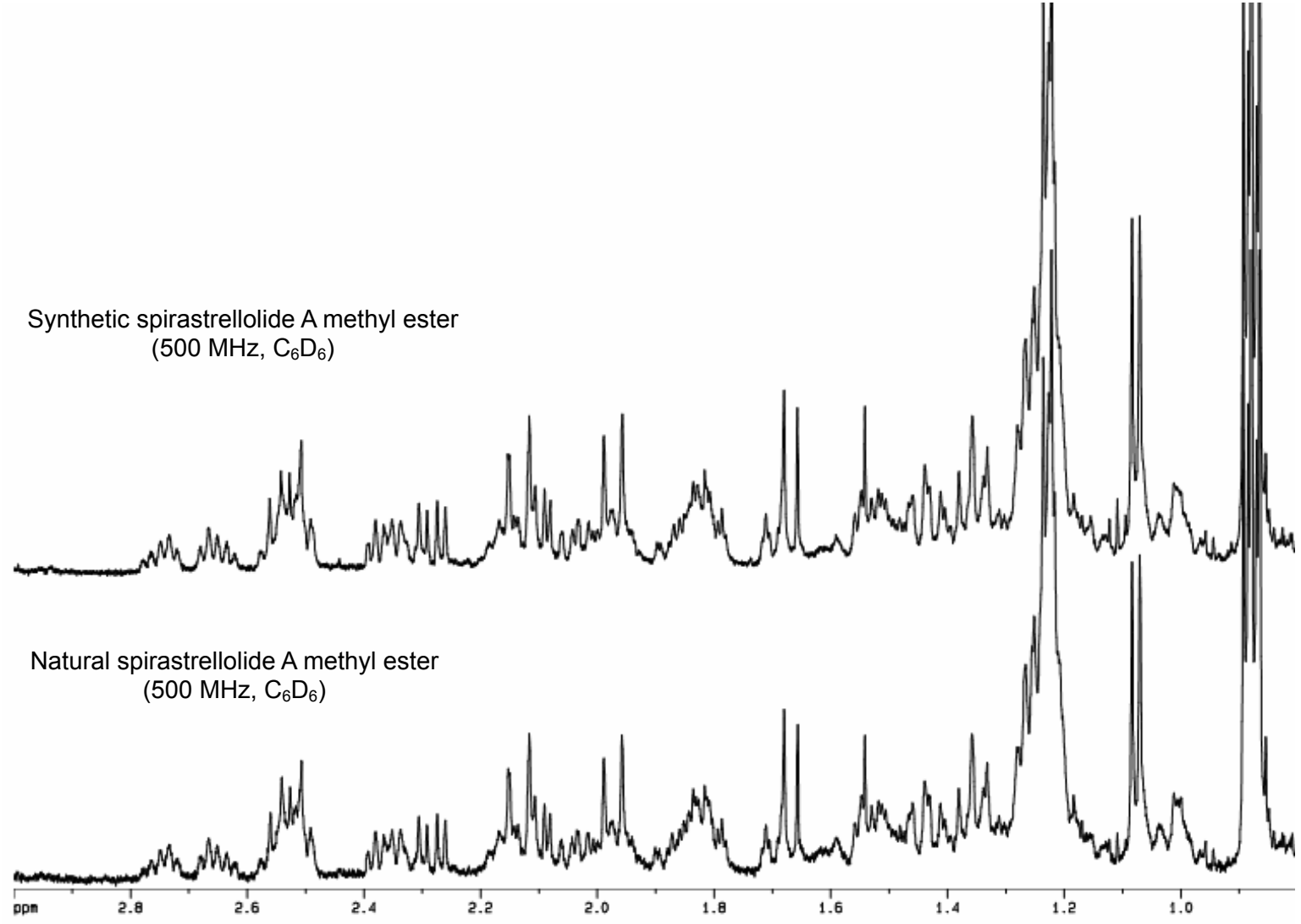


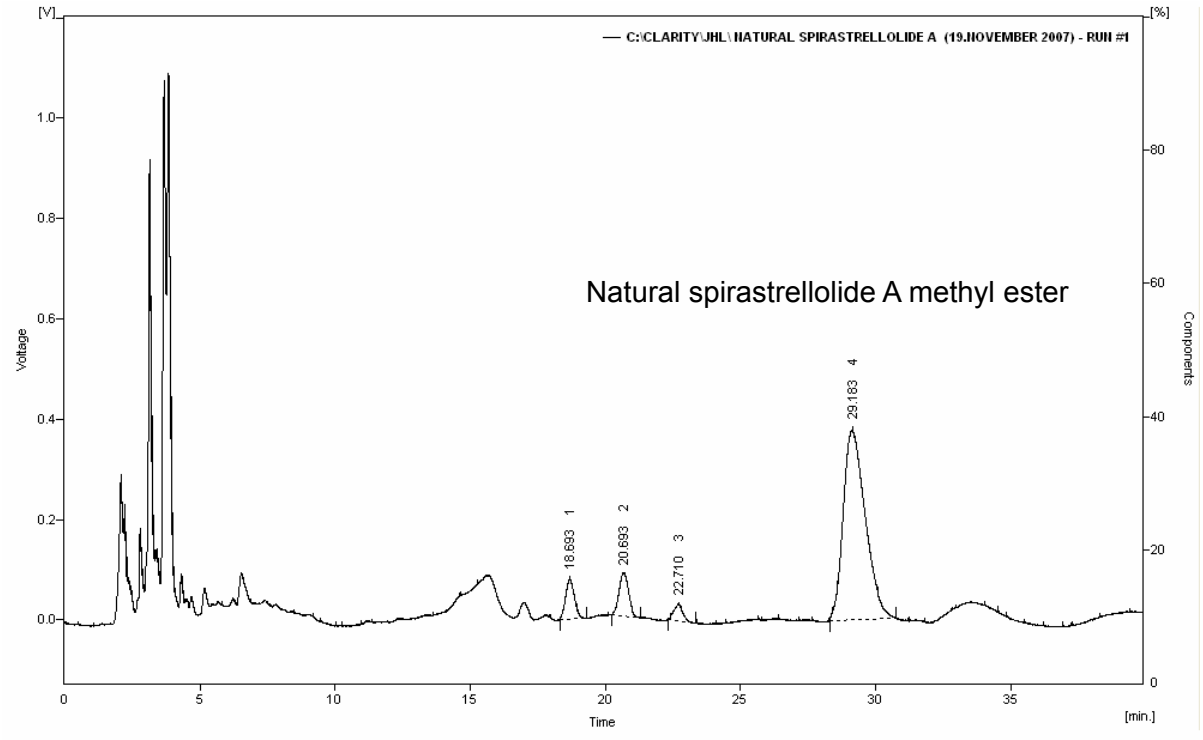
Table 3. ^{1}H NMR data for natural and synthetic spirastrellolide A methyl ester (2)[a]

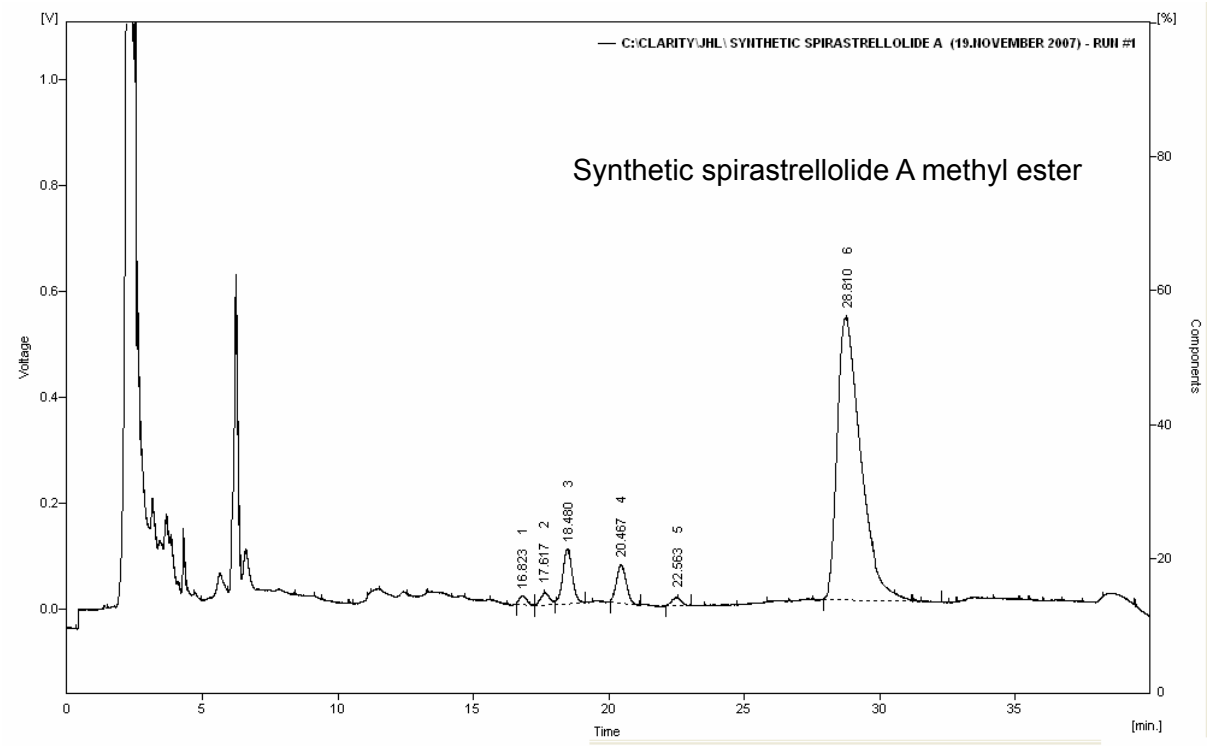
Hydrogen Number	^{1}H NMR (800 MHz, C_6D_6), natural product literature data[b]	^{1}H NMR (500 MHz, C_6D_6), natural product sample[c]	^{1}H NMR (500 MHz, C_6D_6), synthetic sample
2a	2.48 dd (17.2, 10.0)	2.50 m	2.50 m
2b	2.11	2.11	2.11
3	3.68 m	3.68 m	3.68 m
4a	1.00 m	1.00	1.00
4b	0.95 dddd (12.8, 12.8, 12.8, 3.5)	0.95 m	0.95 m
5a	1.50	1.50	1.50
5b	1.24	1.24	1.24
6a	1.17 m	1.17	1.17
6b	1.00 m	1.00	1.00
7	3.67 m	3.67 m	3.67 m
8a	2.02 m	2.00 m	2.00 m
8b	1.52	1.52	1.52
9	4.31 m	4.33 m	4.33 m
10a	1.89 ddd (14.4, 9.9, 3.2)	1.89 m	1.89 m
10b	1.28 ddd (14.4, 5.8, 1.8)	1.25	1.25
11	4.70 br t (9.9)	4.67 br t (10.4)	4.67 br t (10.4)
12a	2.09 ddd (13.6, 9.9, 2.4)	2.09	2.09
12b	1.43 m	1.43	1.43
13	3.94 t (9.9)	3.94 t (10.3)	3.94 t (10.3)
14	1.94	1.94	1.94
15	5.57 dd (9.6, 1.6)	5.58 dd (9.9, 1.4)	5.58 dd (9.9, 1.4)
16	5.54 m	5.54	5.54
18a	1.80 dt (13.2, 3.6)	1.80	1.80
18b	1.45 td (13.2, 4.0)	1.45	1.45
19a	1.98	1.98	1.98
19b	1.85 m	1.85	1.85
20	3.42 ddd (10.6, 10.1, 4.8)	3.41 ddd (10.8, 9.7, 4.4)	3.41 ddd (10.8, 9.7, 4.4)
21	4.37 d (10.6)	4.39 d (9.4)	4.39 d (9.4)
22	4.16	4.17	4.17
23	3.80 br d (8.8)	3.79 dd (9.5, 7.1)	3.79 dd (9.5, 7.1)
24	2.16 m	2.16	2.16
25a	2.36 m	2.35 m	2.35 m
25b	1.37	1.36	1.36

26a	2.53	2.53	2.53
26b	1.38	1.34	1.34
27	3.94 t (9.9)	3.94 t (10.3)	3.94 t (10.3)
28	3.57 t (9.9)	3.56 t (10.2)	3.56 t (10.2)
29	3.83 ddd (11.2, 9.9, 5.6)	3.83 ddd (11.3, 9.8, 5.1)	3.83 ddd (11.3, 9.8, 5.1)
30a	2.11	2.10	2.10
30b	1.36	1.36	1.36
32a	1.70 dt (12.8, 3.2)	1.70	1.70
32b	1.34 m	1.34	1.34
33a	2.13	2.14	2.14
33b	1.22	1.23	1.23
34	1.49 m	1.50 m	1.50 m
36a	2.29 dd (15.4, 6.8)	2.28 dd (15.5, 7.0)	2.28 dd (15.5, 7.0)
36b	1.98 d (15.4)	1.97 d (15.3)	1.97 d (15.3)
37	5.53 m	5.54	5.54
38	4.23 dt (11.2, 3.2)	4.24 dt (11.0, 3.3)	4.24 dt (11.0, 3.3)
39a	3.21 m	3.19 m	3.19 m
39b	2.52 m	2.51 m	2.51 m
40	5.56 m	5.56 m	5.56 m
41	5.90 dt (15.2, 6.8)	5.89 dt (15.4, 6.8)	5.89 dt (15.4, 6.8)
42a	2.75 dt (15.2, 6.8)	2.75 m	2.75 m
42b	2.65 dt (15.2, 6.8)	2.65 m	2.65 m
43	5.68 m	5.67 m	5.67 m
44	5.45 m	5.45 m	5.45 m
45a	2.53	2.54 m	2.54 m
45b	2.37	2.37	2.37
46	4.19 m	4.19 m	4.19 m
48 (C14 Me)	0.89 d (7.2)	0.88 d (7.2)	0.88 d (7.2)
49 (C20 OMe)	3.27 s	3.22 s	3.22 s
50 (C24 Me)	1.23 d (7.2)	1.22 d (6.8)	1.22 d (6.8)
51 (C29 OMe)	3.35 s	3.35 s	3.35 s
52 (C34 Me)	1.07 d (7.2)	1.08 d (6.8)	1.08 d (6.8)
53 (C47 Me ester)	3.32 s	3.32 s	3.32 s
OH	4.57 br s, 4.46 br s, 4.17, 1.67 d (11.2)	4.64 d (6.9), 4.61 d (3.8), 4.04 d (7.6), 1.67 d (12.1)	4.64 d (6.9), 4.61 d (3.8), 4.04 d (7.6), 1.67 d (12.1)

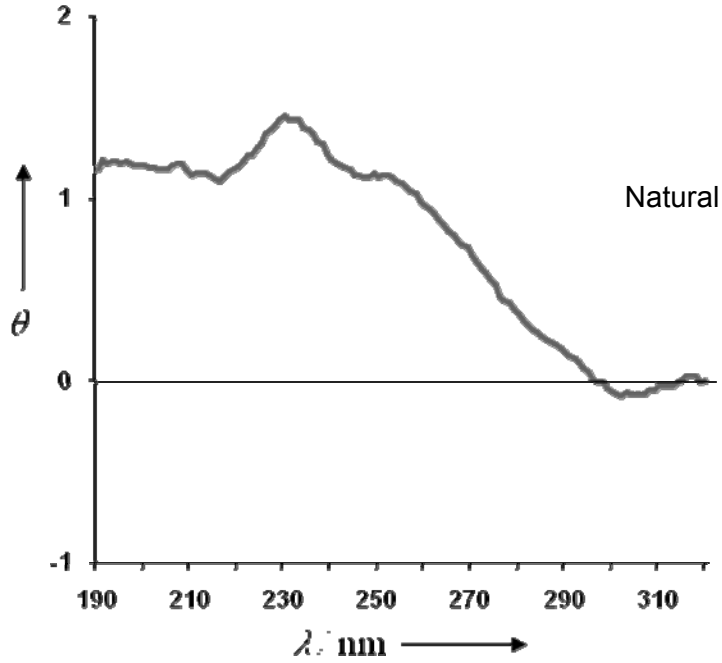
[a] ^{1}H NMR recorded in order: chemical shift (δ_H in ppm), multiplicity, (coupling constant in Hz). [b] D.E. Williams, M. Roberg, R. Van Soest, R. J. Andersen, *J. Am. Chem. Soc*. **2003**, *125*, 5296. [c] A sample of methyl ester of natural spirastrellolide A was kindly provided by Professor R. J. Andersen.

HPLC Chromatograms of natural and synthetic spirastrellolide A methyl ester (2)



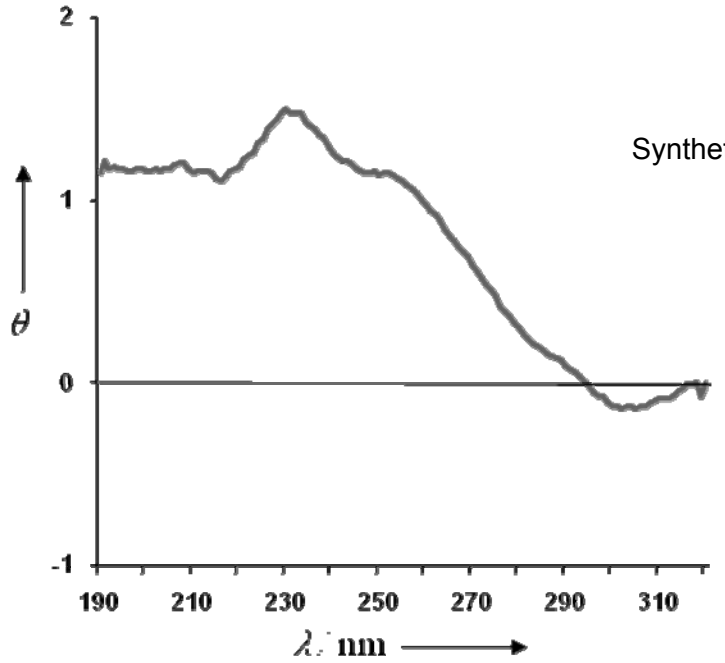


CD Spectra for natural and synthetic spirastrellolide A methyl ester (2)



Natural spirastrellolide A methyl ester

c = 0.000126 M in CH_2Cl_2



Synthetic spirastrellolide A methyl ester

c = 0.000214 M in CH_2Cl_2