Supporting Information

Hypermonins A and B, two 6-norpolyprenylated Acylphloroglucinols with unprecedented skeletons from *Hypericum monogynum*

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1. Experimental section

General experimental procedures

Optical rotations were determined on a JASCO P-1020 polarimeter. UV spectra were detected on a Shimadzu UV-2401PC spectrometer. IR spectra were determined on a Bruker FT-IR Tensor-27 infrared spectrophotometer with KBr disks. CD spectra were recorded with an Applied Photophysics Chirascan spectrometer. ^{1}H, ^{13}C NMR and 2D NMR spectra were recorded on INOVA-400 MHz, and Bruker Avance III 600 MHz spectrometers using TMS as an internal standard. EIMS and HR-EIMS analysis were carried out on Waters Xevo TQS and Agilent 1290 UPLC/6540 Q-TOF mass spectrometers, respectively. HPLC separation was performed on an instrument consisting of a Waters 600 controller, a Waters 600 pump, and a Waters 2487 dual λ absorbance detector with an X-bridge (250 ×10 mm) preparative column packed with C18 (5 μm). Fractions were monitored by TLC (GF 254, Qingdao Marine Chemical Co., Ltd.), and spots were visualized by heating silica gel plates immersed in 5% H_2SO_4 in ethanol.

Plant Material

The leaves and twigs of *H. monogynum* were collected in September 2015, in Leishan, Guizhou Province of China, which were identified by Dr. Wei Gu. A voucher specimen (H20150909) was deposited at the key laboratory of chemistry for natural products of Guizhou Province and Chinese Academy of Sciences.

Extraction and Isolation

The air-dried powder of the plant material (8 kg) were extracted with MeOH (50 L × 3) at 80 °C. The combined MeOH extracts were concentrated under reduced pressure to give a crude residue (1.5 Kg), which was suspended in water. The water layer was partitioned with EtOAc (10 L × 4). The EtOAc portion (500 g) was chromatographed on a silica gel column eluted with petroleum ether/EtOAc and then $CHCl_3$/MeOH to yield ten fractions (A–I), based on TLC analysis. Fraction C (17.5 g) was applied to an RP-C18 column, eluted with a gradient of MeOH-H_2O (50%→100%) to get seven fractions (C1-C7). Fraction C6 (4.3 g) was subjected to CC on Sephadex LH-20 eluted with MeOH, followed by repeated CC over silica gel eluted using a gradient of ether-acetone (40:1 → 1:1) to give 12 subfractions (C6-1–C6-12). Subsequently, purified by semi-preparative HPLC on X-bridge preparative column

with MeCN-H_2O (2.0 mL/min, MeCN:H_2O = 78:22, v/v) to yield **1** (5 mg, t_R = 23.2 min) and **2** (2. 5mg, t_R = 29.1min).

Hypermonin A (1). colorless oil; [α]25 D +46.5 (*c* 0.20, MeOH); UV (MeOH) λ_{max}(log ε) 248 (3.16), 268 (3.09), 316 (2.64) nm; CD (MeOH) λ ($\Delta\varepsilon$) 213 (-11.70), 257 (+8.08), 289 (-3.04), 315(+6.66) nm; IR (KBr) ν_{max} 3390, 3061, 2960, 2923, 2853, 1707, 1653, 1617, 1598, 1582, 1414, 1374, 1306, 1245, 1175, 1138, 1106, 1069, 968, 939, 885, 851, 819, 790, 777, 763, 696, 664, 590, 476, 434 cm^{-1}; ^1H and ^{13}C NMR data, Table 1; HREIMS *m/z* 488.2928.

Hypermonin B (2). colorless oil; [α]25 D +155.42 (*c* 0.24, MeOH); UV (MeOH) λ_{max}(log ε) 246 (3.20) and 300 (2.98) nm; CD (MeOH) λ ($\Delta\varepsilon$) 223 (-16.54), 263 (+25.06), 328(+3.26) nm; IR (KBr) ν_{max} 3424, 3061, 3027, 2962, 2925, 2856, 2733, 1619, 1496, 1450, 1382, 1309, 1278, 1226, 1178, 1153, 1128, 1106, 1079, 1048, 972, 972, 936, 878, 852, 815, 771, 696, 659, 601 cm^{-1}; ^1H and ^{13}C NMR data, Table 1; HREIMS *m/z* 488.2935.

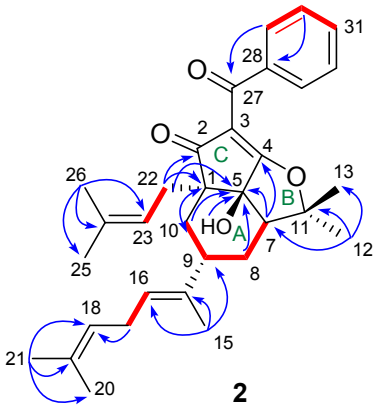
Neuroprotective bioassays

Poorly differentiated PC12 cells were maintained in DMEM medium supplemented with 10% fetal bovine serum (FBS), penicillin(100 U/ml), streptomycin(100 μg/ml), and incubated at 5% CO2 and 37℃. Poorly differentiated PC12 cells were divided into the following groups: untreated, CORT(120 μmol/l), CORT(120 μmol/l) plus DIM(8 μmol/l), CORT(120 μmol/l) plus test compounds(10 μmol/l). Briefly, poorly differentiated PC12 cells were seeded into 96-well culture plates at a density of 1*10^4cells/well. After 24 hours culturing, the wells were added compounds as previously described groups. 48 hours later, MTS solution was added to each well. The absorbance was measured at 492 nm using a Thermo Multiskan FC.

The result of neuroprotective bioassays

no	Cell viability(% of control)	no	Cell viability(% of control)
control	100.00 ± 0.97	model	55.85 ± 0.12
DIM (10 μM)	73.00 ± 0.91		
1 (20 μM)	64.97 ± 0.70	2 (20 μM)	55.95 ± 0.35
1 (10 μM)	62.93 ± 1.00	2 (10 μM)	56.55 ± 1.04
1 (5 μM)	56.63 ± 0.70	2 (5 μM)	55.76 ± 0.37
1 (2.5 μM)	55.29 ± 0.58	2 (2.5 μM)	55.77 ± 1.26

2. Key HMBC (→), COSY (—) and ROESY (⇢) correlations of 2



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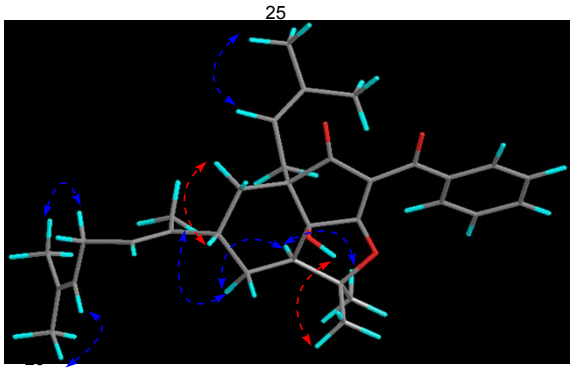

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3. ECD spectra calculation of 1 and 2

Computational methods: The CONFLEX[1, 2] searches based on molecular mechanics with MMFF94S force fields were performed for compounds, which gave 10 stable conformers. Selected conformers with distributions higher than 1% were further optimized by the DFT (density functional theory) method at the B3LYP/6-311G* level in Gaussian 09 program package[3]. The ECD of the conformer of selected conformerswas then calculated by the TDDFT method at the B3LYP/6-311++G** levels with the PCM model in methanol solution. The calculated ECD curve was generated using SpecDis 1.51[4] .

References

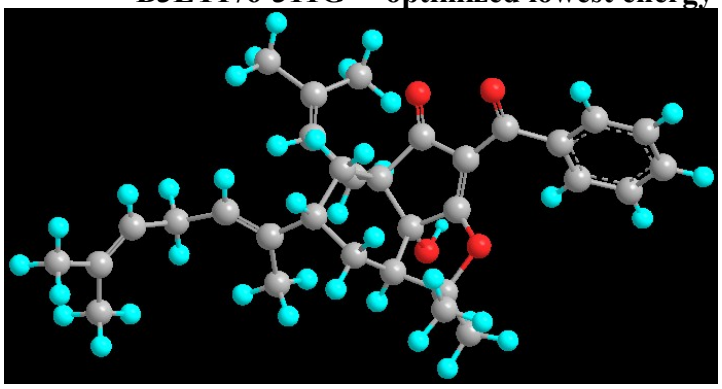
[1] Goto, H.; Osawa, E.; *J. Am. Chem. Soc.***1989**, *111*, 8950–8951.

[2] Goto, H.; Osawa, E.; *J. Chem. Soc., Perkin Trans. 2*, **1993**, 187–198.

[3]. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb,M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.;Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.;Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.;Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.;Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li,X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.;Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.;Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.;Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich,S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.;Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.;Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz,P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.;Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson,B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*,revision D.01; Gaussian, Inc.: Wallingford, CT, 2005.

[4]. Bruhn, T.; Hemberger, Y.; Schaumlöffel, A.; Bringmann, G. *Spec Dis*, version 1.51, University of Würzburg, Germany, 2010.

B3LYP/6-311G optimized lowest energy 3D conformer of 1.**



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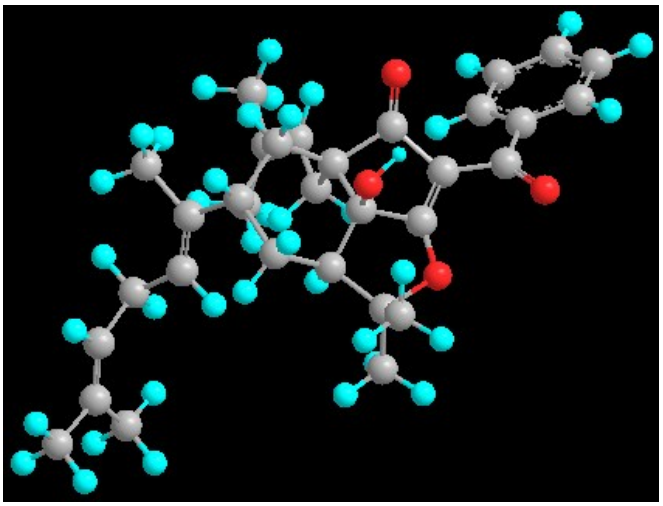
B3LYP/6-311G optimized lowest energy 3D conformer of 2.**



Standard orientation:

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4. Spectra of physico-chemical properties of 1

Figure S1. ^{1}H NMR (600 MHz, DMSO) of **1**

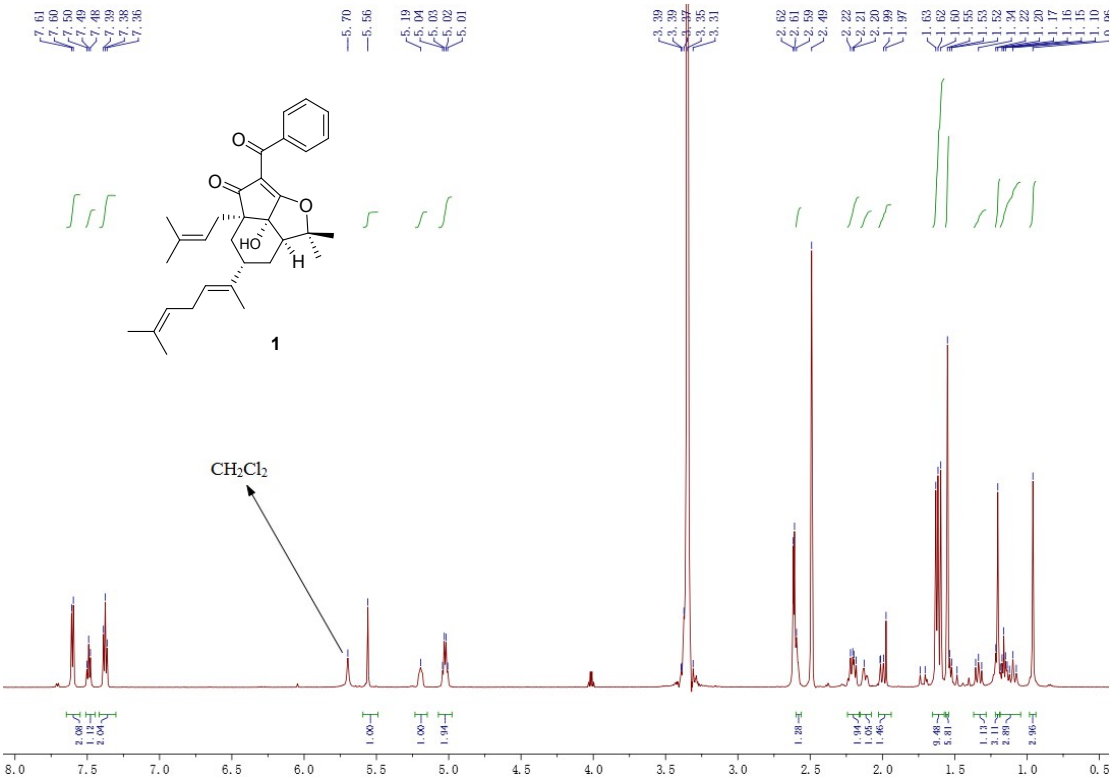


Figure S2. ^{13}C NMR (600 MHz, DMSO) of **1**

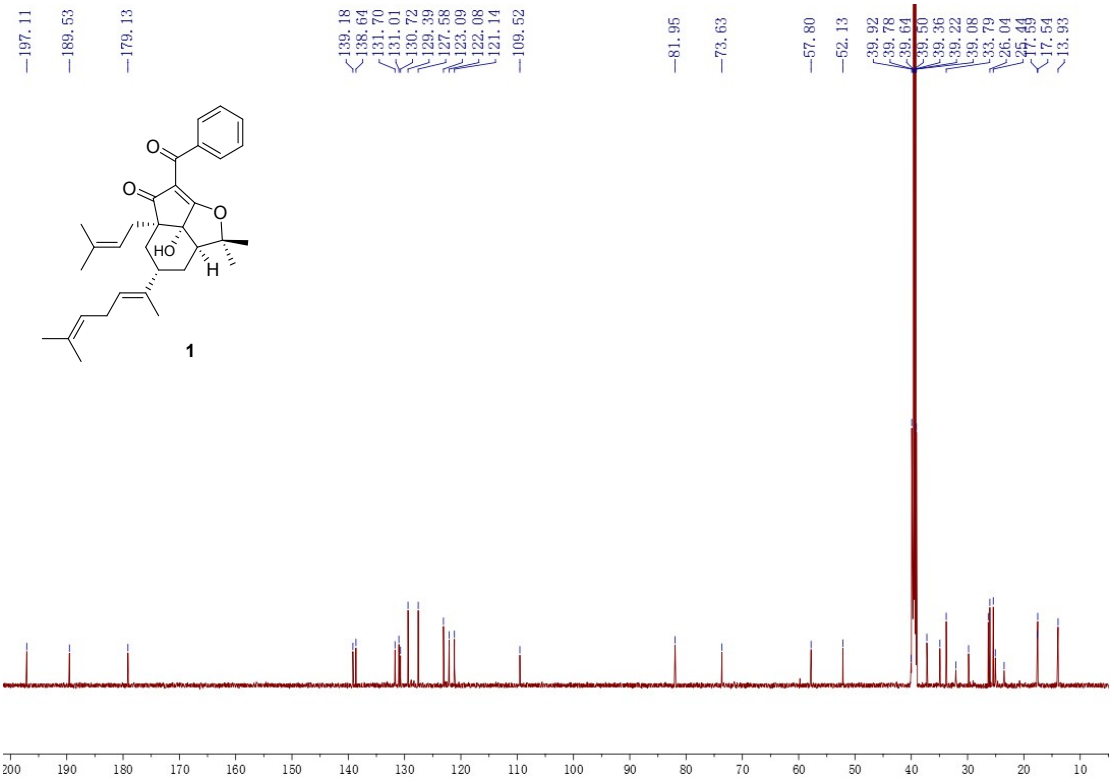


Figure S3. DEPT NMR (600 MHz, DMSO) of **1**

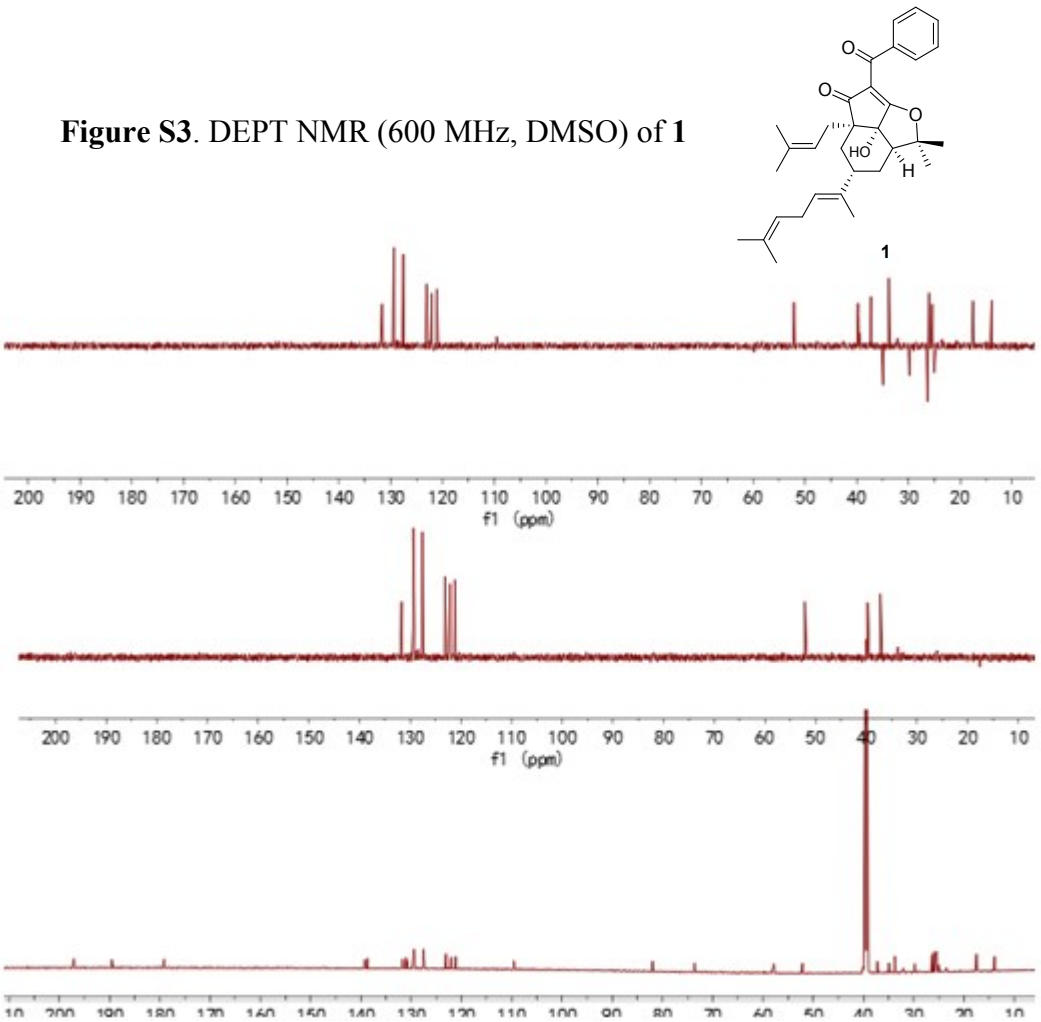


Figure S4. HSQC (600 MHz, DMSO) of **1**

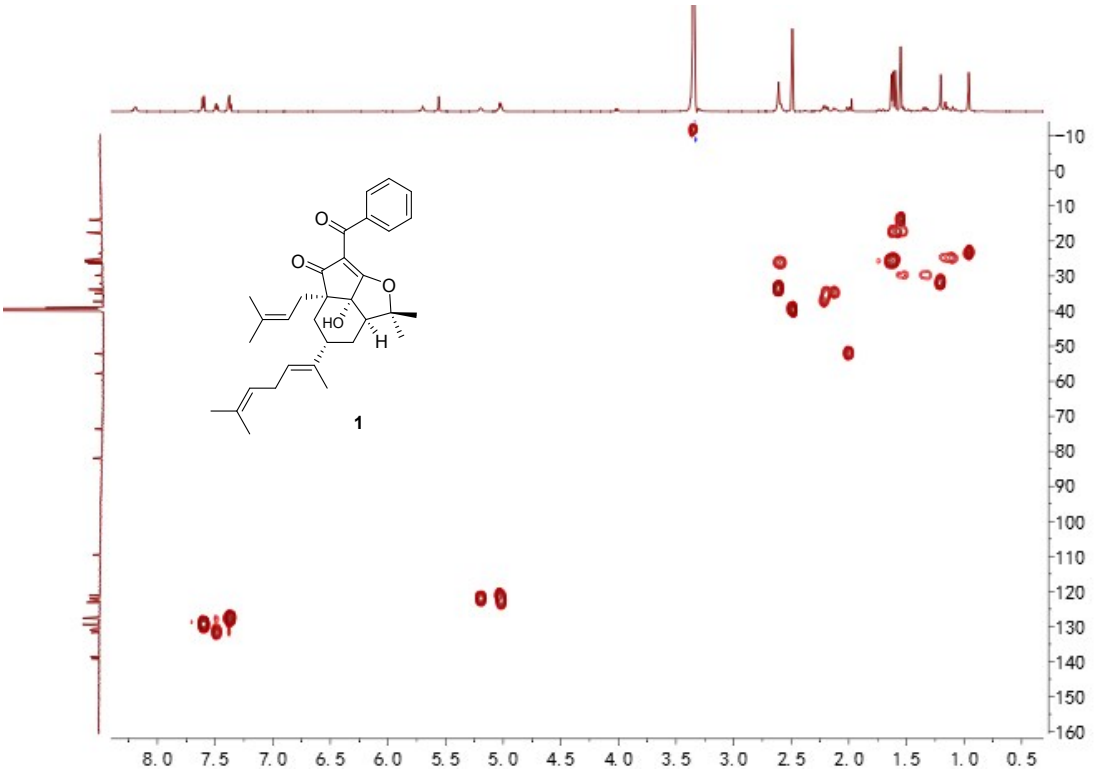


Figure S5. HMBC (600 MHz, DMSO) of **1**

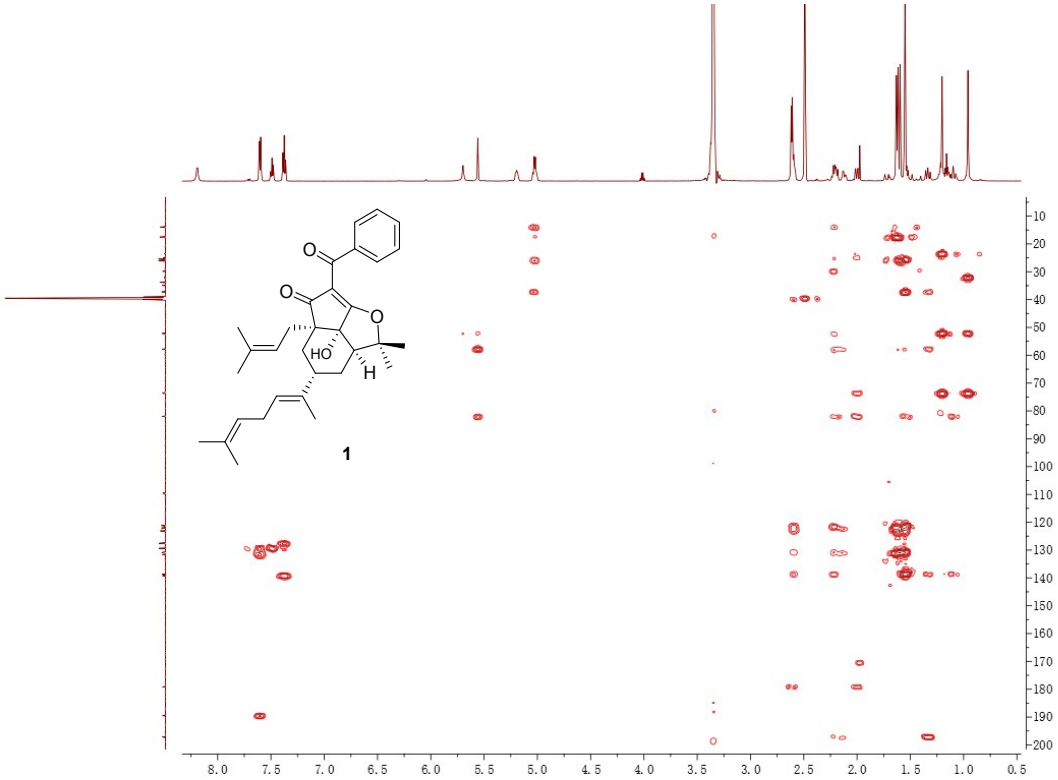


Figure S6. ^{1}H-^{1}H COSY (600 MHz, DMSO) of **1**

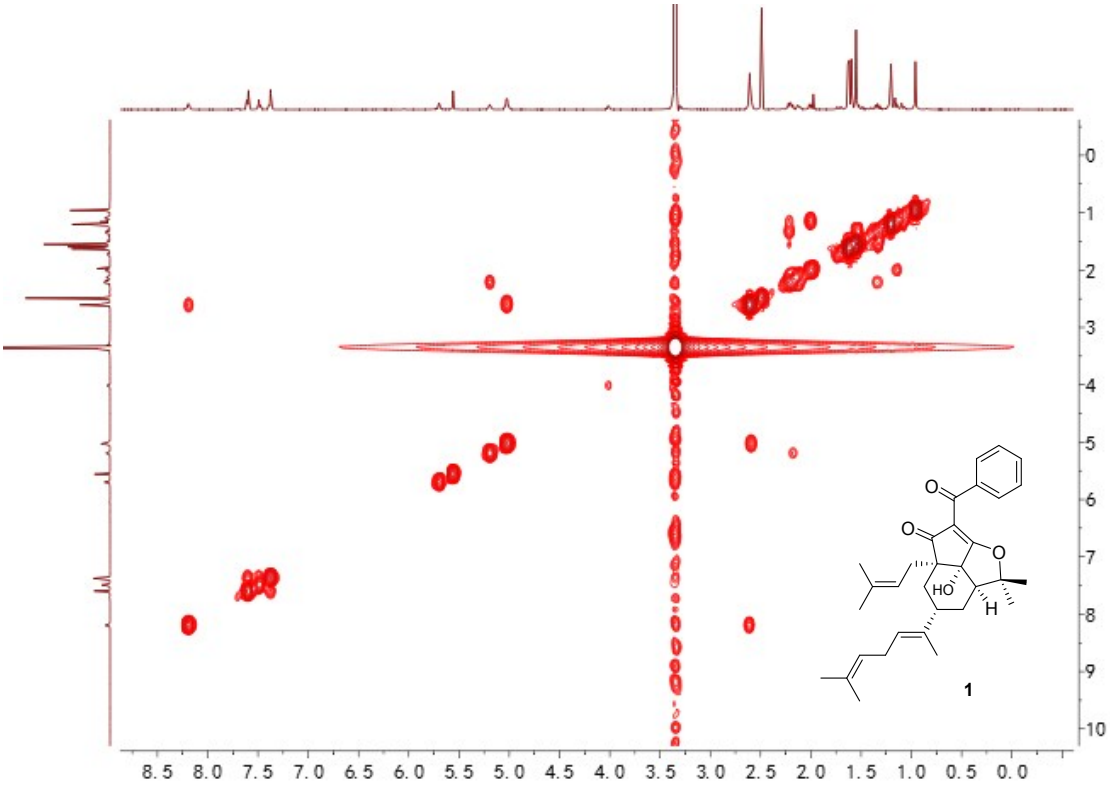


Figure S7. ROESY (600 MHz, DMSO) of **1**

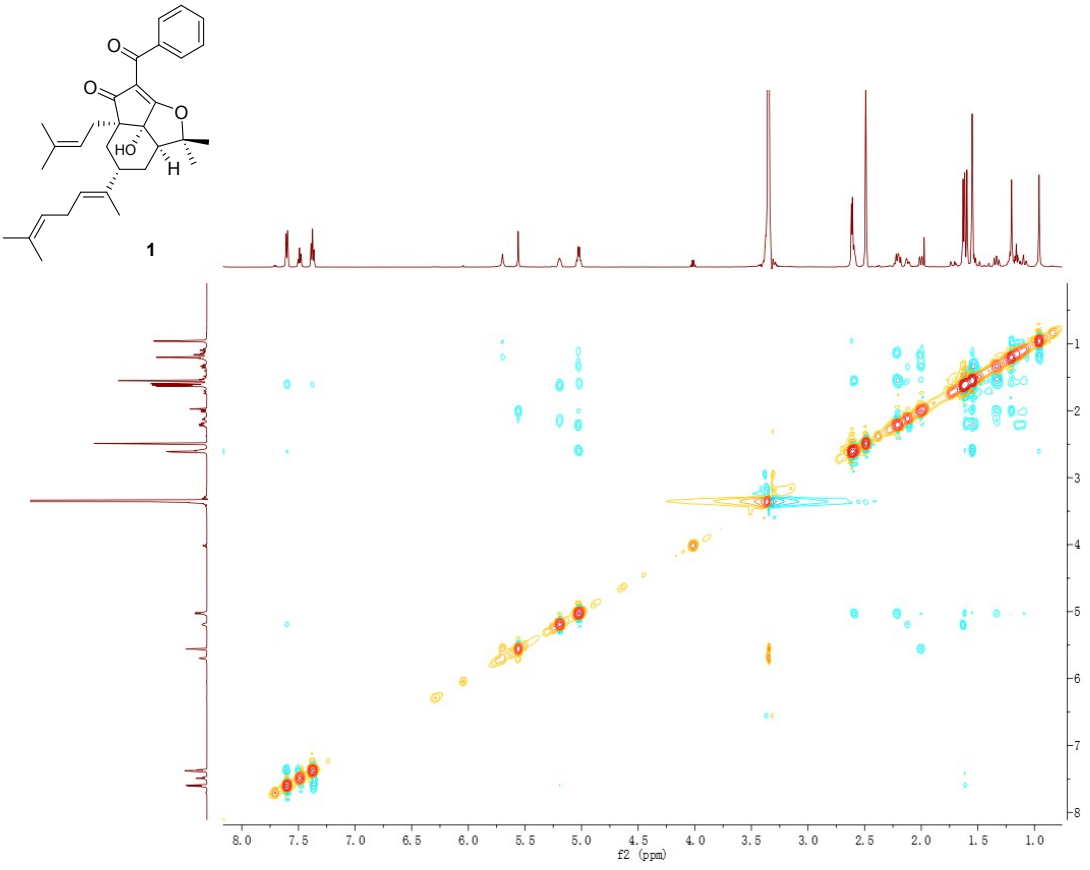


Figure S8. EI-MS spectrum of **1**

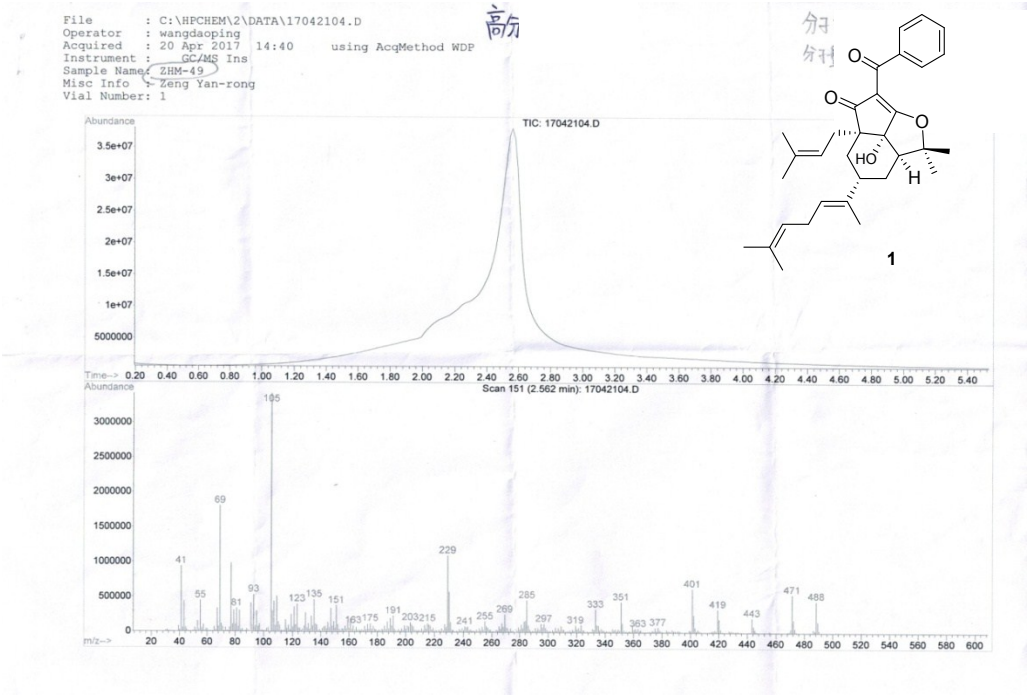


Figure S9. HR-EI-MS spectrum of **1**

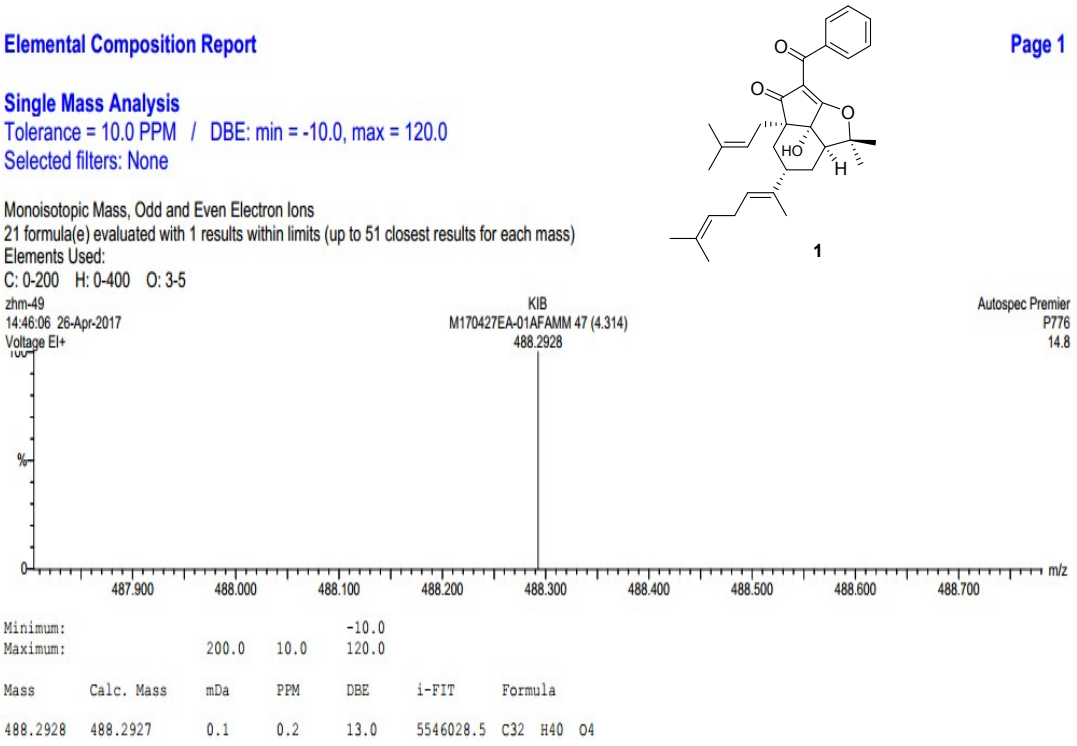


Figure S10. IR (KBr disk) spectrum of **1**

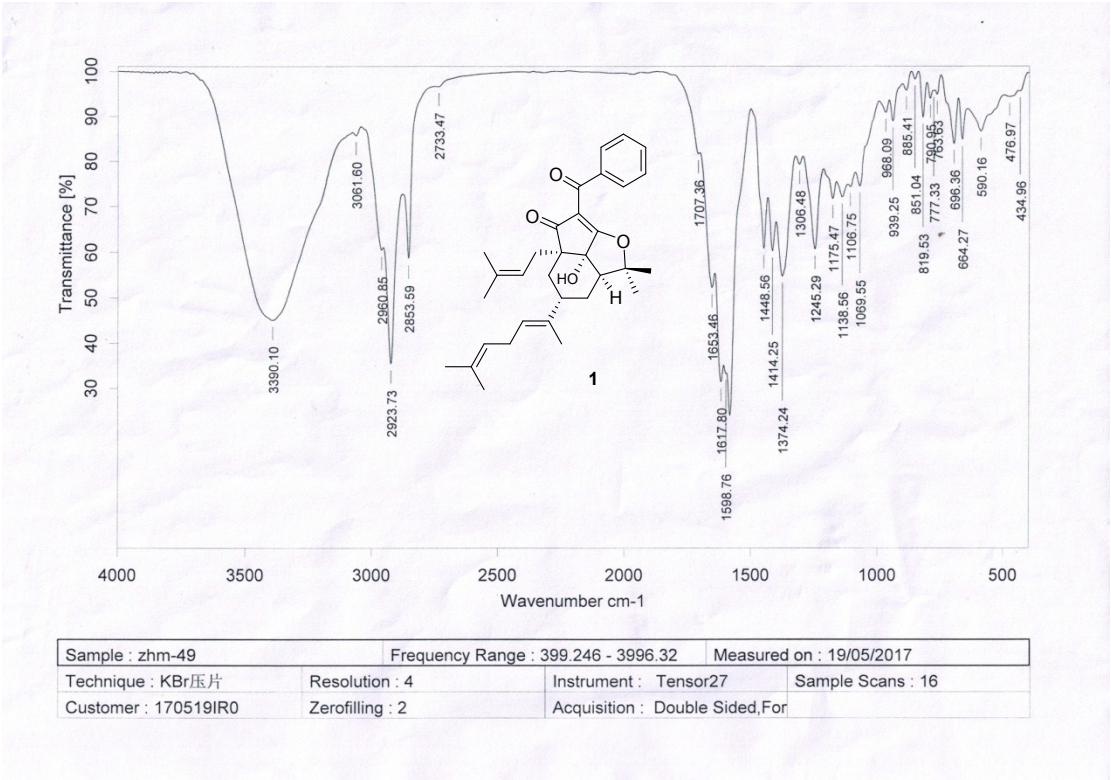
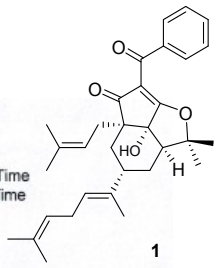


Figure S11. Optical activity of **1**



1

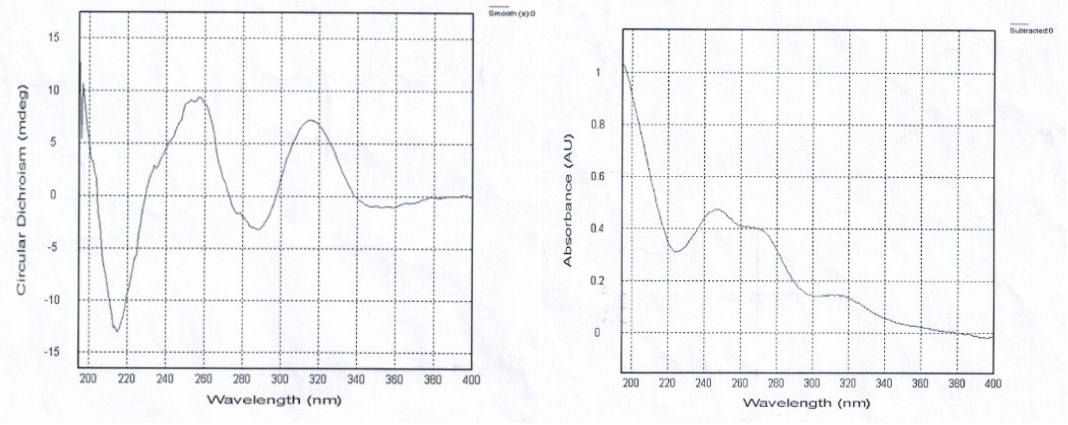
Optical rotation measurement

Model : P-1020 (A060460638)

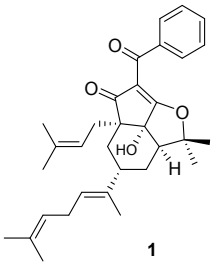
No.	Sample	Mode	Data	Monitor Blank	Temp. Cell Temp Point	Date Comment Sample Name	Light Filter Operator	Cycle Time Integ Time
No.1	21 (1/3)	Sp.Rot	45.5000	0.0091 0.0000	22.0 10.00 Cell	Thu May 11 23:08:11 2017 0.00200g/mL MeOH ZHM-49	Na 589nm	2 sec 2 sec
No.2	21 (2/3)	Sp.Rot	47.0000	0.0094 0.0000	22.0 10.00 Cell	Thu May 11 23:08:16 2017 0.00200g/mL MeOH ZHM-49	Na 589nm	2 sec 2 sec
No.3	21 (3/3)	Sp.Rot	47.0000	0.0094 0.0000	22.0 10.00 Cell	Thu May 11 23:08:22 2017 0.00200g/mL MeOH ZHM-49	Na 589nm	2 sec 2 sec

+46.7000

Figure S12. CD and UV spectrum of **1** in MeOH



File: CD ZHM-49-1mm(195-400)17052003.dsx
ProBinaryX
Attributes :
- Time Stamp :Sat May 20 13:18:24 2017



1

- File ID : {790791F9-ABC0-462b-89D3-69F93DF12D5E }
- Is CFR Compliant : false
- Original unaltered data

Remarks:
- HV (CDDC channel): 0 v
- Time per point: 1 s
- Description: Sample 1
- Concentration: 0.1600mg/mL MeOH
- Pathlength: 1 mm

Settings:
- Time-per-point: 1s (25us x 40000)
- Wavelength: 195nm - 400nm
- Step Size: 1nm
- Bandwidth: 1.0nm

5 Spectra of physico-chemical properties of **2**

Figure S13. ^{1}H NMR (400 MHz, DMSO) of **2**

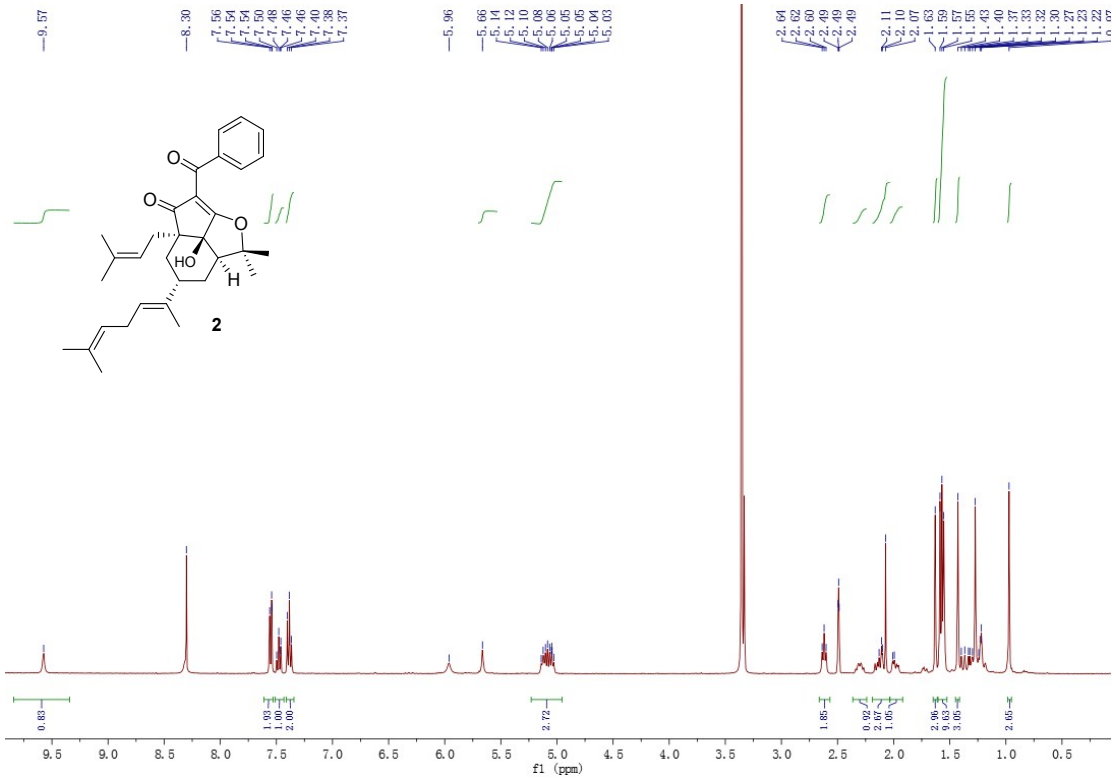


Figure S14. ^{13}C NMR (100 MHz, DMSO) of **2**

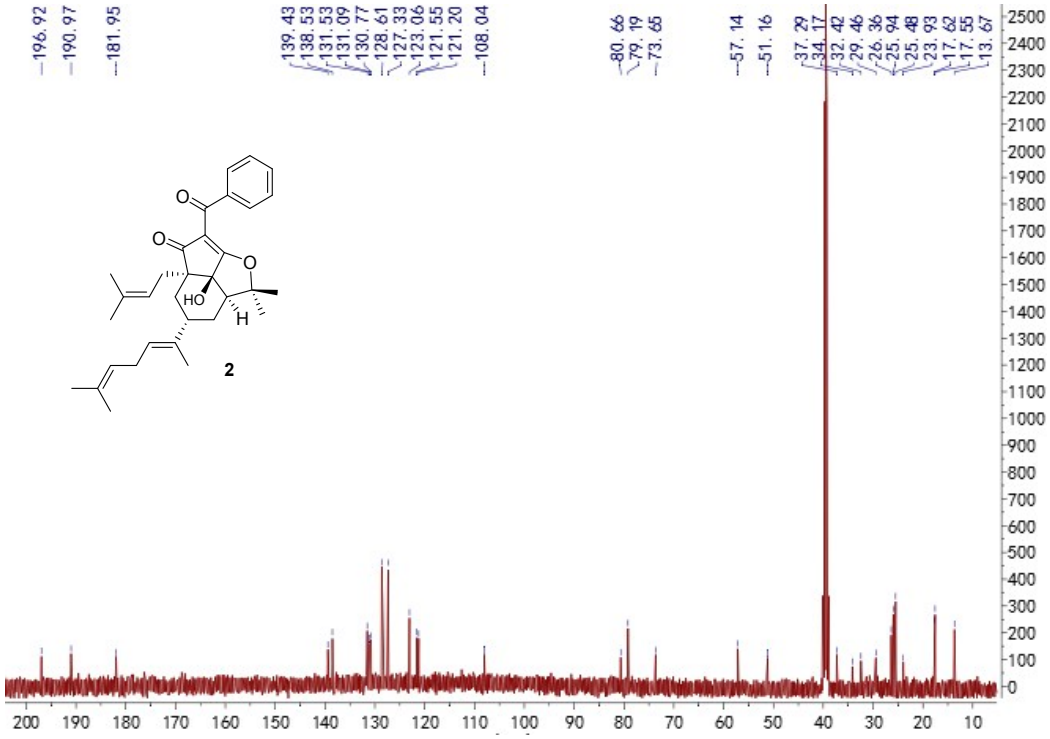


Figure S15. HSQC NMR (400 MHz, DMSO) of **2**

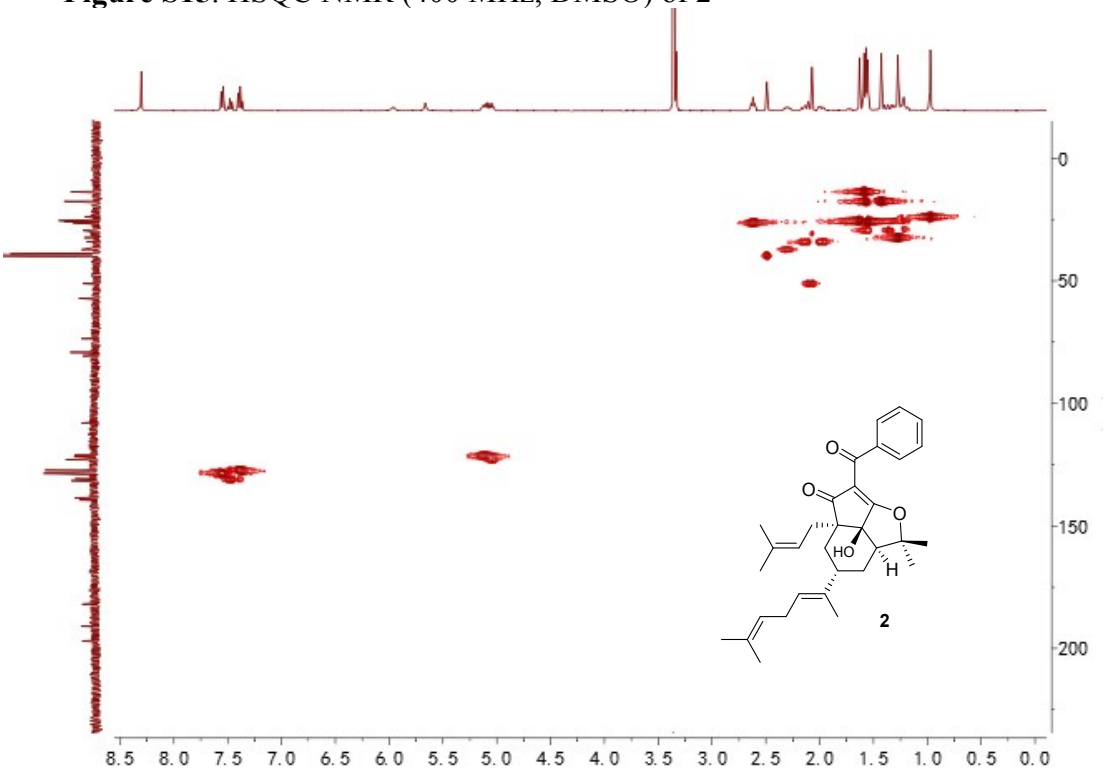


Figure S16. HMBC NMR (400 MHz, DMSO) of **2**

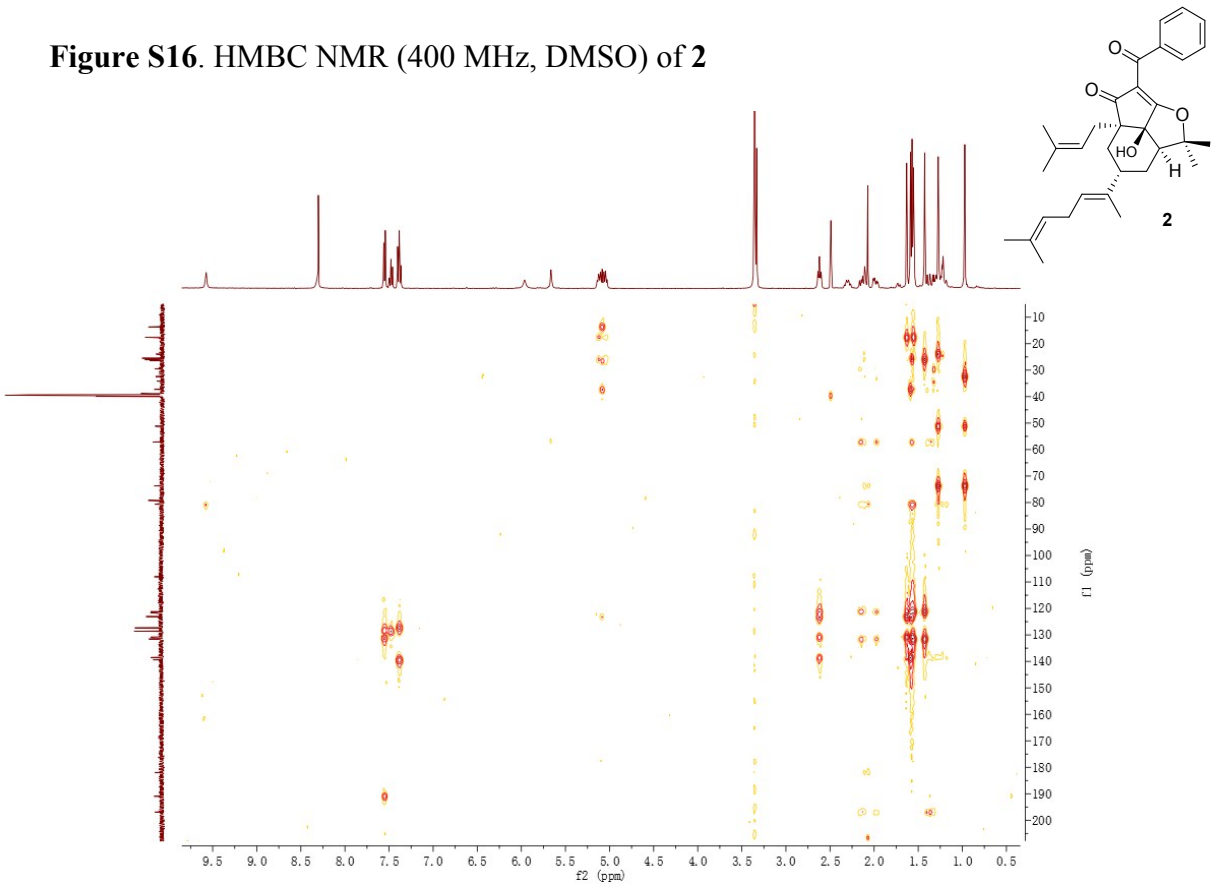


Figure S17.^{1}H-^{1}H COSY (400 MHz, DMSO) of **2**

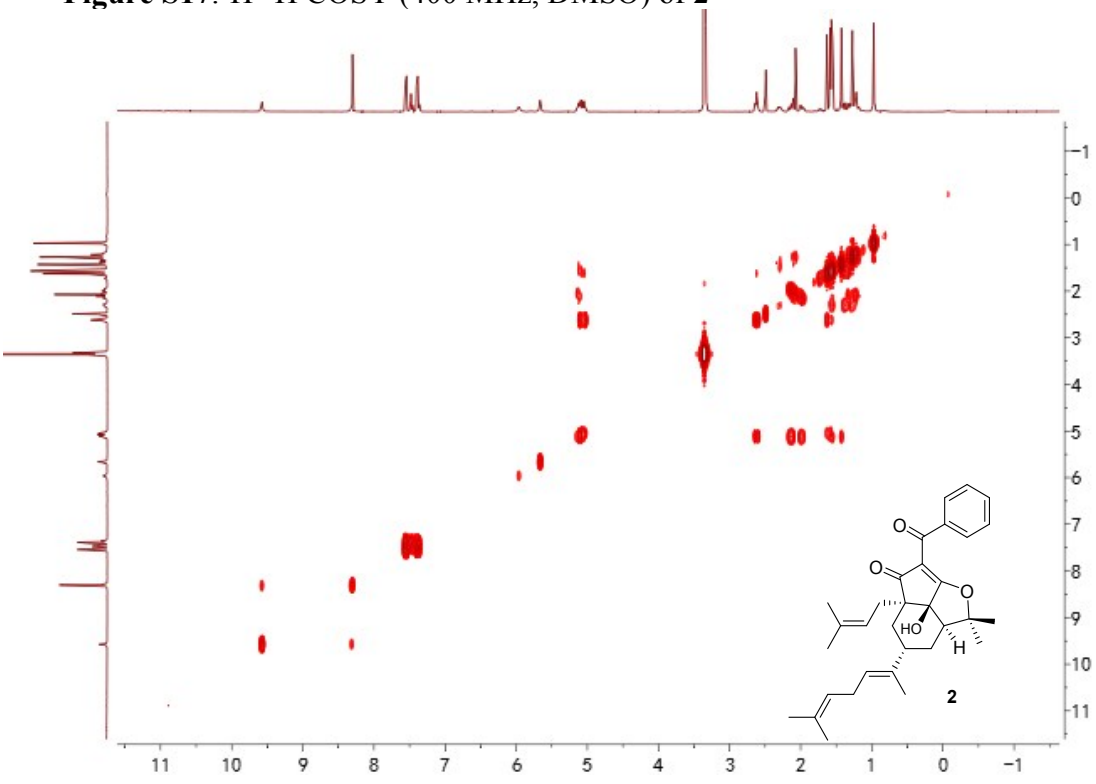


Figure S18. ROESY (400 MHz, DMSO) of **2**

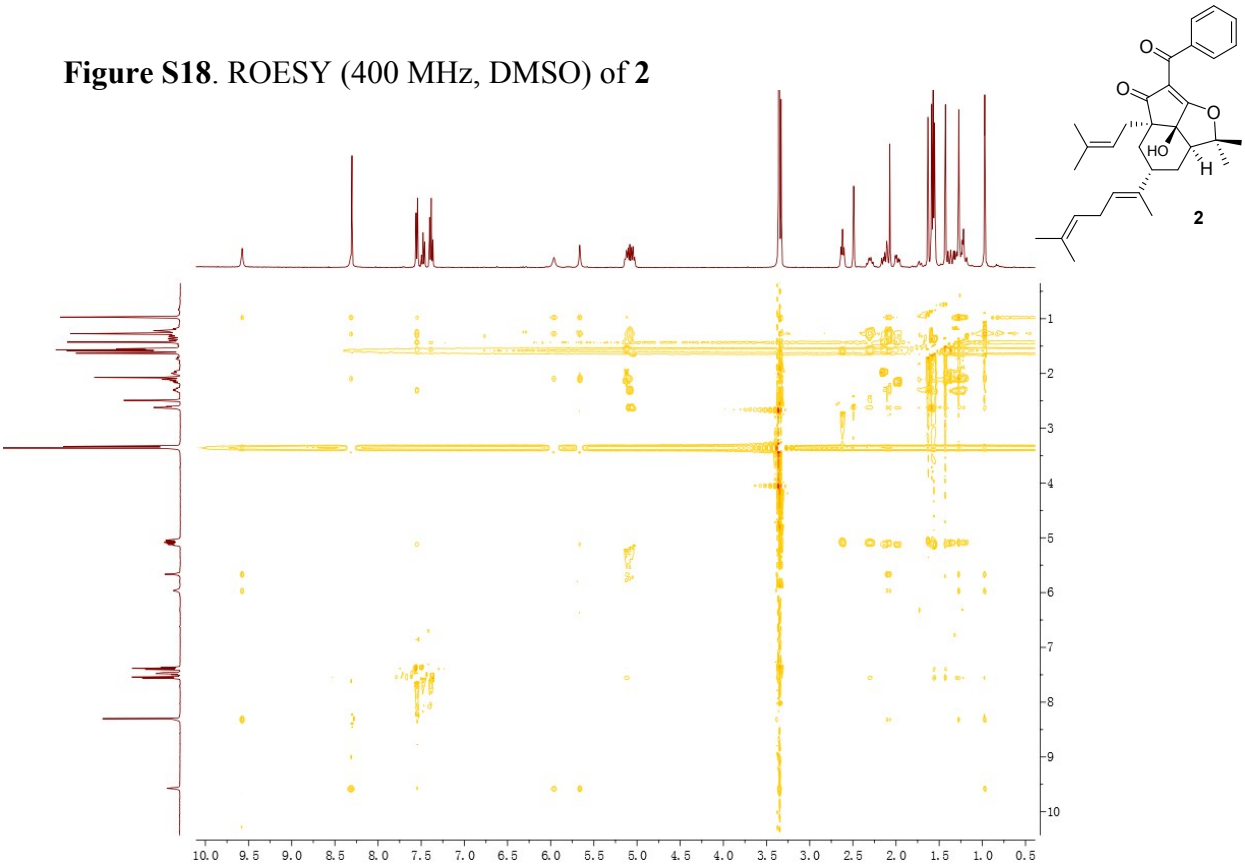


Figure S19. EI-MS spectrum of **2**

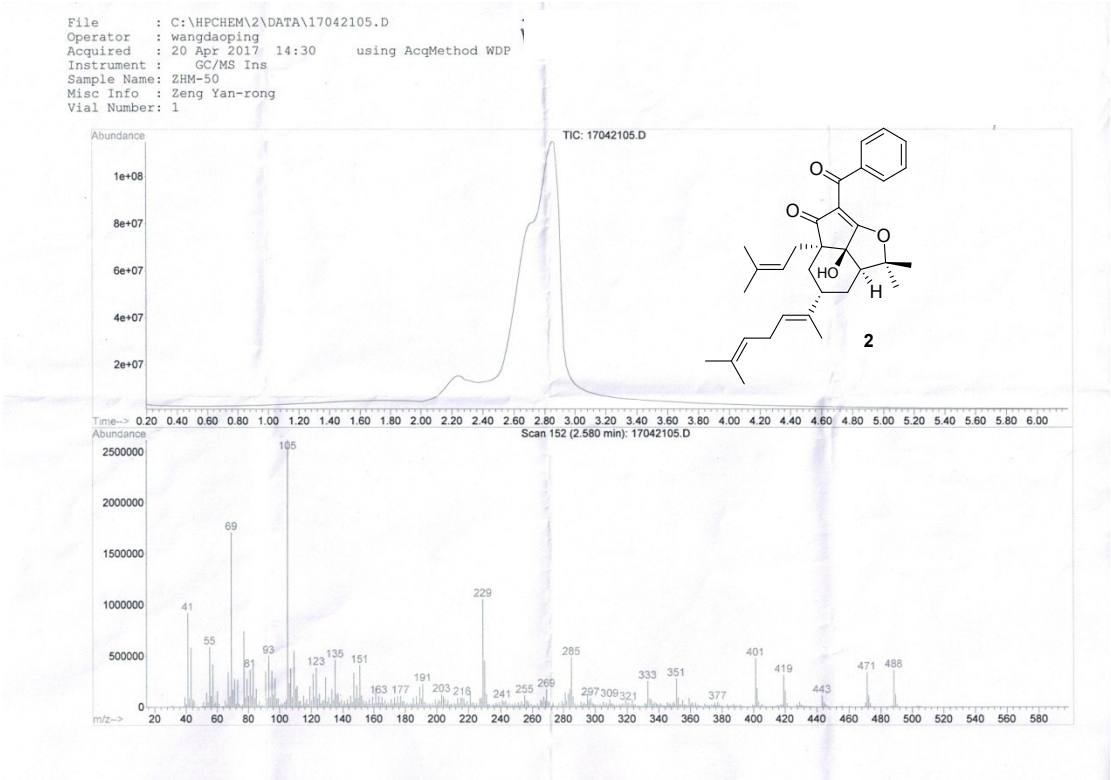


Figure S20. HR-EI-MS spectrum of **2**

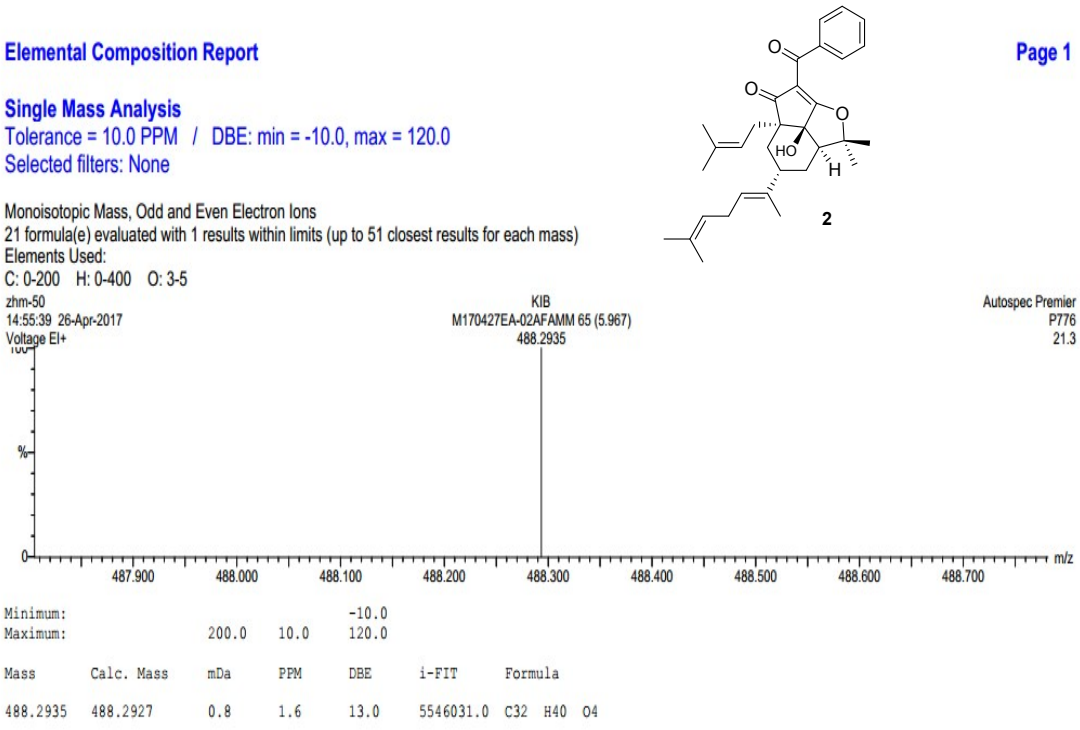


Figure S21. IR (KBr disk) spectrum of **2**

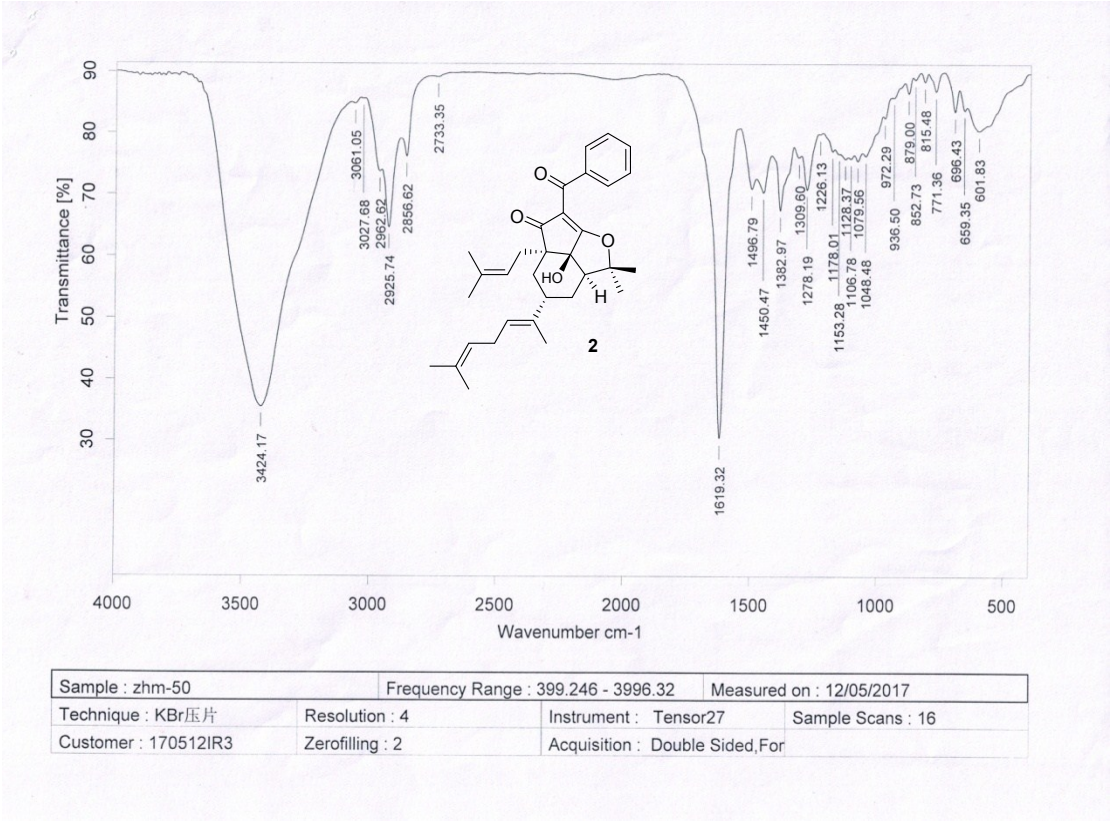
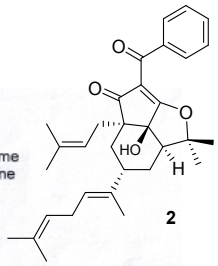


Figure S22. Optical activity of 2



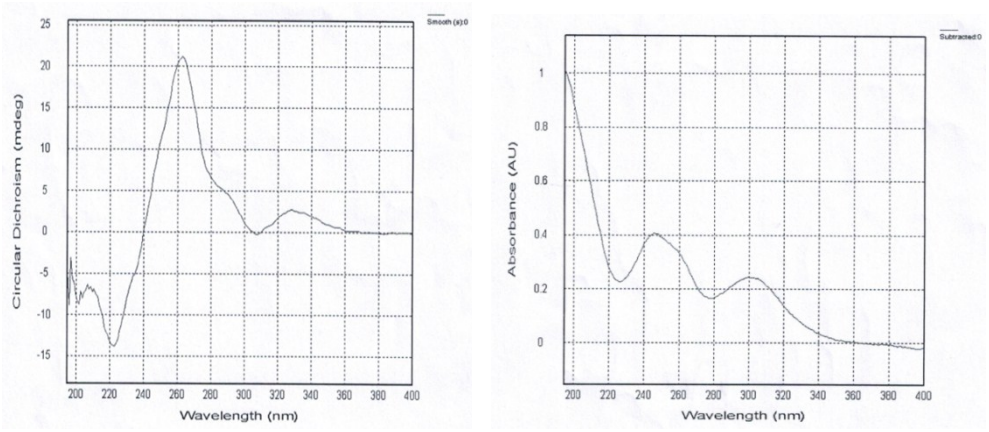
Optical rotation measurement

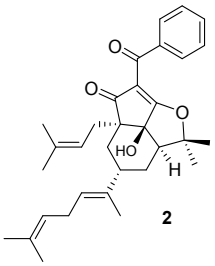
Model : P-1020 (A060460638)

No.	Sample	Mode	Data	Monitor Blank	Temp. Cell Temp Point	Date Comment Sample Name	Light Filter Operator	Cycle Time Integ Time
No.1	22 (1/3)	Sp.Rot	155.8330	0.0374 0.0000	22.1 10.00 Cell	Thu May 11 23:31:03 2017 0.00240g/mL MeOH ZHM-50	Na 589nm	2 sec 2 sec
No.2	22 (2/3)	Sp.Rot	154.5830	0.0371 0.0000	22.1 10.00 Cell	Thu May 11 23:31:08 2017 0.00240g/mL MeOH ZHM-50	Na 589nm	2 sec 2 sec
No.3	22 (3/3)	Sp.Rot	155.8330	0.0374 0.0000	22.1 10.00 Cell	Thu May 11 23:31:14 2017 0.00240g/mL MeOH ZHM-50	Na 589nm	2 sec 2 sec

+155.416°

Figure S23. CD and UV spectrum of **2** in MeOH





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File: CD ZHM-50-1mm(195-400)17052004.dsx
ProBinaryX
Attributes :
- Time Stamp :Sat May 20 13:48:07 2017

- File ID : {7C850735-3BA4-4901-A9B0-1C6CD82B30A3 }
- Is CFR Compliant : false
- Original unaltered data

Remarks:
- HV (CDDC channel): 0 v
- Time per point: 1 s
- Description: Sample 1
- Concentration: 0.1248mg/mL MeOH
- Pathlength: 1 mm

Settings:
- Time-per-point: 1s (25us x 40000)
- Wavelength: 195nm - 400nm
- Step Size: 1nm
- Bandwidth: 1.0nm