SUPPLEMENTARY MATERIALS

Spontaneous Stereoselective Oxidation of Crystalline Avermectin B_{1a} to its C-8a-*(S)*-Hydroperoxide

Jan A. Gliński,[†*] John Proudfoot,[‡] Izabela Madura,[§] Huaping Zhang,[†] Michał Gleńsk,[†⊥] Victor Day,[‖] Marta K. Dudek[∇*]

[†] Planta Analytica LCC, 461 Danbury Road, New Milford, CT 06776, USA

[‡] Discoverybytes LLC, 40 Currituck Road, Newtown, CT 06470, USA

[§] Faculty of Chemistry, Warsaw University of Technology, Noakowskiego 3, 00-664 Warsaw, Poland

[⊥] Department of Pharmacognosy, Wroclaw Medical University, Borowska 211a, 50-556 Wrocław, Poland

[‖] University of Kansas, Chemistry Department, 1567 Irving Hill Road, Lawrence, KS 66045, USA

[∇] Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Sienkiewicza 112, 90-363 Lodz, Poland

Table S1. Crystal and structure refinement datafor **1**.

Empirical formula	C50 H76 N O17.50	
Formula moiety	$C_{48}H_{72}O_{16}$, C_2H_3N, 1.5 H_2O	
Formula weight	971.11	
Temperature	200(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	*C*2	
Unit cell dimensions	a = 39.1619(14) Å	α= 90°
	b = 9.4140(3) Å	β= 105.3027(19)°
	c = 14.9395(6) Å	γ = 90°
Volume	5312.5(3) $Å^3$	
Z	4	
Density (calculated)	1.214 Mg/m^3	
Absorption coefficient	0.756 mm^{-1}	
F(000)	2092	
Crystal size	0.410 x 0.300 x 0.130 mm^3	
Theta range for data collection	2.339 to 70.311°.	
Index ranges	–46<=h<=33, –11<=k<=11, –15<=l<=16	
Reflections collected	35500	
Independent reflections	9151 [$R_{(int)}$ = 0.0465]	
Absorption correction	Multi-scan	
Max. and min. transmission	1.000 and 0.732	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9151 / 1 / 636	
Goodness-of-fit on F^2	1.016	
Final R indices [$I>2\sigma(I)$]	R_1 = 0.0482, *wR2* = 0.1323	
R indices (all data)	R_1 = 0.0502, *wR2* = 0.1348	
Absolute structure parameter *x*	-0.08(7)	
Largest diff. peak and hole	0.463 and -0.363 e·$Å^{-3}$	

Table S2a. Bond lengths [Å] for **1**.

O(1)-C(1)	1.337(4)	O(14)-C(4")	1.421(4)	C(16)-C(17)	1.525(4)
O(1)-C(19)	1.459(4)	O(14)-H(14O)	0.93(6)	C(17)-C(18)	1.516(4)
O(2)-C(1)	1.195(4)	O(15)-C(8A)	1.395(4)	C(18)-C(19)	1.507(4)
O(3)-C(5)	1.434(4)	O(15)-O(16)	1.463(3)	C(19)-C(20)	1.524(4)
O(3)-H(3O)	0.8400	O(16)-H(16O)	0.99(5)	C(20)-C(21)	1.540(4)
O(4)-C(6)	1.433(4)	C(1)-C(2)	1.516(4)	C(21)-C(22)	1.512(4)
O(4)-C(8A)	1.440(4)	C(2)-C(3)	1.504(4)	C(22)-C(23)	1.311(5)
O(5)-C(7)	1.403(4)	C(2)-C(7)	1.561(4)	C(23)-C(24)	1.515(5)
O(5)-H(5O)	0.93(7)	C(3)-C(4)	1.327(5)	C(24)-C(25)	1.523(4)
O(6)-C(21)	1.421(4)	C(4)-C(4A)	1.502(4)	C(24)-C(24A)	1.539(5)
O(6)-C(17)	1.443(3)	C(4)-C(5)	1.509(5)	C(25)-C(26)	1.529(5)
O(7)-C(21)	1.424(4)	C(5)-C(6)	1.532(4)	C(26)-C(26A)	1.523(5)
O(7)-C(25)	1.449(4)	C(6)-C(7)	1.537(4)	C(26)-C(27)	1.537(6)
O(8)-C(1')	1.419(4)	C(7)-C(8)	1.510(4)	C(27)-C(28)	1.527(6)
O(8)-C(13)	1.425(4)	C(8)-C(9)	1.335(4)	C(1')-C(2')	1.521(5)
O(9)-C(1')	1.411(4)	C(8)-C(8A)	1.511(4)	C(2')-C(3')	1.523(5)
O(9)-C(5')	1.439(4)	C(9)-C(10)	1.455(4)	C(3')-C(4')	1.516(4)
O(10)-C(7')	1.365(6)	C(10)-C(11)	1.338(4)	C(4')-C(5')	1.540(4)
O(10)-C(3')	1.434(4)	C(11)-C(12)	1.502(4)	C(5')-C(6')	1.521(4)
O(11)-C(1")	1.423(4)	C(12)-C(12A)	1.535(5)	C(1")-C(2")	1.508(6)
O(11)-C(4')	1.435(4)	C(12)-C(13)	1.544(4)	C(2")-C(3")	1.527(6)
O(12)-C(1")	1.408(5)	C(13)-C(14)	1.527(4)	C(3")-C(4")	1.515(5)
O(12)-C(5")	1.440(4)	C(14)-C(15)	1.331(5)	C(4")-C(5")	1.519(5)
O(13)-C(3")	1.422(5)	C(14)-C(14A)	1.510(4)	C(5")-C(6")	1.519(6)
O(13)-C(7")	1.451(9)	C(15)-C(16)	1.502(4)	N(1S)-C(1S)	1.129(12)
				C(1S)-C(2S)	1.410(13)

Table S2b. Bond angles [°] for **1**.

C(1)-O(1)-C(19)	118.8(2)	C(15)-C(16)-C(17)	110.8(2)
C(6)-O(4)-C(8A)	107.5(2)	O(6)-C(17)-C(18)	110.6(2)
C(21)-O(6)-C(17)	114.2(2)	O(6)-C(17)-C(16)	106.2(2)
C(21)-O(7)-C(25)	113.1(2)	C(18)-C(17)-C(16)	113.0(2)
C(1')-O(8)-C(13)	117.4(2)	C(19)-C(18)-C(17)	110.1(2)
C(1')-O(9)-C(5')	116.1(2)	O(1)-C(19)-C(18)	106.4(2)
C(7')-O(10)-C(3')	115.3(3)	O(1)-C(19)-C(20)	109.3(2)
C(1")-O(11)-C(4')	115.3(3)	C(18)-C(19)-C(20)	110.7(2)
C(1")-O(12)-C(5")	115.2(3)	C(19)-C(20)-C(21)	110.4(2)
C(3")-O(13)-C(7")	112.1(4)	O(6)-C(21)-O(7)	111.4(2)
C(8A)-O(15)-O(16)	106.3(2)	O(6)-C(21)-C(22)	106.1(2)
O(15)-O(16)-H(16O)	100(3)	O(7)-C(21)-C(22)	111.0(3)
O(2)-C(1)-O(1)	124.5(3)	O(6)-C(21)-C(20)	111.7(2)
O(2)-C(1)-C(2)	125.3(3)	O(7)-C(21)-C(20)	105.2(2)
O(1)-C(1)-C(2)	110.3(2)	C(22)-C(21)-C(20)	111.6(2)
C(3)-C(2)-C(1)	112.2(2)	C(23)-C(22)-C(21)	121.5(3)
C(3)-C(2)-C(7)	112.1(2)	C(22)-C(23)-C(24)	124.0(3)
C(1)-C(2)-C(7)	109.2(2)	C(23)-C(24)-C(25)	108.9(3)
C(4)-C(3)-C(2)	123.7(3)	C(23)-C(24)-C(24A)	109.8(3)
C(3)-C(4)-C(4A)	122.4(3)	C(25)-C(24)-C(24A)	111.0(3)
C(3)-C(4)-C(5)	122.7(3)	O(7)-C(25)-C(24)	109.7(2)
C(4A)-C(4)-C(5)	114.8(3)	O(7)-C(25)-C(26)	107.0(2)
O(3)-C(5)-C(4)	112.4(3)	C(24)-C(25)-C(26)	115.8(3)
O(3)-C(5)-C(6)	111.2(3)	C(26A)-C(26)-C(25)	112.3(3)
C(4)-C(5)-C(6)	114.8(3)	C(26A)-C(26)-C(27)	111.9(3)
O(4)-C(6)-C(5)	111.3(3)	C(25)-C(26)-C(27)	110.4(3)
O(4)-C(6)-C(7)	103.4(2)	C(28)-C(27)-C(26)	114.8(4)
C(5)-C(6)-C(7)	116.7(3)	O(9)-C(1')-O(8)	113.2(3)
O(5)-C(7)-C(8)	115.7(2)	O(9)-C(1')-C(2')	111.0(2)
O(5)-C(7)-C(6)	113.4(2)	O(8)-C(1')-C(2')	104.9(3)
C(8)-C(7)-C(6)	99.4(2)	C(1')-C(2')-C(3')	109.6(3)
O(5)-C(7)-C(2)	108.4(2)	O(10)-C(3')-C(4')	110.9(3)
C(8)-C(7)-C(2)	110.4(2)	O(10)-C(3')-C(2')	109.7(3)
C(6)-C(7)-C(2)	109.2(2)	C(4')-C(3')-C(2')	108.3(3)
C(9)-C(8)-C(7)	126.2(3)	O(11)-C(4')-C(3')	111.9(3)
C(9)-C(8)-C(8A)	127.6(3)	O(11)-C(4')-C(5')	105.6(2)
C(7)-C(8)-C(8A)	105.9(2)	C(3')-C(4')-C(5')	110.1(2)
O(15)-C(8A)-O(4)	109.9(2)	O(9)-C(5')-C(6')	105.0(3)
O(15)-C(8A)-C(8)	108.7(2)	O(9)-C(5')-C(4')	112.0(2)

O(4)-C(8A)-C(8)	105.8(2)	C(6')-C(5')-C(4')	112.6(3)
C(8)-C(9)-C(10)	126.3(3)	O(12)-C(1")-O(11)	112.8(3)
C(11)-C(10)-C(9)	122.0(3)	O(12)-C(1")-C(2")	111.7(3)
C(10)-C(11)-C(12)	125.4(3)	O(11)-C(1")-C(2")	107.4(3)
C(11)-C(12)-C(12A)	110.8(3)	C(1")-C(2")-C(3")	112.3(3)
C(11)-C(12)-C(13)	110.9(2)	O(13)-C(3")-C(4")	109.8(3)
C(12A)-C(12)-C(13)	111.4(3)	O(13)-C(3")-C(2")	110.8(4)
O(8)-C(13)-C(14)	113.5(2)	C(4")-C(3")-C(2")	107.8(3)
O(8)-C(13)-C(12)	105.9(2)	O(14)-C(4")-C(3")	111.4(3)
C(14)-C(13)-C(12)	111.1(2)	O(14)-C(4")-C(5")	111.7(3)
C(15)-C(14)-C(14A)	123.5(3)	C(3")-C(4")-C(5")	109.4(3)
C(15)-C(14)-C(13)	122.9(3)	O(12)-C(5")-C(6")	106.0(3)
C(14A)-C(14)-C(13)	113.6(3)	O(12)-C(5")-C(4")	110.4(3)
C(14)-C(15)-C(16)	126.5(3)	C(6")-C(5")-C(4")	112.9(3)

Table S2c. Torsion angles [°] for **1**.

C(19)-O(1)-C(1)-O(2)	7.1(4)	C(18)-C(19)-C(20)-C(21)	-52.5(3)
C(19)-O(1)-C(1)-C(2)	-172.7(2)	C(17)-O(6)-C(21)-O(7)	61.3(3)
O(2)-C(1)-C(2)-C(3)	39.0(4)	C(17)-O(6)-C(21)-C(22)	-177.8(2)
O(1)-C(1)-C(2)-C(3)	-141.2(3)	C(17)-O(6)-C(21)-C(20)	-56.1(3)
O(2)-C(1)-C(2)-C(7)	-85.8(4)	C(25)-O(7)-C(21)-O(6)	69.5(3)
O(1)-C(1)-C(2)-C(7)	93.9(3)	C(25)-O(7)-C(21)-C(22)	-48.4(3)
C(1)-C(2)-C(3)-C(4)	-153.1(3)	C(25)-O(7)-C(21)-C(20)	-169.3(2)
C(7)-C(2)-C(3)-C(4)	-29.9(4)	C(19)-C(20)-C(21)-O(6)	52.2(3)
C(2)-C(3)-C(4)-C(4A)	-178.0(3)	C(19)-C(20)-C(21)-O(7)	-68.9(3)
C(2)-C(3)-C(4)-C(5)	5.7(6)	C(19)-C(20)-C(21)-C(22)	170.7(3)
C(3)-C(4)-C(5)-O(3)	-131.2(4)	O(6)-C(21)-C(22)-C(23)	-109.2(3)
C(4A)-C(4)-C(5)-O(3)	52.2(4)	O(7)-C(21)-C(22)-C(23)	12.0(4)
C(3)-C(4)-C(5)-C(6)	-2.9(5)	C(20)-C(21)-C(22)-C(23)	129.0(3)
C(4A)-C(4)-C(5)-C(6)	-179.5(3)	C(21)-C(22)-C(23)-C(24)	5.3(5)
C(8A)-O(4)-C(6)-C(5)	163.9(2)	C(22)-C(23)-C(24)-C(25)	11.9(4)
C(8A)-O(4)-C(6)-C(7)	37.8(3)	C(22)-C(23)-C(24)-C(24A)	133.5(4)
O(3)-C(5)-C(6)-O(4)	36.6(4)	C(21)-O(7)-C(25)-C(24)	67.6(3)
C(4)-C(5)-C(6)-O(4)	-92.3(3)	C(21)-O(7)-C(25)-C(26)	-166.0(2)
O(3)-C(5)-C(6)-C(7)	155.0(3)	C(23)-C(24)-C(25)-O(7)	-45.6(3)
C(4)-C(5)-C(6)-C(7)	26.0(4)	C(24A)-C(24)-C(25)-O(7)	-166.6(3)
O(4)-C(6)-C(7)-O(5)	-165.2(2)	C(23)-C(24)-C(25)-C(26)	-166.9(3)
C(5)-C(6)-C(7)-O(5)	72.3(3)	C(24A)-C(24)-C(25)-C(26)	72.2(4)
O(4)-C(6)-C(7)-C(8)	-41.7(3)	O(7)-C(25)-C(26)-C(26A)	-66.6(4)
C(5)-C(6)-C(7)-C(8)	-164.3(3)	C(24)-C(25)-C(26)-C(26A)	56.1(4)
O(4)-C(6)-C(7)-C(2)	73.9(3)	O(7)-C(25)-C(26)-C(27)	59.0(3)
C(5)-C(6)-C(7)-C(2)	-48.7(4)	C(24)-C(25)-C(26)-C(27)	-178.3(3)
C(3)-C(2)-C(7)-O(5)	-75.2(3)	C(26A)-C(26)-C(27)-C(28)	-61.5(5)
C(1)-C(2)-C(7)-O(5)	49.7(3)	C(25)-C(26)-C(27)-C(28)	172.6(4)
C(3)-C(2)-C(7)-C(8)	157.1(3)	C(5')-O(9)-C(1')-O(8)	-63.4(3)
C(1)-C(2)-C(7)-C(8)	-78.0(3)	C(5')-O(9)-C(1')-C(2')	54.3(3)
C(3)-C(2)-C(7)-C(6)	48.8(3)	C(13)-O(8)-C(1')-O(9)	-59.7(3)
C(1)-C(2)-C(7)-C(6)	173.7(2)	C(13)-O(8)-C(1')-C(2')	179.0(2)
O(5)-C(7)-C(8)-C(9)	-22.6(4)	O(9)-C(1')-C(2')-C(3')	-57.7(3)
C(6)-C(7)-C(8)-C(9)	-144.4(3)	O(8)-C(1')-C(2')-C(3')	64.9(3)
C(2)-C(7)-C(8)-C(9)	100.9(3)	C(7')-O(10)-C(3')-C(4')	-115.8(5)
O(5)-C(7)-C(8)-C(8A)	152.8(2)	C(7')-O(10)-C(3')-C(2')	124.6(5)
C(6)-C(7)-C(8)-C(8A)	31.0(3)	C(1')-C(2')-C(3')-O(10)	-179.1(2)
C(2)-C(7)-C(8)-C(8A)	-83.7(3)	C(1')-C(2')-C(3')-C(4')	59.7(3)
O(16)-O(15)-C(8A)-O(4)	-77.0(3)	C(1")-O(11)-C(4')-C(3')	-91.6(3)

O(16)-O(15)-C(8A)-C(8)	167.6(2)	C(1")-O(11)-C(4')-C(5')	148.6(3)
C(6)-O(4)-C(8A)-O(15)	-134.7(3)	O(10)-C(3')-C(4')-O(11)	65.8(3)
C(6)-O(4)-C(8A)-C(8)	-17.5(3)	C(2')-C(3')-C(4')-O(11)	-173.8(2)
C(9)-C(8)-C(8A)-O(15)	-76.7(4)	O(10)-C(3')-C(4')-C(5')	-177.1(3)
C(7)-C(8)-C(8A)-O(15)	108.0(3)	C(2')-C(3')-C(4')-C(5')	-56.7(3)
C(9)-C(8)-C(8A)-O(4)	165.3(3)	C(1')-O(9)-C(5')-C(6')	-174.0(3)
C(7)-C(8)-C(8A)-O(4)	-10.0(3)	C(1')-O(9)-C(5')-C(4')	-51.5(3)
C(7)-C(8)-C(9)-C(10)	179.4(3)	O(11)-C(4')-C(5')-O(9)	172.9(2)
C(8A)-C(8)-C(9)-C(10)	5.0(5)	C(3')-C(4')-C(5')-O(9)	51.9(3)
C(8)-C(9)-C(10)-C(11)	179.5(3)	O(11)-C(4')-C(5')-C(6')	-69.1(4)
C(9)-C(10)-C(11)-C(12)	-179.2(3)	C(3')-C(4')-C(5')-C(6')	169.9(3)
C(10)-C(11)-C(12)-C(12A)	-95.9(4)	C(5")-O(12)-C(1")-O(11)	-67.9(4)
C(10)-C(11)-C(12)-C(13)	139.9(3)	C(5")-O(12)-C(1")-C(2")	53.2(4)
C(1')-O(8)-C(13)-C(14)	-76.3(3)	C(4')-O(11)-C(1")-O(12)	-71.2(4)
C(1')-O(8)-C(13)-C(12)	161.5(2)	C(4')-O(11)-C(1")-C(2")	165.3(3)
C(11)-C(12)-C(13)-O(8)	61.3(3)	O(12)-C(1")-C(2")-C(3")	-52.1(4)
C(12A)-C(12)-C(13)-O(8)	-62.5(3)	O(11)-C(1")-C(2")-C(3")	72.1(4)
C(11)-C(12)-C(13)-C(14)	-62.4(3)	C(7")-O(13)-C(3")-C(4")	-140.4(5)
C(12A)-C(12)-C(13)-C(14)	173.8(3)	C(7")-O(13)-C(3")-C(2")	100.6(6)
O(8)-C(13)-C(14)-C(15)	-9.4(4)	C(1")-C(2")-C(3")-O(13)	175.1(3)
C(12)-C(13)-C(14)-C(15)	109.8(3)	C(1")-C(2")-C(3")-C(4")	54.9(4)
O(8)-C(13)-C(14)-C(14A)	173.2(3)	O(13)-C(3")-C(4")-O(14)	57.5(4)
C(12)-C(13)-C(14)-C(14A)	-67.5(3)	C(2")-C(3")-C(4")-O(14)	178.3(3)
C(14A)-C(14)-C(15)-C(16)	0.4(5)	O(13)-C(3")-C(4")-C(5")	-178.5(3)
C(13)-C(14)-C(15)-C(16)	-176.7(3)	C(2")-C(3")-C(4")-C(5")	-57.7(4)
C(14)-C(15)-C(16)-C(17)	125.9(3)	C(1")-O(12)-C(5")-C(6")	-179.7(3)
C(21)-O(6)-C(17)-C(18)	58.5(3)	C(1")-O(12)-C(5")-C(4")	-57.1(3)
C(21)-O(6)-C(17)-C(16)	-178.6(2)	O(14)-C(4")-C(5")-O(12)	-177.5(3)
C(15)-C(16)-C(17)-O(6)	178.3(2)	C(3")-C(4")-C(5")-O(12)	58.8(4)
C(15)-C(16)-C(17)-C(18)	-60.2(3)	O(14)-C(4")-C(5")-C(6")	-59.0(4)
O(6)-C(17)-C(18)-C(19)	-56.9(3)	C(3")-C(4")-C(5")-C(6")	177.2(4)
C(16)-C(17)-C(18)-C(19)	-175.8(2)	C(17)-C(18)-C(19)-O(1)	173.9(2)
C(1)-O(1)-C(19)-C(18)	142.9(3)	C(17)-C(18)-C(19)-C(20)	55.3(3)
C(1)-O(1)-C(19)-C(20)	-97.4(3)	O(1)-C(19)-C(20)-C(21)	-169.4(2)

Table S3. Hydrogen bonds [Å and °] for **1**.

D-H...A	D (D–H)	D (H…A)	D (D…A)	∠ D–H…A
O(5)-H(5O)...O(2W)	0.93(7)	1.83(7)	2.740(3)	168(6)
O(14)-H(14O)...O(2)#1	0.93(6)	2.37(6)	3.209(4)	151(5)
O(14)-H(14O)...O(5)#1	0.93(6)	2.20(6)	2.806(3)	122(4)
O(16)-H(16O)...O(14)#2	0.99(5)	1.67(5)	2.655(4)	175(4)
C(8A)-H(8A1)...O(4)#3	1.00	2.63	3.492(4)	144.1
C(6')-H(6'A)...O(2)#1	0.98	2.58	3.393(5)	140.8
C(1")-H(1")...O(10)	1.00	2.43	3.123(5)	126.2
C(5")-H(5")...O(2)#1	1.00	2.53	3.339(4)	138.0
O(2W)-H(2W1)...O(1W)	0.85(7)	1.84(7)	2.688(6)	177(8)
C(2S)-H(2SB)...O(15)	0.98	2.25	3.063(11)	140.0

Symmetry transformations used to generate equivalent atoms: #1 *x*,*y*,*z*–1#2 *x*,*y*+1,*z*+1#3 –*x*+1,*y*,-*z*+1

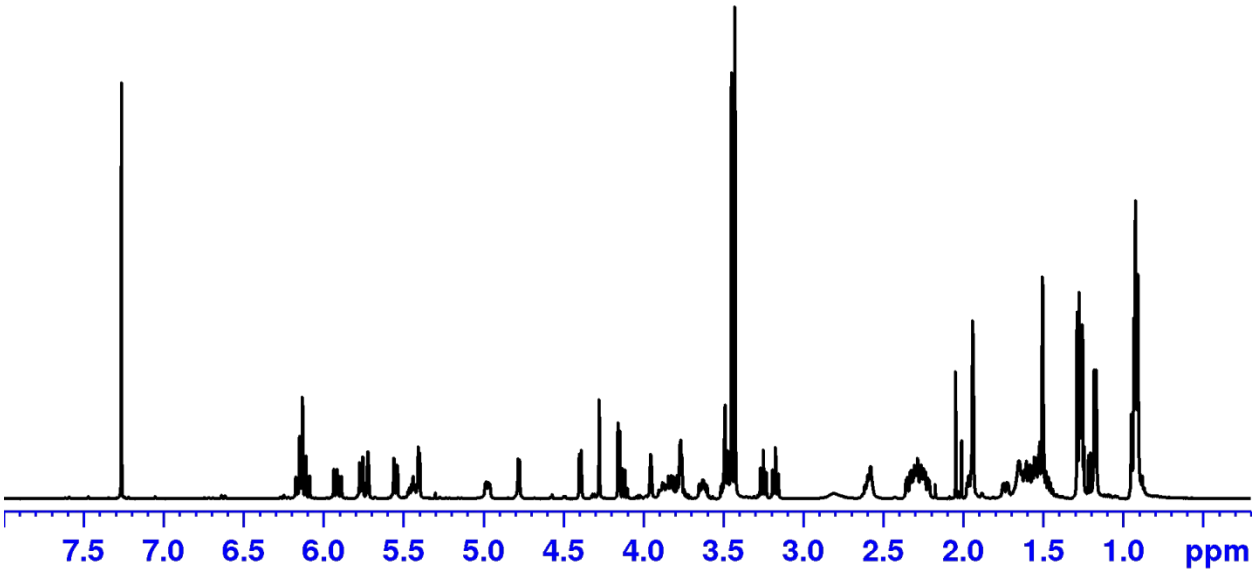


Figure S1. ^{1}H NMR spectrum of **1** (500 MHz, $CDCl_3$)

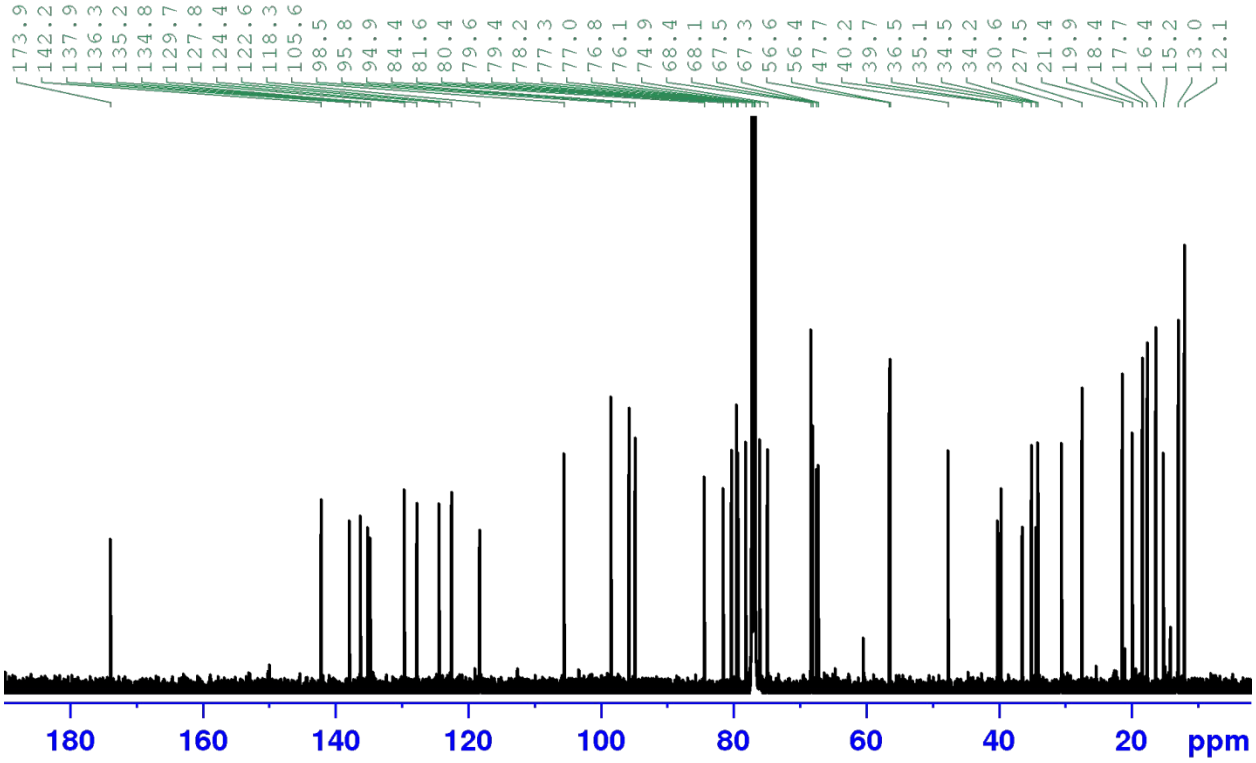


Figure S2. ^{13}C NMR spectrum of **1** (500 MHz, $CDCl_3$)

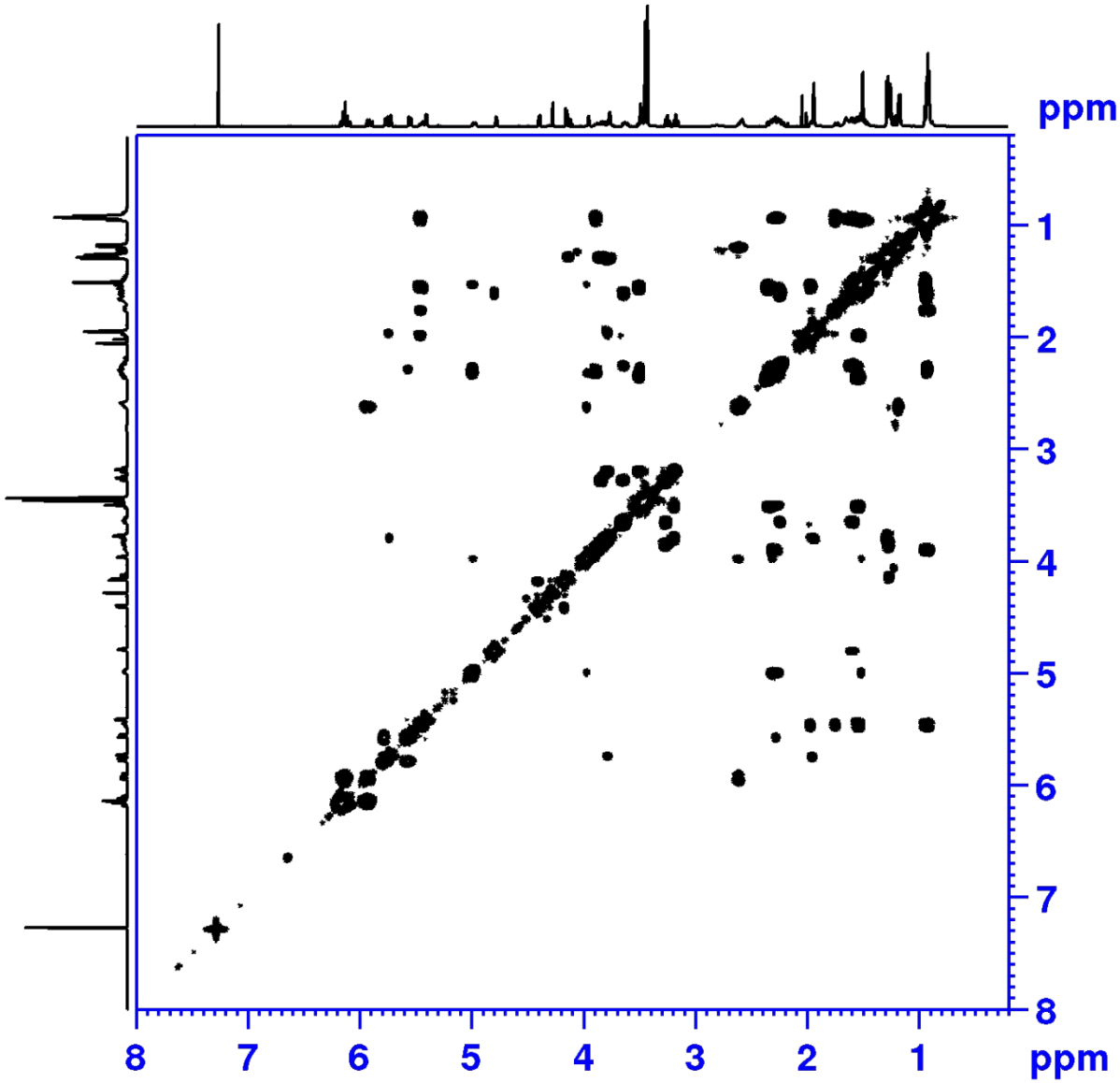


Figure S3. ^{1}H-^{1}H COSY NMR spectrum of **1** (500 MHz, $CDCl_3$)

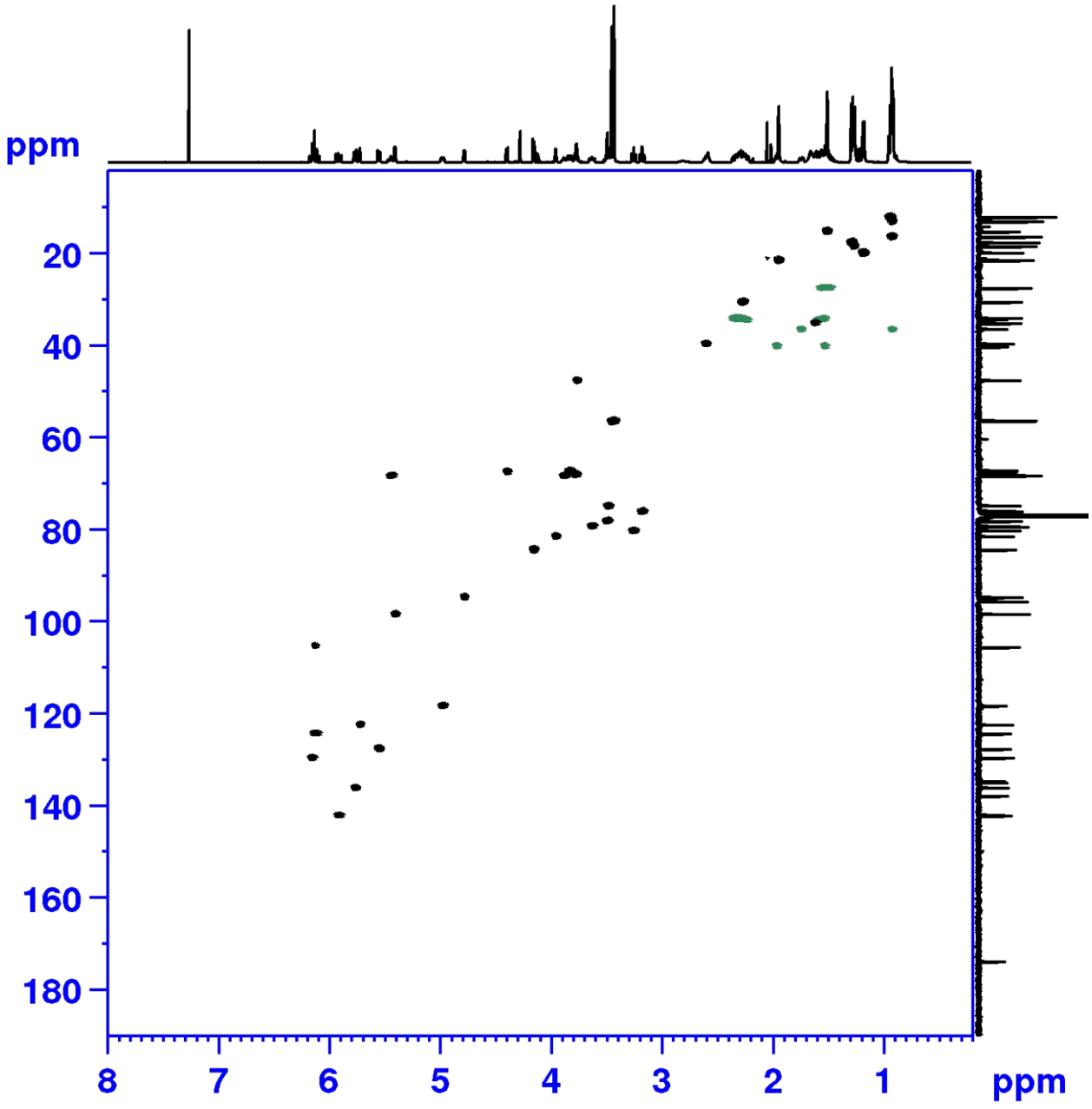


Figure S4. ^{1}H-^{13}C CH_2-edited-HSQC NMR spectrum of **1** (500 MHz, $CDCl_3$)

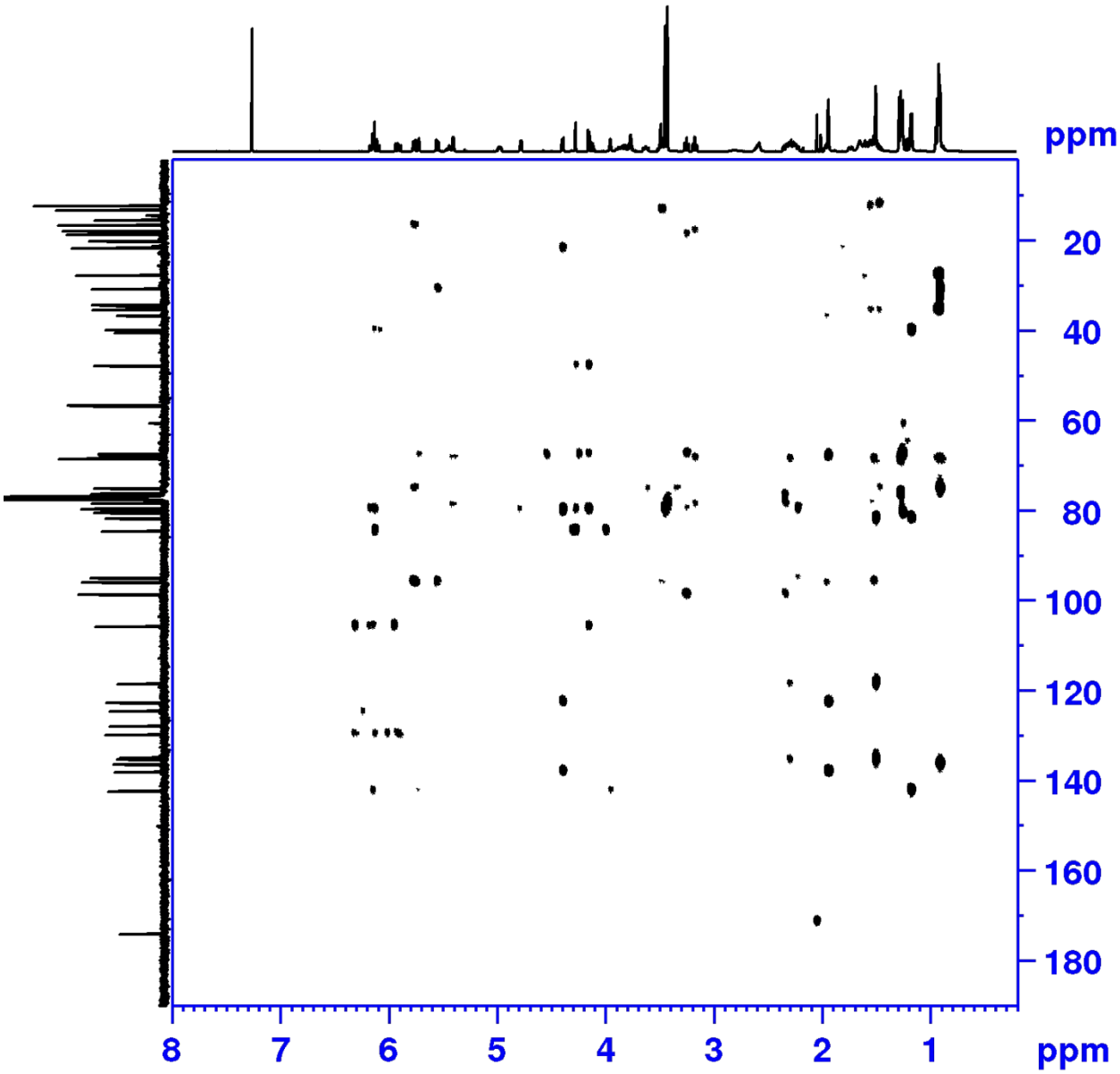
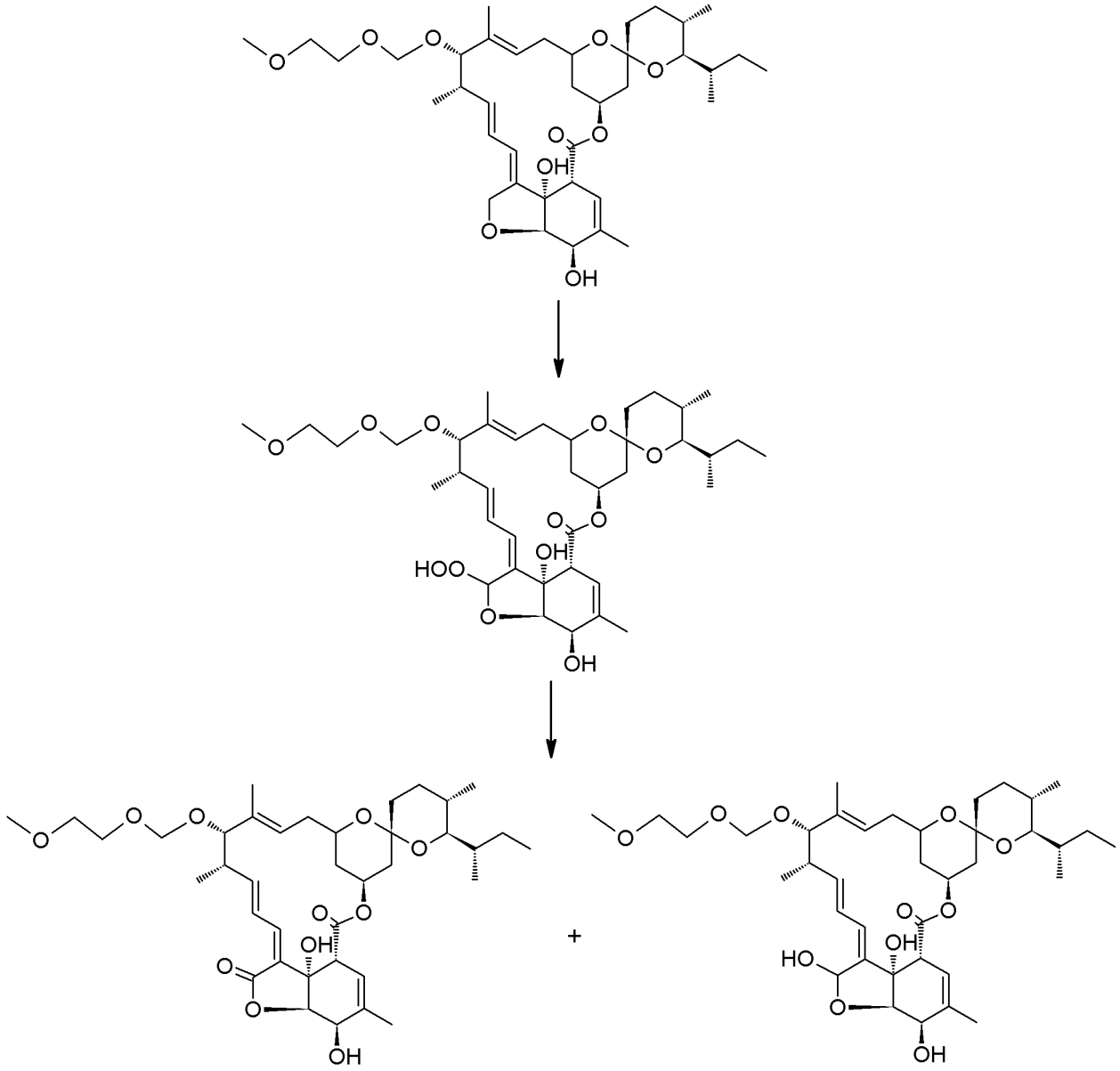


Figure S5. ^{1}H-^{13}C HMBC NMR spectrum of **1** (500 MHz, $CDCl_3$)



Oxidation reaction of an avermectin derivative, which were found to run through an unstable hydroperoxide derivative (taken from Faulkner, A. J.; Qingxi, W.; DeMontigny, P.; Murphy, J. S. *J. Pharm. Biomed. Anal.* **1997**, *15*, 523–536.)