Electronic Supplementary Information

Isolation and Total Synthesis of Dysidone A: A New Piperidone Alkaloid from the Marine Sponge *Dysidea* sp.

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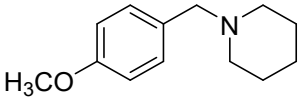
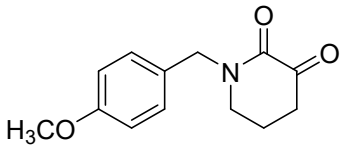
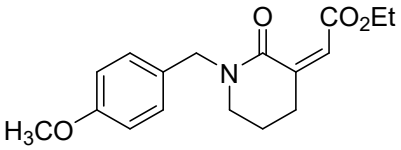
Procedure for the total synthesis and analytical data of related compounds:



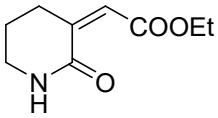
1-(4-methoxybenzyl) piperidine (1a): Dissolve piperidine (1.7 g, 20 mmol, 1.0 equiv) and *N*, *N*-diisopropylethylamine (3.88 g, 30 mmol, 1.5 equiv) in dichloromethane, the solution was stirred at 0 °C for 5 min, and p-methoxybenzyl chloride (3.13 g, 20 mmol, 1.0 equiv) was then added and resulting the solution was reacted at room temperature for 12 h. The resulting reaction solution was washed with saturated brine, and the aqueous layer was extracted three times with dichloromethane, the organic layer was dried over anhydrous. The residue was purified by flash chromatography (silica gel, petroleum / ethyl acetate = 15:1) to afford the *N*-(4-methoxybenzyl) piperidine (3.7 g, 72.8 mmoL, 90.9 %) as a white liquid. Physical properties and spectroscopic data in accordance with the literature 1[1]. m.p, 182-183 °C. ^{1}H NMR (300M, $CDCl_3$): δ 7.22 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 3.80 (s, 3H), 3.41 (s, 2H), 2.35 (s, 4H), 1.56 (m, 4H), 1.47-1.30 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.5, 130.5, 130.4, 113.4, 63.2, 55.2, 54.3, 26.0, 24.4; HRESIMS *m/z*: 206.1535 $[M + H]^+$ (calcd for $C_{13}H_{20}NO$, 206.1539).



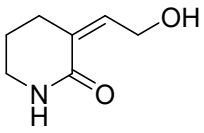
1-(4-Methoxybenzyl) piperidine-2,3-dione (1b): To a solution of **1a** (0.25 g, 1.2 mmol, 1.0 equiv) in THF (80 mL) was added PIDA (0.77 g, 2.4 mmol, 2.0 equiv) and I_2 (0.61 g, 1.2 mmol, 2.0 equiv), and the reaction mixture was at RT for 6 h. PIDA and then additional PIDA (0.39 g) was added for another 12 hours. then the reaction was quenched with saturated sodium thiosulfate (48 mL), extracted with EtOAc, dried over Na_2SO_4. The residue was purified by flash chromatography (silica gel, petroleum / ethyl acetate = 5:1) to afford (0.13 g, 45.6 %) of **1b** as a white liquid. Physical properties and spectroscopic data in accordance with the literature 2[2]. m.p, 108-109 °C; ^{1}H NMR (300M, $CDCl_3$): δ 7.15 (d, *J* = 8.7 Hz, 2H), 6.78 (*d*, *J* = 8.7 Hz, 2H), 4.53 (s, 2H), 3.71 (s, 3H), 3.38 (t, *J* = 6.0 Hz, 2H), 2.63 (t, *J* = 6.9 Hz, 2H), 2.08-2.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.7, 159.2, 157.7, 129.7, 127.6, 114.0, 55.1, 50.3, 46.4, 38.4, 21.5. HRESIMS *m/z*: 234.1129 $[M + H]^+$ (calcd for $C_{13}H_{16}NO_3$ 234.1125).



Ethyl (*Z*)-2-[1-[(4-methoxybenzyl) methyl]-2-oxo-3-piperidinylidene] acetate (1c): Dissolve NaH (0.08 g, 3.2 mmoL, 1.6 equiv) in dry DMF (10 mL), the solution was stirred at 0 °C, and triethylphosphonoacetate (0.673 g, 3.0 mmol, 1.5 equiv) was then added. 15 minutes later, **1b** (0.466 g, 2.0 mmol, 1.0 equiv) was dissolved in THF and added dropwise to the mixture reaction and resulting the solution was reacted at RT for 12 h. TLC followed the reaction. Upon stirring for 12 h, the reaction was quenched with water and extracted with DCM, dried over Na_2SO_4. The residue was purified by flash chromatography (silica gel, petroleum / ethyl acetate = 1:1) to afford (0.23 g, 76.0 %) of **1c** as a white liquid. Analytical data for **1c**: m.p, 166-167 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.06 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 8.7 Hz, 2H), 5.85 (s, 1H), 4.41 (s, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.63 (s, 3H), 3.10 (t, *J* = 6.0 Hz, 2H), 3.39 (t, *J* = 6.0 Hz, 2H), 1.75-1.67 (m, 2H), 1.20 (t, *J* = 7.1, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6, 161.8, 158.6, 135.2, 129.2, 128.4, 128.5, 113.5, 60.4, 54.8, 49.2, 46.5, 29.7, 22.2, 13.7. HRESIMS *m/z*: 304.1537 $[M + H]^+$ (calcd for $C_{17}H_{22}NO_4$ 304.1543).



Dysidone B (1d): To a solution of **1c** (0.21 g, 0.7 mmoL, 1.0 equiv) in *t*-Butanol and water mixture (4:1 volume ratio), added cerium ammonium nitrate (0.15 g, 0.9 mmoL, 1.3 equiv) to the reaction mixture. The mixture was stirred at RT for 1 h and then diluted with 10 % NaCl, extracted with EtOAc, dried over Na_2SO_4. The residue was purified by flash chromatography (silica gel, ethyl acetate = 0:100) to afford (0.06 g, 43.0 %) of **1d** as a white liquid. Analytical data for **1d**: m.p, 168-169 °C; ^{1}H NMR (300M, $CDCl_3$): δ 6.86 (s, 1H), 5.97 (s, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.35-3.30 (m, 2H), 2.56-2.52(m, 2H), 1.92-1.83(m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$): δ 168.0, 164.1, 134.7, 127.4, 60.9, 42.1, 29.8, 22.6, 13.9; HRESIMS *m/z*: 184.0962 $[M + H]^+$ (calcd for $C_9H_{14}NO_3$ 184.0968).



Synthetic dysidone A (1): Dissolved **1d** (0.13 g, 0.7 mmoL, 1.0 equiv) in dry dichloromethane (3 mL), under nitrogen atmosphere was added, then dissolve diisobutylaluminum hydride (1 mL) in dry dichloromethane (1 mL), then the temperature was lowered to -78 °C. TLC followed the reaction. H_2O, 1M sodium hydroxide and water in sequence, with an interval of 17 seconds between each addition, the mixture was diluted with H_2O, extracted with CH_2Cl_2, dried over Na_2SO_4. The residue was purified by HPLC (3 mL/min, MeOH: H_2O = 10: 90, 210 nm) to afford (0.09 g, 78.0 %) of **1** as a light-yellow oil. Analytical data for **1**: m.p., 170-171 °C; ^{1}H NMR (300M, $CDCl_3$): δ 6.19 (m, 1H), 5.98 (brs, 1H), 4.33 (d, J = 6.1 Hz, 2H), 3.38 (m, 2H), 2.53 (m, 2H), 1.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 141.6, 130.8, 59.4, 42.7, 31.9, 22.9; HRESIMS *m/z*: 164.0684 $[M + Na]^+$ (calcd for $C_7H_{11}NO_2Na$, 164.0687).

References

1. V. Werner, M. Ellwart, A. J. Wagner and P. Knochel, Preparation of tertiary amines by the reaction of Iminium Ions derived from unsymmetrical aminals with zinc and magnesium organometallics, *Org. Lett.*, 2015, **17**, 2026-2029.

2. J. Romero-Ibanez, S. Cruz-Gregorio, L. Quintero and F. Sartillo-Piscil, Concise and environmentally friendly asymmetric total synthesis of the putative structure of a biologically active 3-hydroxy-2-piperidone alkaloid, *Synthesis*, 2018, **50**, 2878-2886.

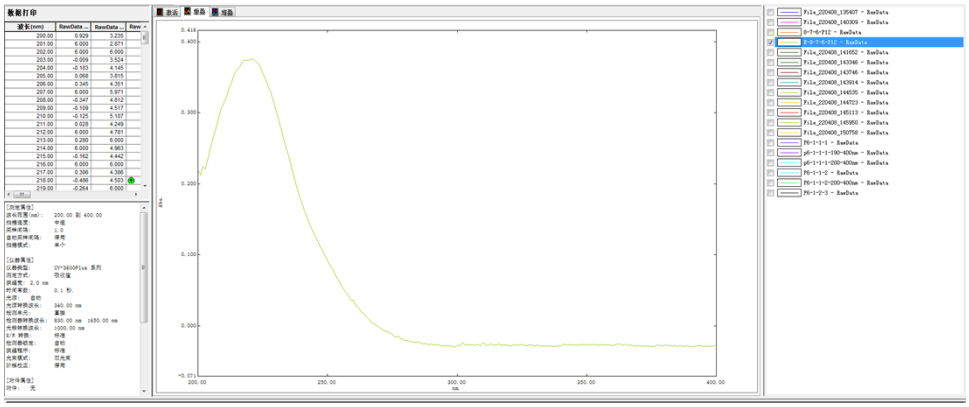


Figure S1 UV spectrum of natural dysidone A (1) in $CDCl_3$

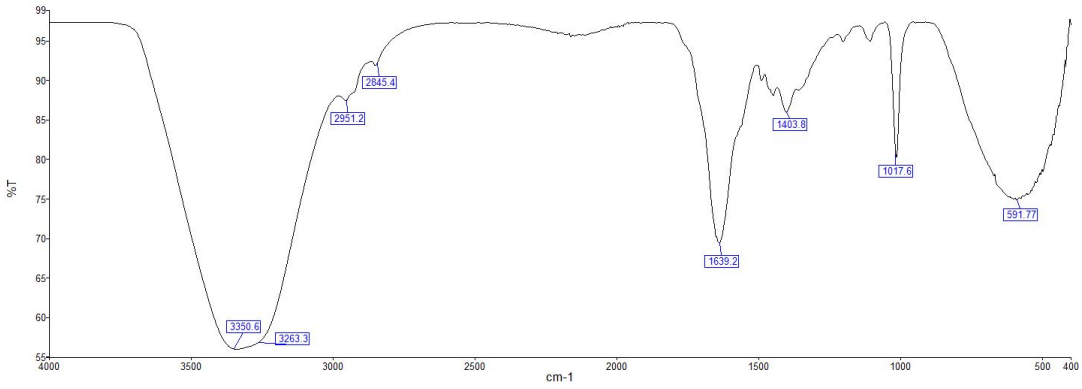


Figure S2 IR spectrum of natural dysidone A (1) in $CDCl_3$

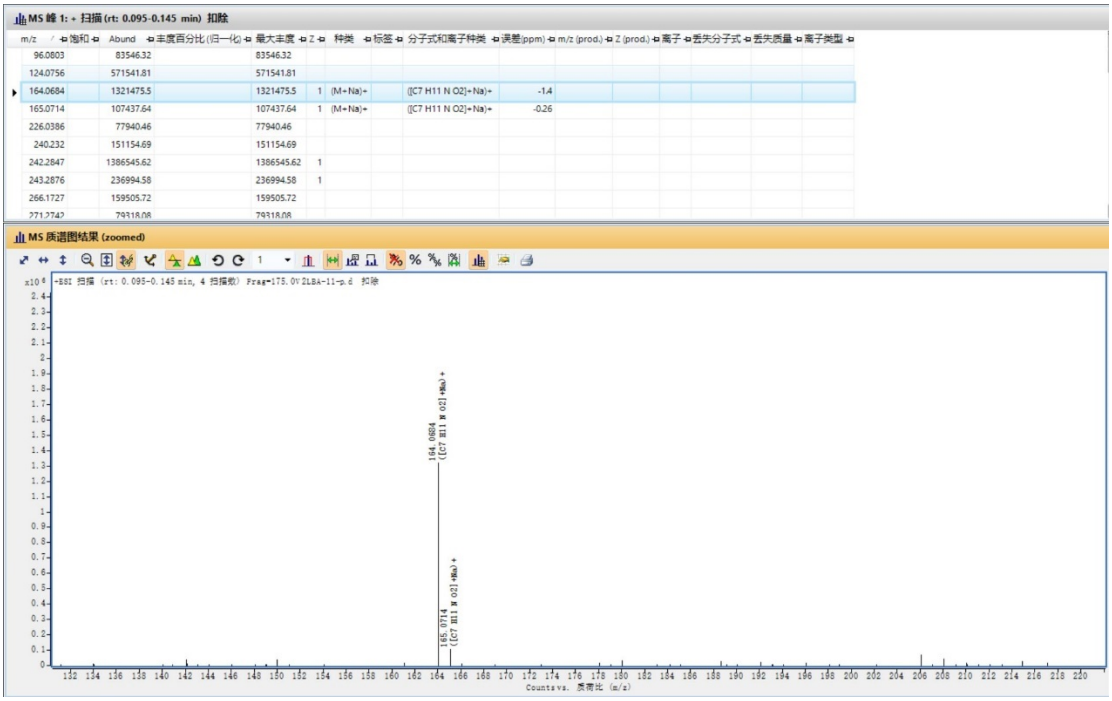


Figure S3 HRESIMS spectrum of natural dysidone A (1) in $CDCl_3$

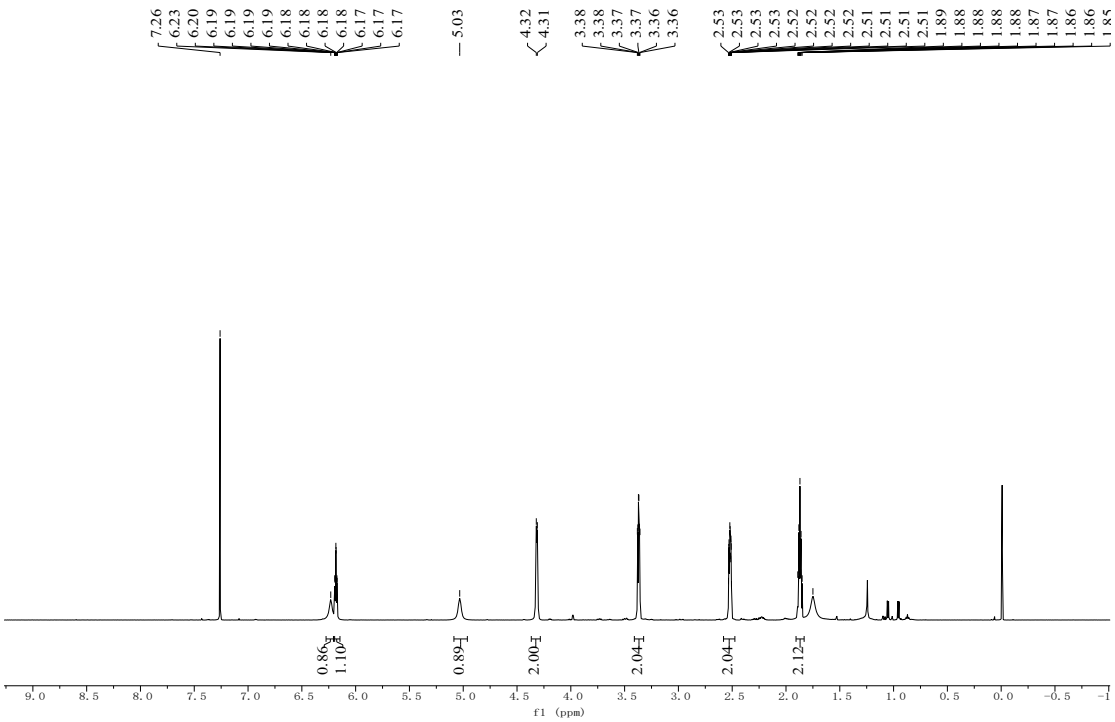


Figure S4 ^{1}H NMR spectrum of natural dysidone A (1) in $CDCl_3$

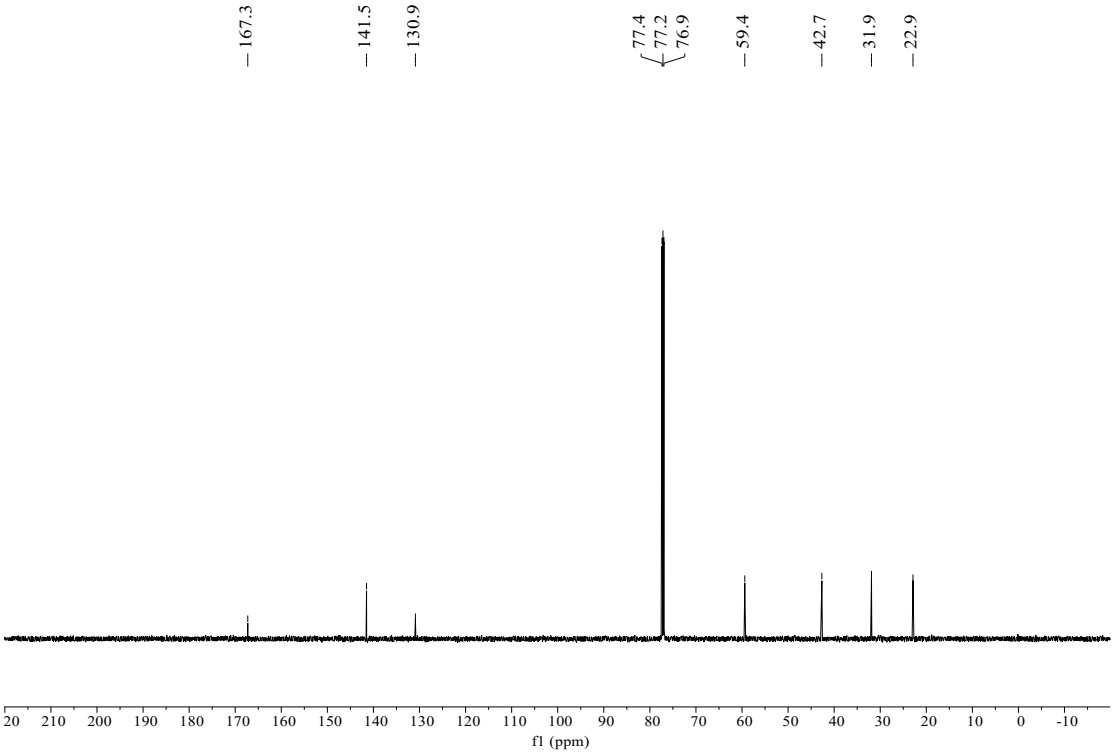


Figure S5 ^{13}C NMR spectrum of natural dysidone A (1) in $CDCl_3$

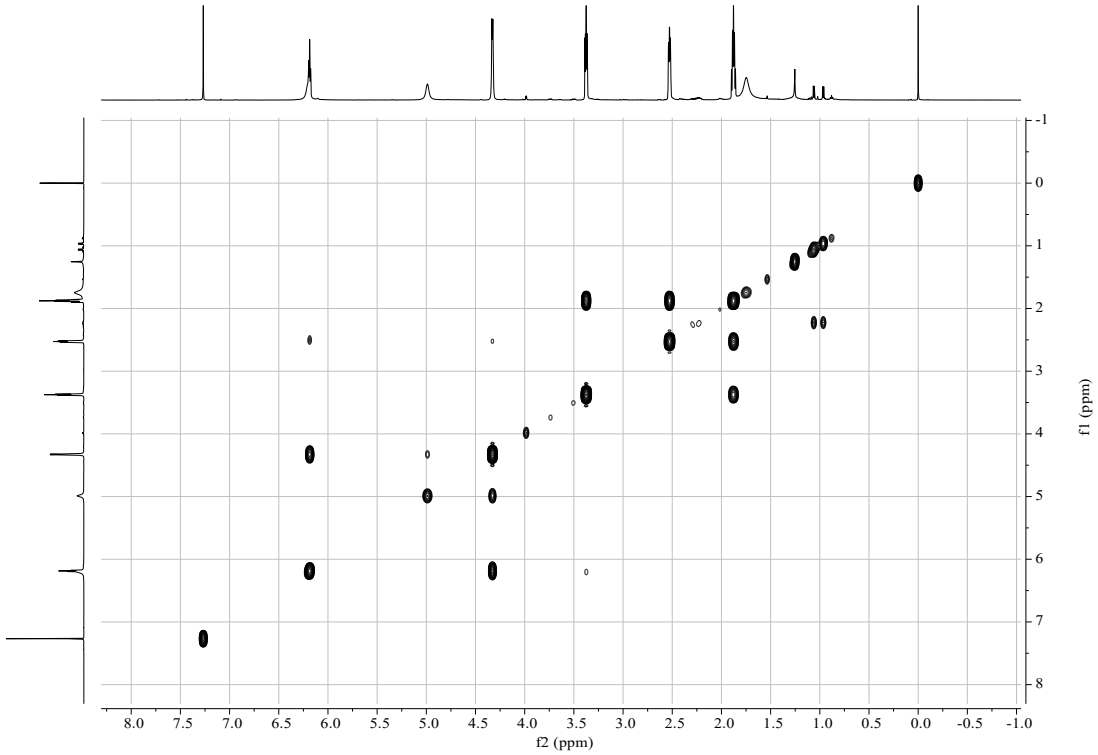


Figure S6 ^{1}H-^{1}H COSY spectrum of natural dysidone A (1) in $CDCl_3$

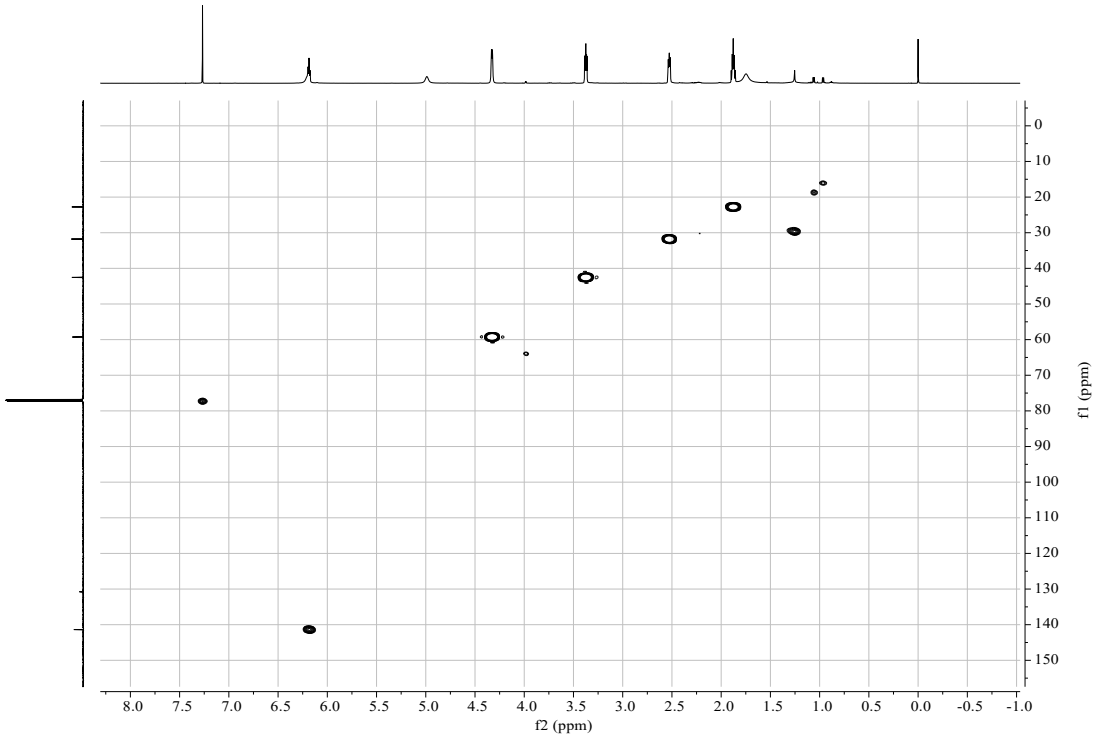


Figure S7 HSQC spectrum of natural dysidone A (1) in $CDCl_3$

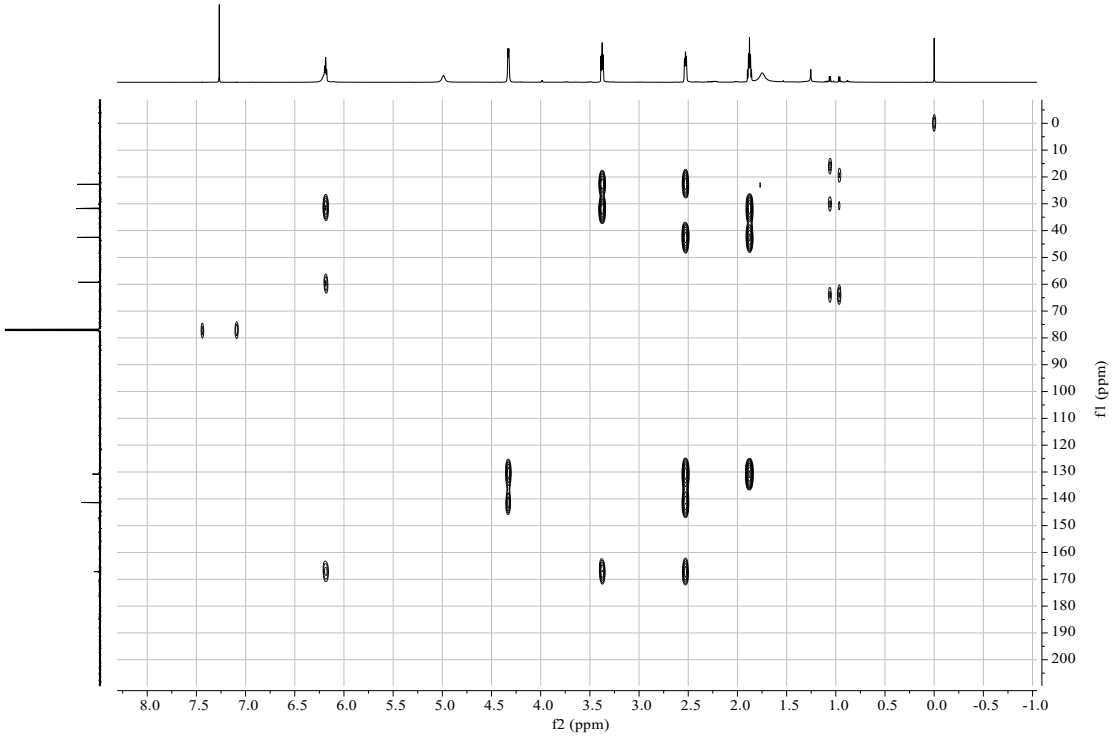


Figure S8 HMBC spectrum of natural dysidone A (1) in $CDCl_3$

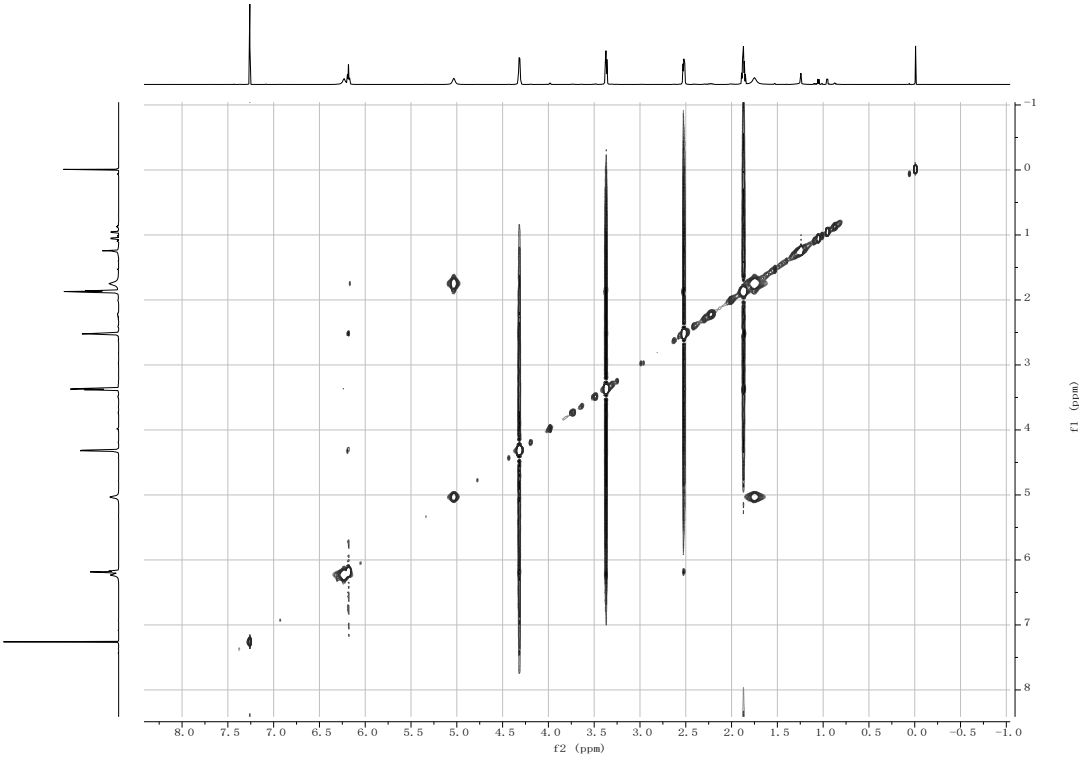


Figure S9 NOESY spectrum of natural dysidone A (1) in $CDCl_3$

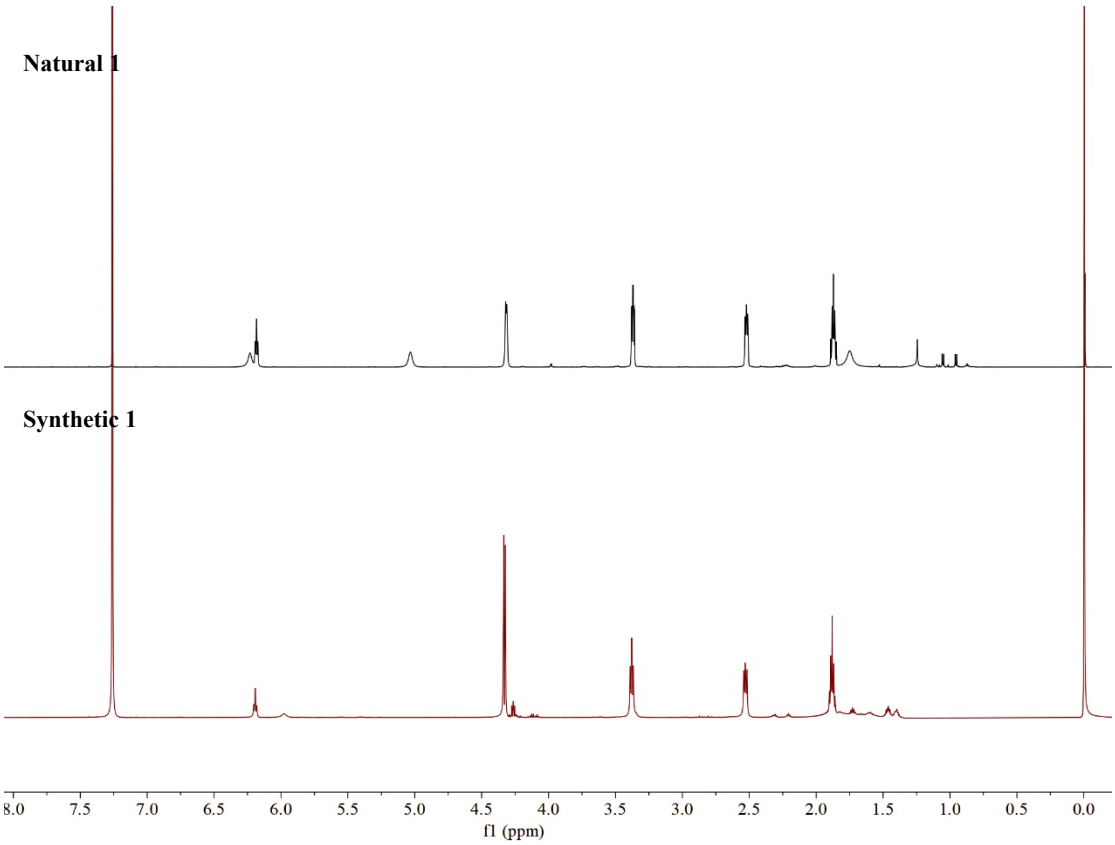


Figure S10 ^{1}H NMR spectra of natural and synthetic 1 in $CDCl_3$

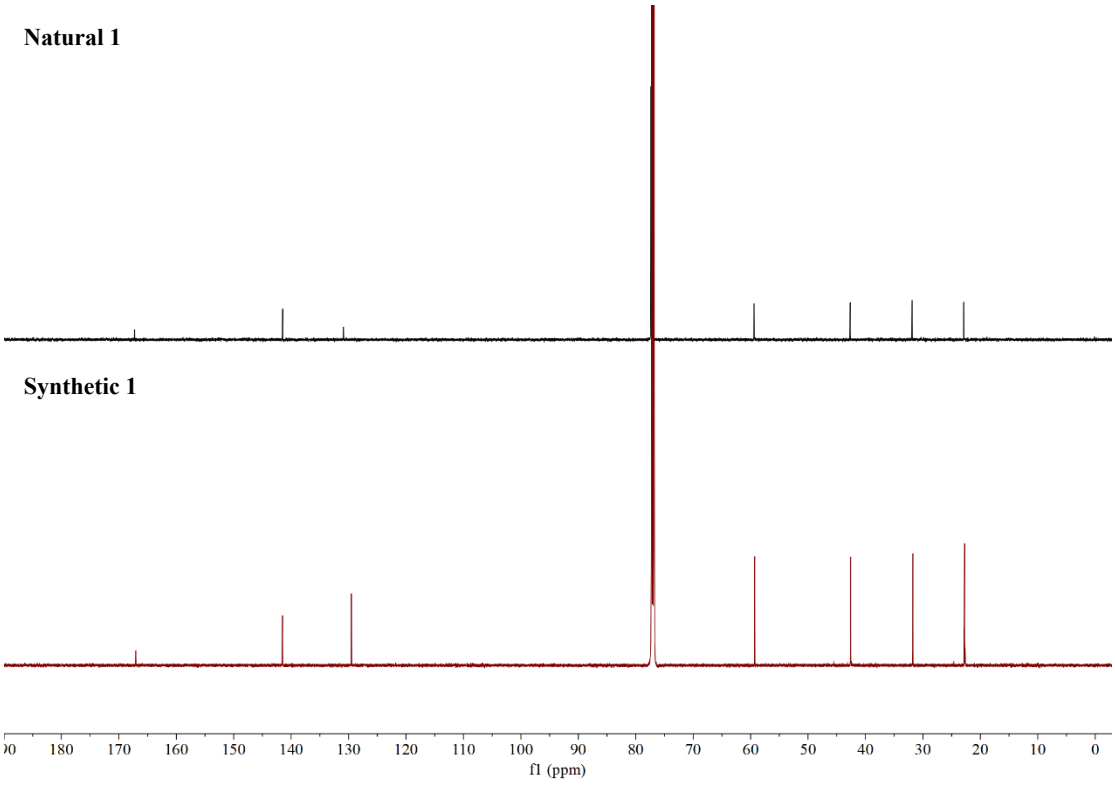


Figure S11 ^{13}C NMR spectra of natural and synthetic 1 in $CDCl_3$