Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Haber-independent, asymmetric synthesis of the marine alkaloid *epi*-leptosphaerin from a chitin-derived chiral pool synthon

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SUPPORTING INFORMATION

Contents

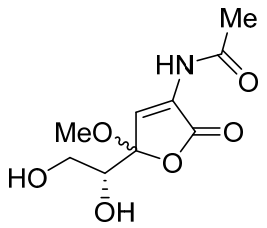
Experimental Procedures

General

All reactions were performed under an atmosphere of dry nitrogen using oven dried glassware unless otherwise stated. Commercially available starting materials and reagents were used as received unless otherwise noted. Anhydrous solvents were used as supplied. Methanol, pyridine and N,N-dimethylformamide were dried using an LC Technology solvent purification system. Thin layer chromatography (TLC) was performed using F254 0.2 mm silica plates, followed by visualisation with UV irradiation at 254 nm, and staining with ethanolic vanillin solution. Flash column chromatography was performed using 63 -100 μm silica gel. Infrared (IR) spectra were recorded with an FT-IR spectrometer using a diamond ATR sampling accessory. Absorption maxima are expressed in wavenumbers (cm^{-1}). Melting points were collected using a Kofler hot-stage apparatus and have not been corrected. NMR spectra were recorded at 298 K in D_2O, $(CD_3)_2CO$, $CDCl_3$ or pyridine – d_5 solution using a spectrometer operating at 400 MHz for ^1H nuclei and 100 MHz for ^{13}C nuclei. Chemical shifts are reported in ppm on the δ scale and were measured relative to the protium solvent that the sample was measured in: D_2O (δ 4.79 ppm) peak (^1H NMR) $(CD_3)_2CO$ (δ 2.05 ppm) peak (^1H NMR) or δ 29.8 and 206.3 ppm (^{13}C NMR), $CDCl_3$ (δ 7.26 ppm) peak (^1H NMR) or δ 77.2 ppm (^{13}C NMR) and pyridine – d_5 (δ 8.74, 7.58 and 7.22 ppm) peak (^1H NMR) or δ 150.4, 135.9 and 123.9 ppm (^{13}C NMR) . ^1H NMR shift values are reported as chemical shift δ, relative integral, multiplicity (s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet, b, broad), coupling constant (J, reported in Hertz [Hz]) and assignment. ^{13}C NMR shift values are reported as chemical shift δ and assignment. Assignments were made with the aid of COSY, HSQC (edited), and HMBC experiments. High resolution mass spectra were obtained using electrospray ionisation on a microTOF QII mass spectrometer. Samples were dissolved in an appropriate solvent (DMSO, DCM, MeOH or MeCN) and diluted to a nominal concentration of 3 μg mL^{-1} using either MeOH or MeCN, prior to direct infusion into the instrument. X-ray diffraction measurements of single crystals were performed on a Rigaku Oxford Diffraction XtaLAB-Synergy-S single-crystal diffractometer with a PILATUS 200K hybrid pixel array detector using Cu Kα radiation (λ = 1.54184 Å). The data were processed with the

SHELX2018-3 and Olex2 software packages.[1-3] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were inserted at calculated positions or located directly and refined with a riding model or without restrictions. Mercury 2020.3.1[4] was used to visualize the molecular structure. Crystal growth for X-ray crystallographic analysis purposes was achieved using slow vapour diffusion.

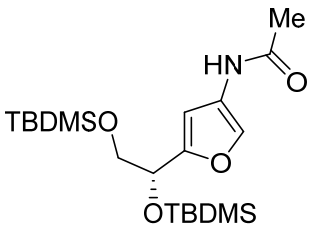
***N*-(5-((*R*)-1,2-dihydroxyethyl)-5-methoxy-2-oxo-2,5-dihydrofuran-3-yl)acetamide (5)**



4,5,6,7-Tetrachloro-2',4',5',7'-tetraiodofluorescein (Rose Bengal) (11 mg, 0.0108 mmol, 1 mol %) was added to a solution of Di-HAF[5] (200 mg, 1.08 mmol) in methanol (80 mL). The solution was purged with oxygen for 20 min. and cooled to -78 °C. The mixture was irradiated with a desk lamp under an oxygen atmosphere for 2 h, then warmed to room temperature. The solvent was evaporated *in vacuo* and the crude material purified by flash column chromatography eluting with dichloromethane-methanol (9.5:0.5) to give the *title compound* as a colourless oil. (40.4 mg, 0.175 mmol, 16%, *dr* 1:0.39); HRMS (ESI) *m/z* $[M + Na]^+$, calcd for $C_9H_{13}NO_6Na$ 254.0635, found 254.0628; ν_{max}/cm^{-1} (neat) 3283, 3040, 2944, 2844, 1767, 1694, 1657, 1533, 1371, 1313, 1153, 1037; δ_H (400 MHz, $(CD_3)_2CO$) 9.15 (1 H, br s, NH), 7.08 (0.4 H, s, ArH), 7.04 (1 H, s, Ar*H), 4.35 (1 H, m, OH), 4.22 (0.4 H, s, OH), 3.91 – 3.87 (1 H, m, C*H), 3.81 – 3.78 (1.4 H, m, 0.5 x 1 C*H_2, 1 x CH), 3.70 – 3.67 (0.4 H, m, 0.5 x 1 CH_2), 3.59 – 3.51 (1.4 H, m, 0.5 x 1 C*H_2, 0.5 x 1 CH_2), 3.22 (1.2 H, s, OMe), 3.21 (3 H, s, OMe*), 2.19 (3 H, s, C*H_3), 2.18 (1.2 H, s, Me)); δ_C 100 MHz, $(CD_3)_2CO$ 170.3 (C*), 170.2 (C), 167.7 (C*), 131.0 (C), 130.5 (C*), 124.1 (C*H), 122.9 (CH), 112.1 (C), 111.6 (C*), 75.5 (CH), 74.9 (C*H), 63.2 (CH_2), 62.9 (C*H_2), 51.5 (OMe), 51.3 (OMe*), 23.4 (Me + Me*), 1 x C not observed.

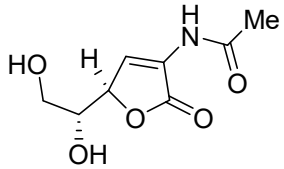
* Denotes the major diastereomer.

***N*-(5-(2,2,3,3,8,8,9,9-Octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)furan-3-yl)acetamide (6)**



To a solution of Di-HAF (200 mg, 1.08 mmol) in dry DMF (8 mL) was added imidazole (485 mg, 7.13 mmol, 6.6 eq.) followed by *tert*-butyldimethylsilyl chloride (488 mg, 3.24 mmol, 3 eq.). The mixture was stirred at room temperature. for 2 h. The reaction mixture was diluted with ethyl acetate (70 mL) and washed with water (3 x 30 mL). The organic layer was dried (Na_2SO_4), filtered, concentrated *in vacuo* and the crude residue purified by flash chromatography on silica gel eluting with light petroleum/acetone (10:1) to give the *title compound* as a pale orange oil (272 mg, 0.657 mmol, 61%); $[\alpha]_D^{24}$ + 16.9 (*c* 1.0, MeOH); HRMS (ESI) *m/z* $[M + Na]^+$, calcd for $C_{20}H_{39}NO_4Si_2Na$ 436.2310, found 436.2308; ν_{max}/cm^{-1} (neat) 3283, 2954, 2930, 2886, 2858, 1661, 1573, 1472, 1464, 1362, 1252, 1125, 1093, 1006, 968, 831, 775, 666, 556; δ_H (400 MHz, $(CD_3)_2CO$) 9.11 (1 H, br s, NH), 7.92 (1 H, d, *J* 1.0, CH), 6.29 (1 H, s, CH), 4.70 (1 H, t, *J* 6.0, CH), 3.81 (1 H, dd, *J* 5.4, 4.7, CH of CH_2), 3.75 (1 H, dd, *J* 6.8, 3.4, CH of CH_2), 2.02 (3 H, s, Ac), 0.88 (9 H, s, ^{t}Bu), 0.87 (9 H, s, ^{t}Bu), 0.09 (3 H, s, SiMe), 0.05 (3 H, s, SiMe), 0.03 (3 H, s, SiMe), 0.00 (3 H, s, SiMe); δ_C (100 MHz, $(CD_3)_2CO$) 167.8 (C), 154.4 (C), 131.3 (CH), 126.6 (C), 102.7 (CH), 70.9 (CH), 67.6 (CH_2), 26.3 (C(Me)$_3$), 26.2 (C(Me)$_3$), 23.0 (Ac), 18.9 (C), 18.8 (C), -3.2 (C), -4.6 (SiMe), -4.8 (SiMe), -5.2 (SiMe), -5.3 (SiMe), 3 x C not observed

***epi*-Leptosphaerin**

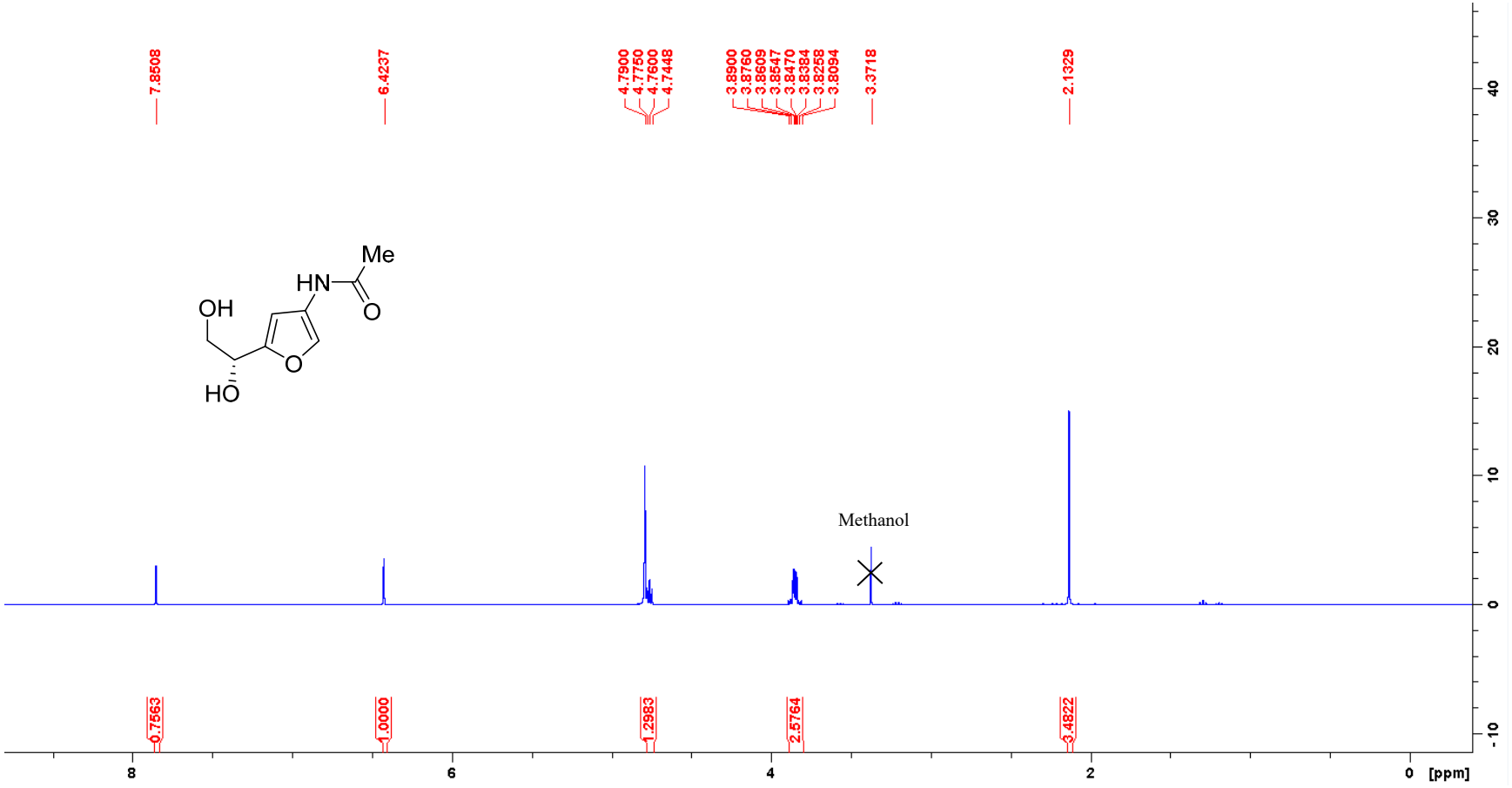


4,5,6,7-Tetrachloro-2',4',5',7'-tetraiodofluorescein (Rose Bengal) (5 mg, 0.00484 mmol, 1 mol %) was added to a solution of **6** (200 mg, 0.484 mmol) in methanol (80 mL). The solution was purged

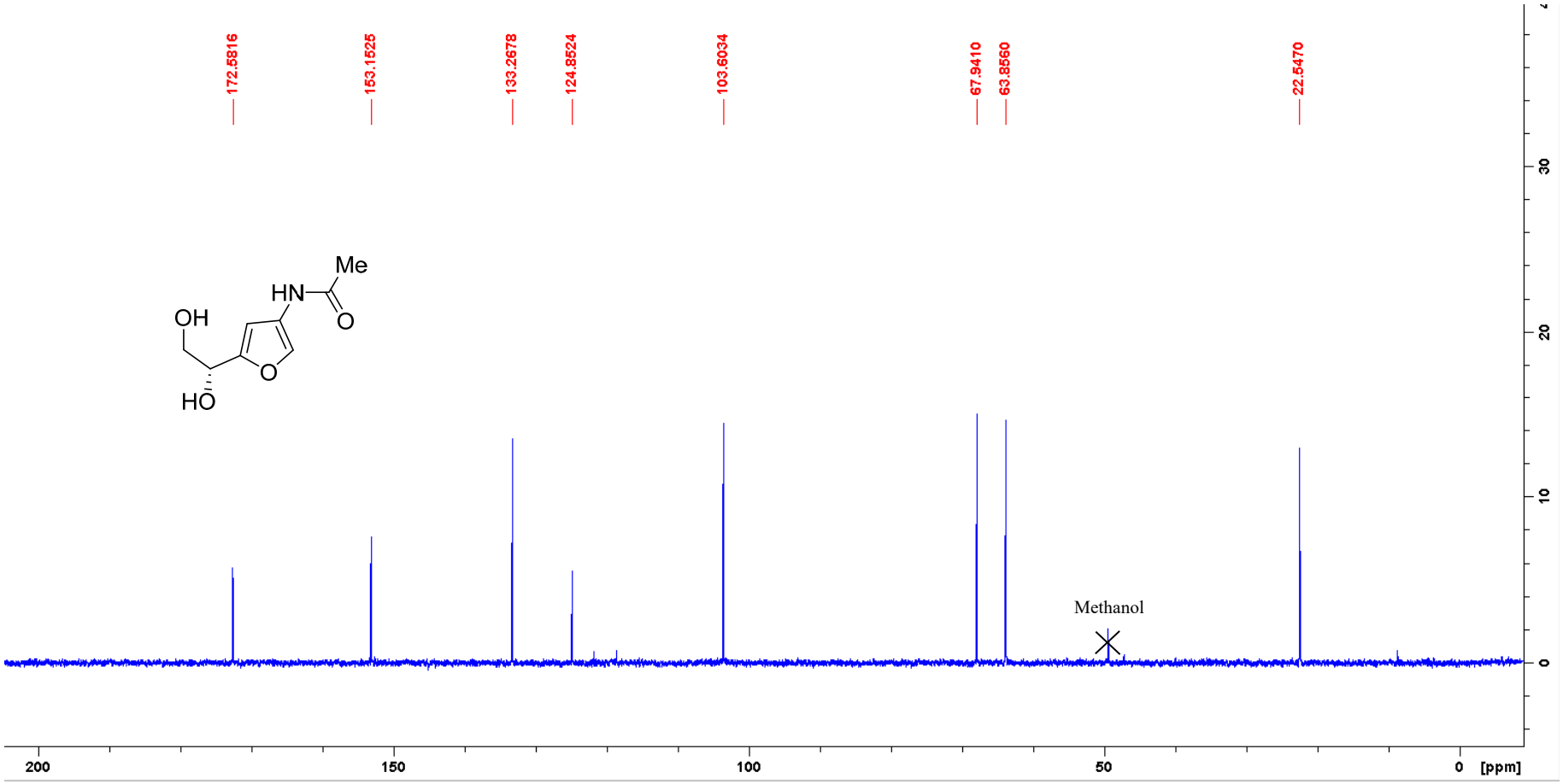
with oxygen for 30 minutes and cooled to -78 °C. The mixture was irradiated with a lamp under an oxygen atmosphere for 2 hours before it was allowed to warm to room temperature. The solvent was evaporated *in vacuo* and the remaining oil was dissolved in dichloromethane (16 mL). An oxalic acid solution (0.127M, 18.5 mL) was added and the mixture was stirred for 50 min. at room temperature. The aqueous phase was extracted with dichloromethane (3 x 40 mL) and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo.* The catalyst was removed from the crude mixture using flash chromatography on silica with an eluent of light petroleum/acetone (3:1), giving the crude hydroxybutenolide **7** (~176 mg) as an orange oil that was used immediately in the next step.

The crude hydroxybutenolide (~176 mg, 0.38 mmol) was dissolved in methanol (9 mL) and the solution was cooled to 0 °C. Cerium trichloride heptahydrate (71.2 mg, 0.191 mmol, 0.5 mol eq.) and sodium borohydride (57.8 mg, 1.528 mmol, 4 mol eq.) were added and the resulting mixture was stirred for 1.5 h at 0 °C. Concentrated HCl was added dropwise until the solution turned a pale orange and had a pH of ~2, after which the mixture was stirred for a further 1 h at 0 °C. The mixture was allowed to warm to room temperature and then the solvent was evaporated *in vacuo*. The crude residue was purified using flash chromatography on silica gel eluting with dichloromethane-methanol (20:1) gave the *title compound* as a colourless solid (15 mg, 0.0746 mmol, 15.4% from **6**); **NMR data see Table S1**; $[\alpha]_D^{24}$ – 32.9 (*c* 0.07, H_2O) [lit[6] $[\alpha]_D^{25}$ +6.5 (*c* 0.07, H_2O)]; mp 175.1 - 175.6 ºC (lit[6] mp not provided]; HRMS (ESI) *m/z* $[M + Na]^+$, calcd for $C_8H_{11}NO_5Na$ 224.0529, found 224.0529; ν_{max}/cm^{-1} (neat) 3436, 3352, 3299, 3137, 1741, 1692, 1653, 1532, 1404, 1377, 1341, 1314, 1252, 1201, 1133, 1102, 1073, 1030, 918, 866, 833, 776;

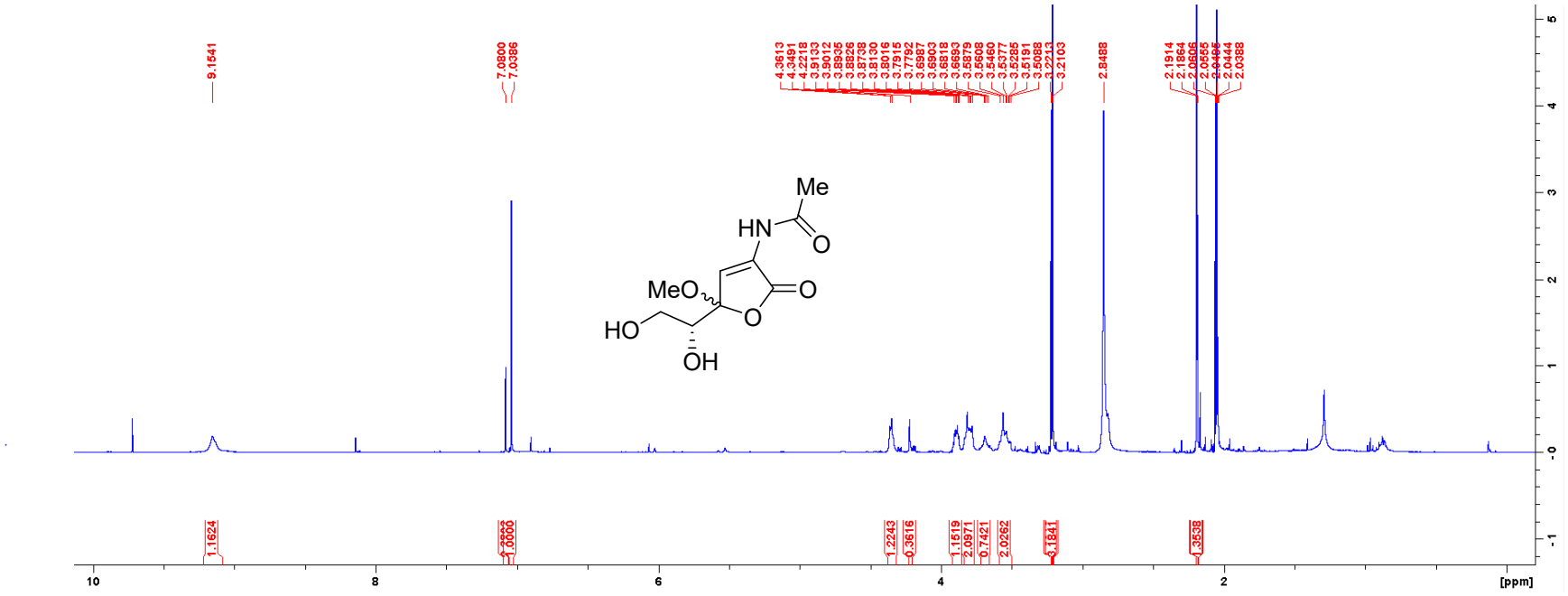
^{1}H NMR spectrum of Di-HAF (400 MHz, D_2O)



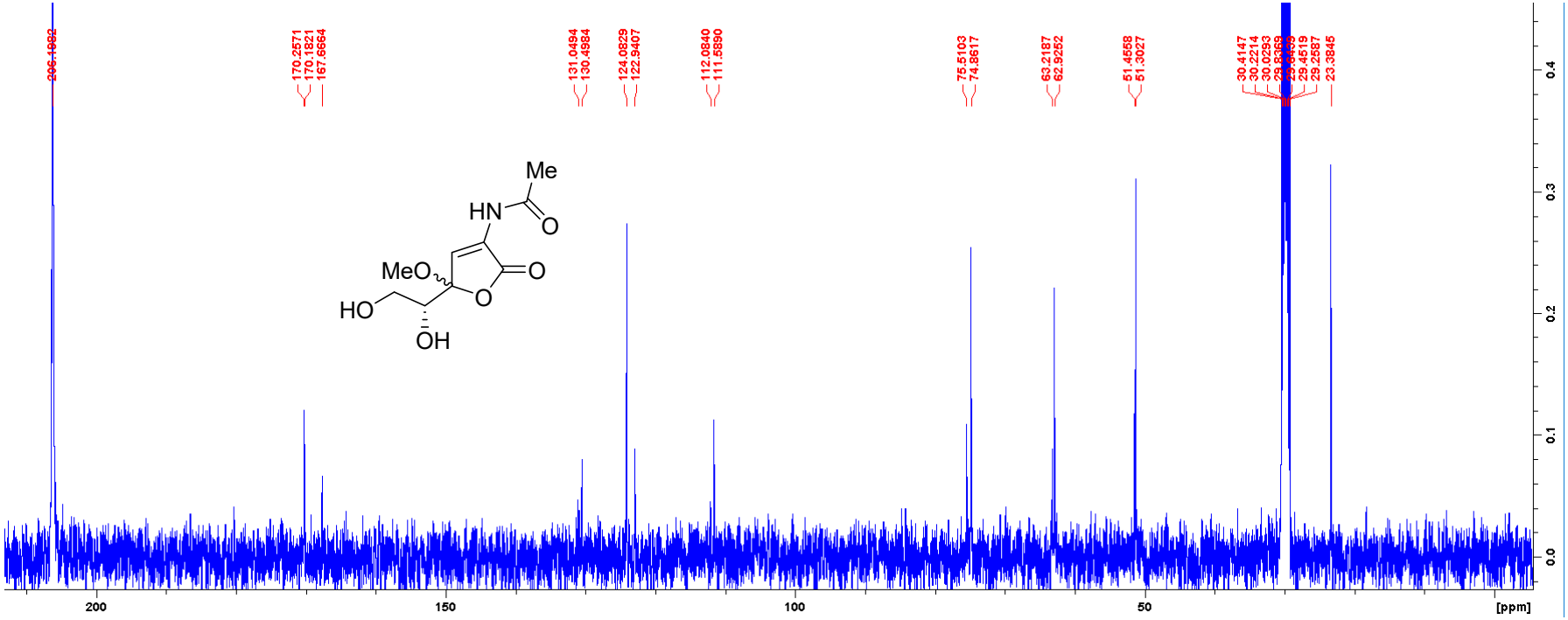
^{13}C NMR spectrum of Di-HAF (100 MHz, D_2O)



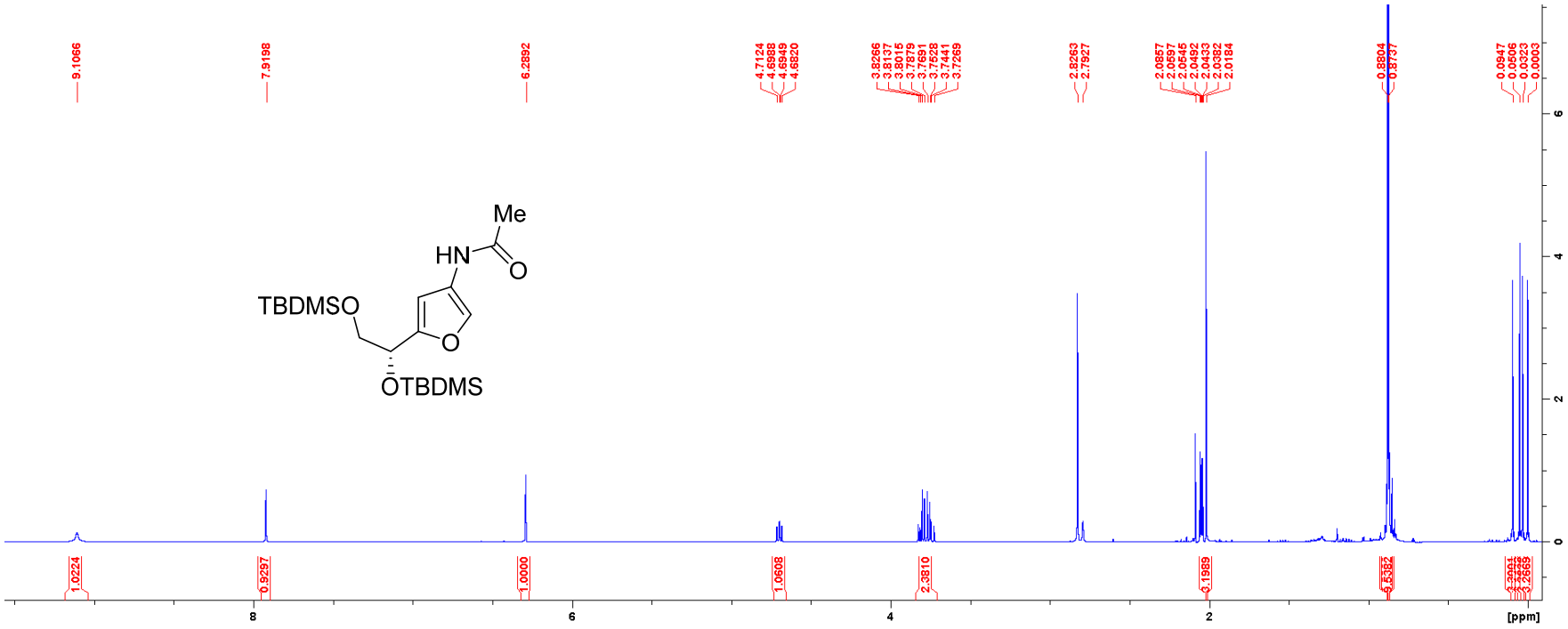
^{1}H NMR spectrum of **5** (400 MHz, $(CD_3)_2CO$)



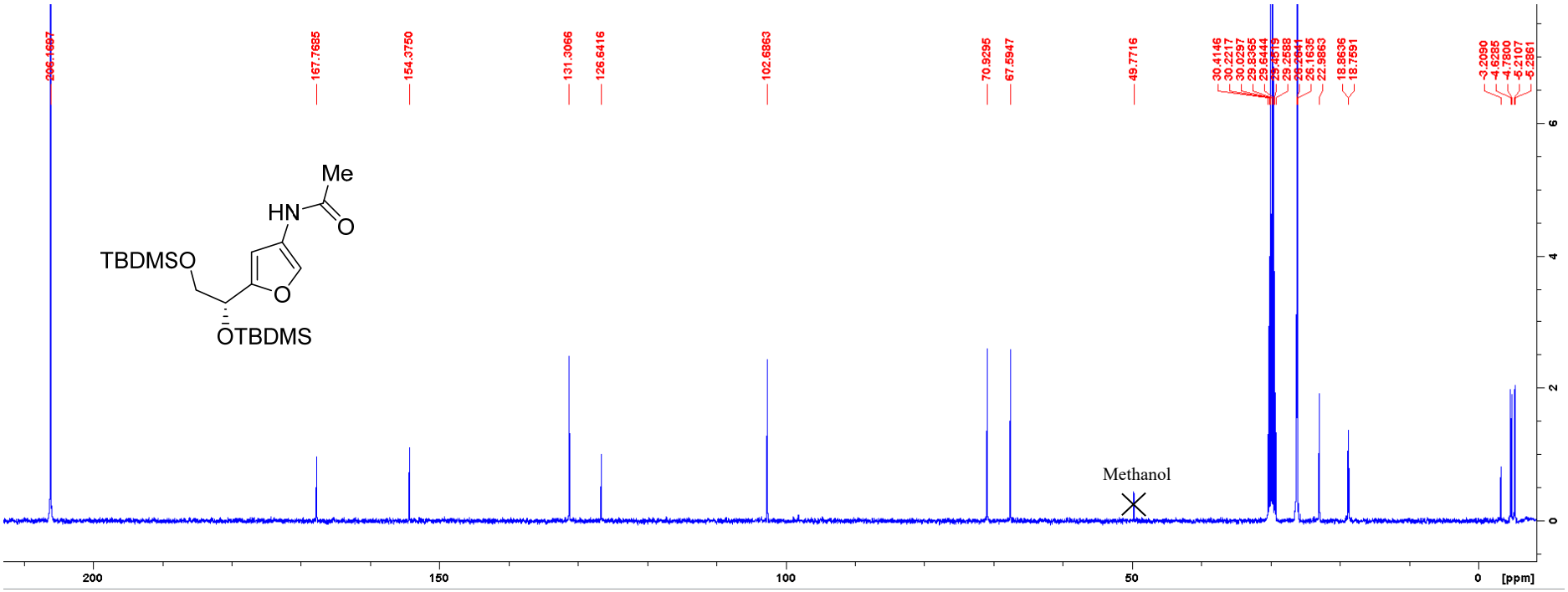
^{13}C NMR spectrum of **5** (100 MHz, $(CD_3)_2CO$)



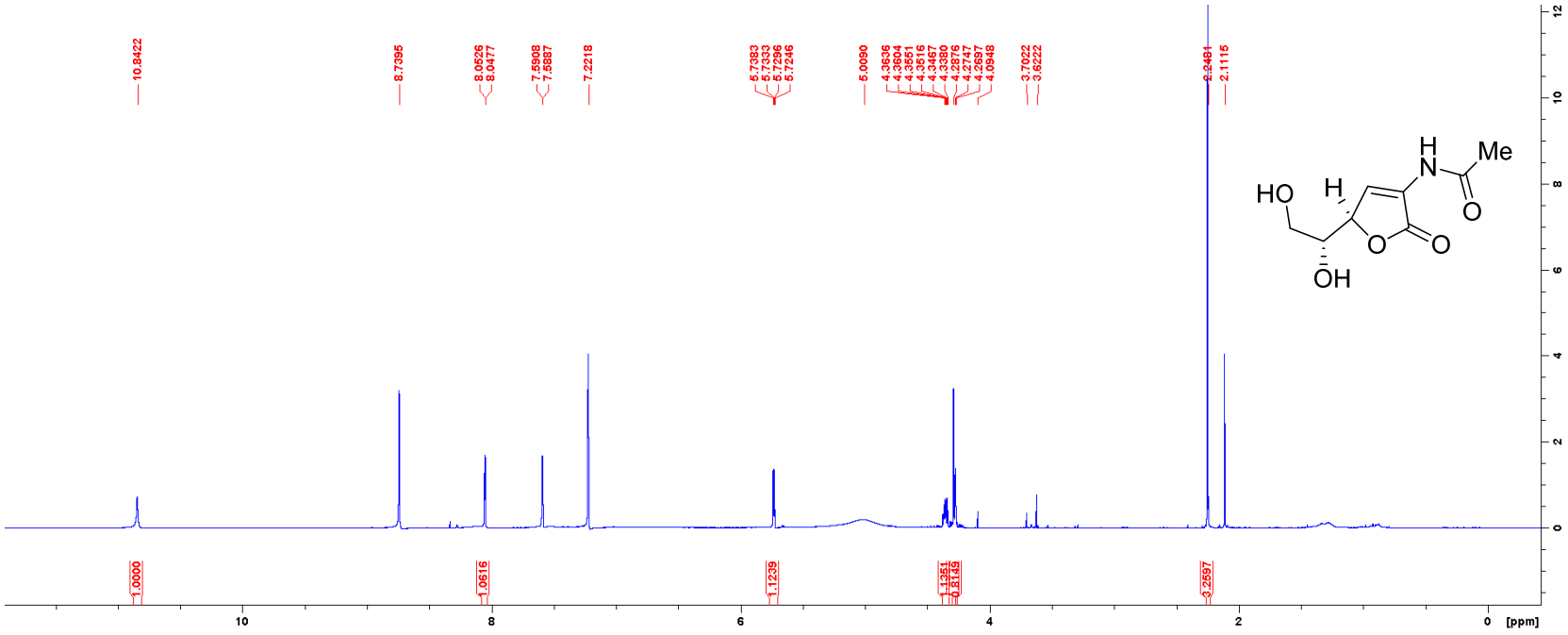
^{1}H NMR spectrum of **6** (400 MHz, $(CD_3)_2CO$)



^{13}C NMR spectrum of **6** (100 MHz, $(CD_3)_2CO$)



^{1}H NMR spectrum of *epi*-leptosphaerin (400 MHz, pyridine-d_5)



^{13}C NMR spectrum of *epi*-leptosphaerin (100 MHz, pyridine-d_5)

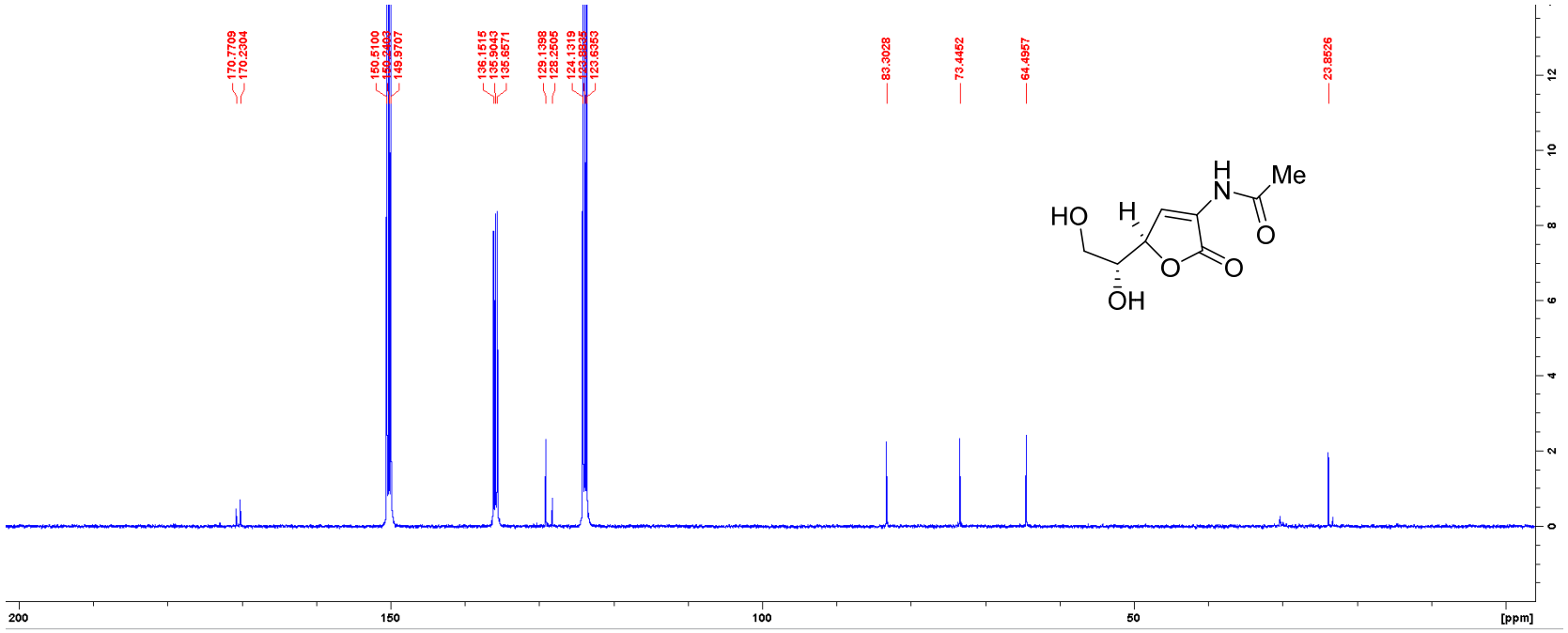
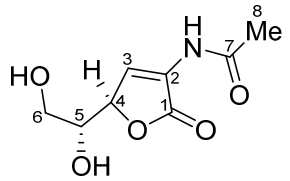


Table S1



^{1}H NMR (pyridine-d_5) ppm				^{13}C NMR (pyridine- d_5) ppm			
Isolated[6]	**Synthesised (this work)**	**Assignment**	**Difference**	**Isolated[6]**	**Synthesised (this work)**	**Assignment**	**Difference**
10.86 (1 H, s, NH)	10.84 (1 H, s, NH)	NH	0.02	170.8	170.8	C-1	0
8.05 (1H, d, *J* 2.0, CH)	8.05 (1 H, d, *J* 2.0, CH)	H-3	0	170.2	170.2	C-7	0
5.73 (1H, dd, *J* 3.3, 2.0, CH)	5.73 (1 H, dd, *J* 2.0, 1.5 CH)	H-4	0	129.1	129.1	C-3	0
4.35 (1H, bs, CH)	4.35 (1 H, m, CH)	H-5	0	128.3	128.3	C-2	0
4.29 (2H, m, CH_2)	4.29 (1 H, s 1 x CH of CH_2)	1 x H of H_2-6	0	83.3	83.3	C-4	0
2.25 (3 H, s, Me)	4.27 (1 H, d, *J* 2.0, 1 x CH of CH_2)	1 x H of H_2-6	0.02	73.4	73.4	C-5	0
	2.25 (3 H, s, Me)	H_3-8	0	64.5	64.5	C-6	0
				23.8	23.9	C-8	-0.1

Compound	***epi*-leptosphaerin**
CCDC number	2177368
Empirical formula	$C_8H_{11}NO_5$
Formula weight	201.18
Temperature/K	100.0(3)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	6.0853(2)
b/Å	6.9127(2)
c/Å	21.3235(4)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	896.99(4)
Z	4
ρ_{calc}g/cm^3	1.490
μ/mm^{-1}	1.079
F(000)	424.0
Crystal size/mm^3	0.12 × 0.1 × 0.1
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	8.294 to 135.466
Index ranges	$-7 \leq h \leq 7$, $-8 \leq k \leq 8$, $-25 \leq l \leq 9$
Reflections collected	5090
Independent reflections	1620 [R_{int} = 0.0343, R_{sigma} = 0.0339]
Data/restraints/parameters	1620/0/137
Goodness-of-fit on F^2	1.058
Final R indexes [I>=2σ (I)]	R_1 = 0.0294, wR_2 = 0.0731
Final R indexes [all data]	R_1 = 0.0307, wR_2 = 0.0741
Largest diff. peak/hole / e Å^{-3}	0.17/-0.19
Flack parameter	0.08(14)

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