Supporting Information

Photo-induced Scandium-catalyzed biomimetic skeleton conversion of lathyrane to naturally rare eupholathone *Euphorbia* diterpenes

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Contents

1. General information

All chemicals were obtained from commercial sources and used without further purification. Irradiation of photochemical reactions were carried out using in Rogetech®-RLH-18 (Figure S1). Light source is IP68 double density 12vdc water proof blue LEDs with spectral range of 441–445 nm or purple LEDs with spectral range of 391–395 nm. The irradiation vessel material is borosilicate glass. The distance from the light source to the irradiation vessel is about 2 cm with none filters used. Unless otherwise specified, reactions were carried out under air in 10 mL glass tube. Reactions were monitored by thin layer chromatography (TLC) using 254 nm UV light to visualize the course of reactions. Flash column chromatography (CC) was performed using silica gel (200–300 mesh, Qingdao Haiyang Chemical Co., Ltd., Qingdao, People's Republic of China). HRESIMS data were acquired using a Waters Acquity UPLC/Q–TOF micro mass spectrometer. NMR spectra were recorded on Bruker AV 400 MHz or 600 MHz spectrometers. Chemical shifts (δ) were reported in ppm with TMS as internal standard. The abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet. Structural assignments were made with additional information from gCOSY, gHMQC, gHMBC and gNOESY experiments.

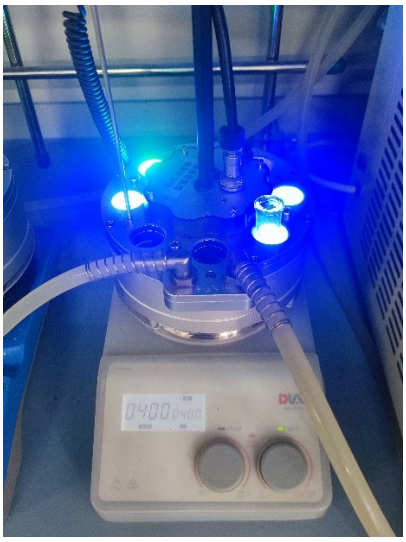
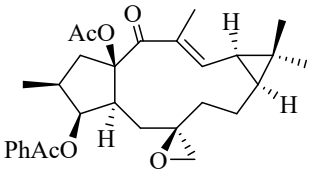


Figure S1. Photochemical reaction apparatus

2. Extraction of starting lathyrane-type compound *Euphorbia* factor L_1

Starting compound *Euphorbia* factor L_1 was isolated in multigram amounts by column chromatography from the EtOH extraction of the *Euphorbia lathyris* seeds. The extraction process was performed as shown in the Supporting Information of our previous report.[1-2] The

seeds of *E. lathyris* were purchased from Yuzhou, Henan Province, People's Republic of China, in December 2021 and were identified by Professor Qin-Er Yang of the Institute of Botany, Chinese Academy of Sciences. Voucher specimens (NO. 361520211216E) have been deposited in the School of Life Science and Engineering, Southwest Jiaotong University, Sichuan, People's Republic of China. The dried and powered seeds of *E. lathyris* (3 kg) was soaked in EtOH for five times at room temperature, and each extraction lasted three days. The solvent was evaporated to afford the crude residue. The crude residue (90 g) was extracted successively with petroleum ether and MeCN (for three times). The dried MeCN extract was separated by a silica gel CC eluting with petroleum ether/EtOAc (v/v 10:1) to afford *Euphorbia* factor L_1 (5 g) as the white amorphous powder.



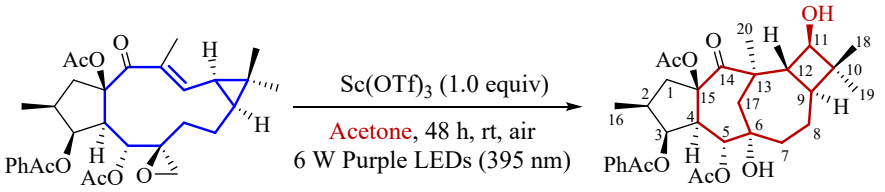
Euphorbia factor L_1

Euphorbia factor L_1: White amorphous powder; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 – 7.25 (m, 5H), 6.61 (dd, J = 1.6, 10.0 Hz, 1H), 6.62 (d, J = 9.2 Hz, 1H), 5.49 (t, J = 3.2 Hz, 1H), 3.62 – 3.54 (m, 2H), 3.31 (q, J = 8.4 Hz, 1H), 2.48 (d, J = 3.2 Hz, 1H), 2.32 – 2.30 (m, 1H), 2.18 – 2.14 (m, 1H), 2.13 (s, 3H), 2.12 – 2.06 (m, 1H), 2.02 (s, 3H), 1.89 – 1.85 (m, 4H), 1.75 – 1.68 (m, 1H), 1.49 (dd, J = 8.0, 11.6 Hz, 1H), 1.22 (s, 3H), 1.21 (s, 3H), 1.13 – 1.07 (m, 1H), 0.97 – 0.90 (m, 1H), 0.66 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0, 171.0, 170.9, 169.7, 143.8, 136.1, 133.9, 129.6, 128.6, 127.4, 91.9, 80.8, 65.3, 59.1, 55.5, 50.1, 48.0, 41.7, 37.9, 34.9, 33.7, 29.1, 29.0, 25.7, 22.0, 21.2, 20.2, 16.9, 13.6, 12.5; The above-mentioned NMR spectral data was consistent with those of *Euphorbia* factor L_1 reported in the literature.[3]

3. General procedure for eupholathone-type *Euphorbia* diterpenes 1-3

To a 10 mL glass tube equipped with a stir bar was added *Euphorbia* factor L_1 (0.1 mmol, 1.0 equiv.), $Sc(OTf)_3$ (0.1 mmol, 1.0 equiv.) and the solvent (1 mL) under air. The reaction was stirred at room temperature under irradiation with 6 W purple LEDs (395 nm) for 48 h. Upon completion of the reaction, the mixture was alkalified with saturated $NaHCO_3$ aqueous solution, followed by extracting with DCM. Then, the organic layers were combined, washed

with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatograph to afford the eupholathone-type diterpenes (**1-3**).



Lathyrane-type diterpene
Euphorbia factor L_1

Eupholathone-type diterpene
Euphornin E (**1**, 92%)

Euphornin E (**1**, 52 mg, 92% yield) was purified by flash silica gel CC (petroleum ether/EtOAc = 3:1) and obtained as white power, which was recrystallized as colorless needle crystal from petroleum ether/CH_2Cl_2 (about 3:1) at room temperature; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33 – 7.25 (m, 5H, H-4'/H-5'/H-6'/H-7'/H-8'), 6.13 (d, J = 10.0 Hz, 1H, H-5), 5.54 (t, J = 4.4 Hz, 1H, H-3), 3.61 – 3.59 (m, 3H, H_2-2'/H-11), 3.36 (dd, J = 15.6, 10.4 Hz, 1H, H-1a), 2.84 (dd, J = 10.8, 8.0 Hz, 1H, H-12), 2.59 (dd, J = 9.6, 4.0 Hz, 1H, H-4), 2.31 (br s, 1H, OH), 2.23 – 2.18 (m, 1H, H-2), 2.19 (s, 3H, H_3-2'''), 2.05 (br s, 1H, OH), 1.99 (s, 3H, H_3-2''), 1.79 (d, J = 15.6 Hz, 1H, H-17b), 1.69 – 1.62 (m, 3H, H-8b/H-7a/H-17a), 1.60 – 1.56 (m, 1H, H-8a), 1.53 (dd, J = 15.6, 8.4 Hz, 1H, H-1b), 1.46 – 1.39 (m, 1H, H-7b), 1.25 – 1.20 (m, 1H, H-9), 1.10 (s, 3H, H_3-20), 1.04 (s, 3H, H_3-18), 1.01 (s, 3H, H_3-19), 0.72 (d, J = 6.8 Hz, 3H, H_3-16); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.4 (C-14), 172.0 (C-1'''), 171.5 (C-1'), 169.7 (C-1''), 133.8 (C-3'), 129.6 (C-4'/8'), 128.6 (C-5'/7'), 127.3 (C-6'), 92.6 (C-15), 79.0 (C-3), 75.7 (C-6), 73.6 (C-11), 67.3 (C-5), 51.0 (C-17), 49.8 (C-12), 49.1 (C-13), 49.0 (C-4), 41.5 (C-1), 41.4 (C-2'), 40.6 (C-7), 39.6 (C-10), 38.9 (C-9), 35.9 (C-2), 28.2 (C-18), 24.1 (C-8), 22.7 (C-20), 22.4 (C-2'''), 21.0 (C-2''), 16.3 (C-19), 14.7 (C-16); HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{32}H_{42}O_9Na$ 593.2722; Found 593.2725. The above-mentioned NMR spectral data was consistent with those of euphornin E reported in the literature.[4]

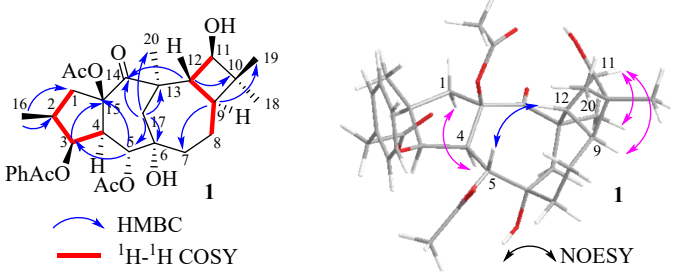


Figure S2. The key HMBC, ^{1}H-^{1}H COSY, and NOESY correlations of compound **1**

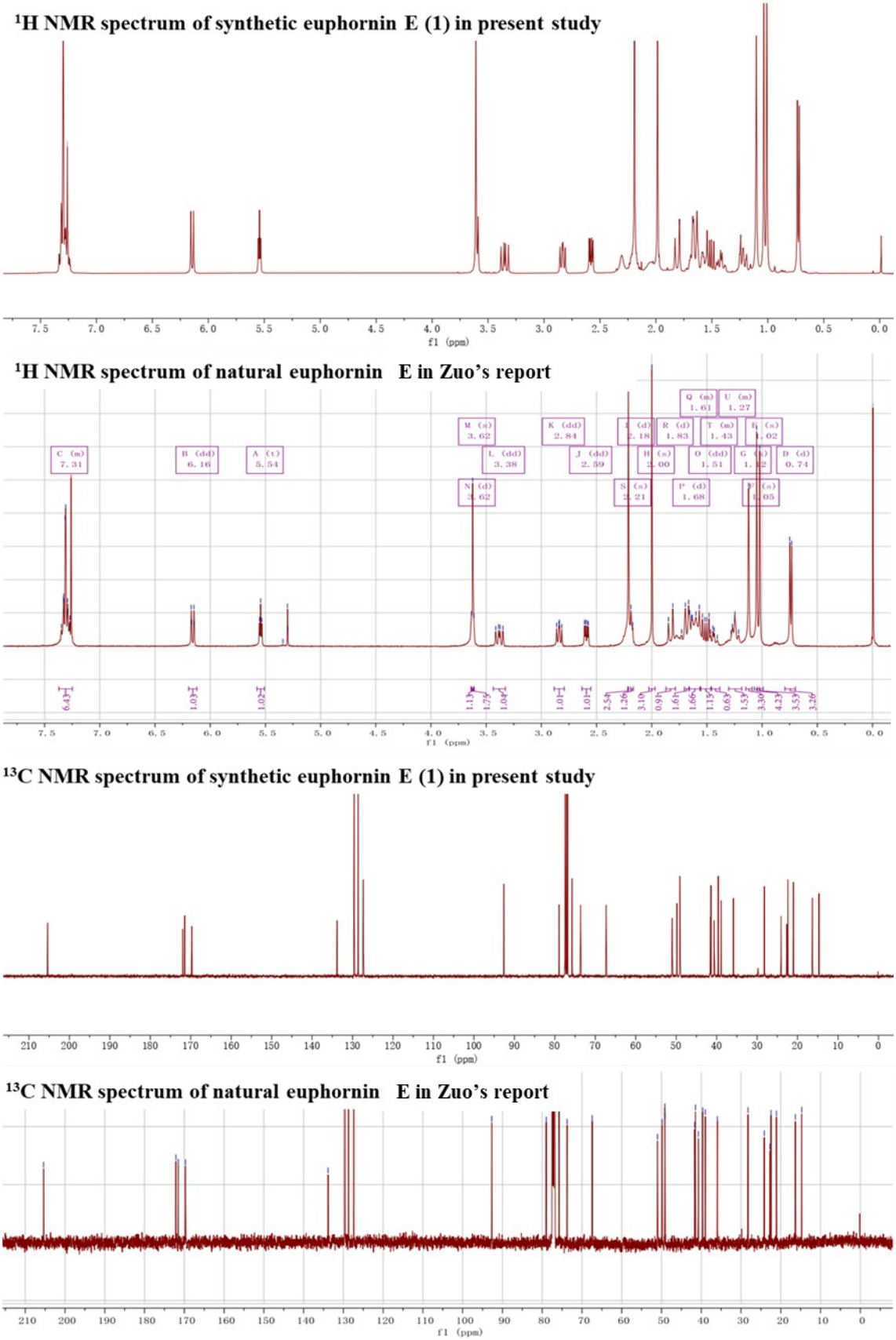
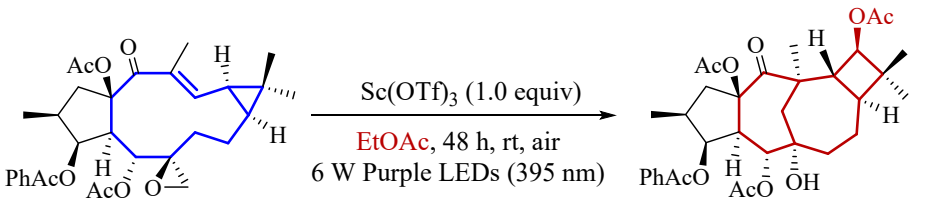


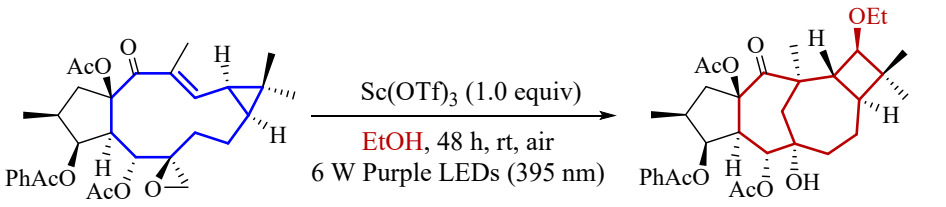
Figure S3. Comparison of NMR spectra of the natural and synthetic euphornin E (**1**)



Lathyrane-type diterpene
Euphorbia factor L_1

Eupholathone-type diterpene
2 (90%)

Compound **2** (55 mg, 90% yield) was purified by flash silica gel CC (petroleum ether/EtOAc = 4:1) and obtained as white power; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 – 7.28 (m, 5H), 6.17 (d, J = 9.6 Hz, 1H), 5.54 (t, J = 4.2 Hz, 1H), 4.63 (d, J = 9.0 Hz, 1H), 3.62 (s, 2H), 3.34 (dd, J = 16.2, 10.8 Hz, 1H), 3.15 (dd, J = 10.8, 8.4 Hz, 1H), 2.61 (dd, J = 9.6, 3.6 Hz, 1H), 2.22 (s, 3H), 2.20 – 2.16 (m, 2H), 2.04 (s, 3H), 2.00 (s, 3H), 1.86 – 1.83 (m, 1H), 1.65 – 1.64 (m, 3H), 1.61 – 1.58 (m, 3H), 1.38 – 1.34 (m, 1H), 1.16 (s, 3H), 1.11 (s, 3H), 0.99 (s, 3H), 0.74 (d, J = 6.6 Hz, 3H); ^{13}C NMR: δ 204.2, 171.4, 170.3, 169.8, 169.4, 133.8, 129.6, 128.7, 127.4, 92.4, 79.1, 75.7, 74.5, 67.2, 50.6, 49.2, 49.0, 47.1, 41.4, 41.0, 40.5, 40.4, 39.1, 36.1, 29.8, 28.0, 24.3, 22.9, 22.2, 21.1, 21.0, 16.8, 14.7; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{34}H_{44}O_{10}Na$ 635.2827; Found 635.2808.



Lathyrane-type diterpene
Euphorbia factor L_1

Eupholathone-type diterpene
3 (90%)

Compound **3** (54 mg, 90% yield) was purified by flash silica gel CC (petroleum ether/EtOAc = 5:1) and obtained as white power, which was recrystallized as colorless needle crystal from petroleum ether/CH_2Cl_2 (about 5:1) at room temperature; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.27 (m, 5H), 6.18 (d, J = 10.0 Hz, 1H), 5.52 (t, J = 4.4 Hz, 1H), 3.60 (s, 2H), 3.33 – 3.26 (m, 3H), 3.17 (d, J = 8.0 Hz, 1H), 3.02 (dd, J = 10.8, 8.4 Hz, 1H), 2.60 (dd, J = 10.0, 4.0 Hz, 1H), 2.18 (s, 3H), 2.18 – 2.17 (m, 1H), 1.99 (s, 3H), 1.83 – 1.73 (m, 2H), 1.71 (s, 1H), 1.68 – 1.62 (m, 3H), 1.58 – 1.52 (m, 1H), 1.48 – 1.41 (m, 1H), 1.20 – 1.15 (m, 1H), 1.11 (t, J = 6.8 Hz, 3H), 1.11 – 1.10 (m, 3H), 1.07 (s, 3H), 1.00 (s, 3H), 0.71 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.1, 171.5, 169.7, 169.5, 133.9, 129.6, 128.7, 127.4, 92.1,

81.2, 79.1, 77.4, 75.8, 67.4, 65.8, 50.7, 49.2, 49.1, 48.4, 41.4, 40.7, 40.6, 40.2, 38.6, 35.9, 29.1, 24.0, 23.2, 22.4, 21.1, 16.7, 15.4, 14.7; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{34}H_{46}O_9Na$ 621.3034; Found 621.3001.

4. Single-crystal X-ray data of compounds 1 and 3

The measurements were performed on an Oxford Xcalibur Eos diffractometer with Mo Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods using SHELXL-97, and all atoms were refined anisotropically using full-matrix least-squares difference Fourier techniques. Crystallographic data for the structure of **1** and **3** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 2254435 and 2254434, respectively. Copies of these data can be obtained, free of charge, on application to the CCDC via www.ccdc.cam.ac.uk/conts/retrieving.html (or 12 Union Road, Cambridge CB2 1EZ, UK, fax: + 441223 336033, e-mail: deposit@ccdc.cam.ac.uk).

Table S1. Crystal data of **1** and **3**

	1	**3**
Empirical formula	$C_{32}H_{42}O_9$	$C_{34}H_{46}O_9$
Formula weight	570.65	598.71
Temperature/K	293.15	293.15
Crystal system	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
a/Å	8.3664(11)	8.3112(8)
b/Å	14.008(2)	17.6981(19)
c/Å	25.247(5)	23.629(3)
α/°	90	90
β/°	90	90
γ/°	90	90
Volume/Å^3	2958.9(8)	3475.7(6)
Z	4	4
P_{calc} g/cm^3	1.281	1.144
μ/mm^{-1}	0.093	0.082
F(000)	1224.0	1288.0
Crystal size/mm^3	0.35 × 0.3 × 0.25	0.35 × 0.3 × 0.25
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2θ range for data collection/°	6.036 to 52.746	5.752 to 52.742
Reflections collected	9099	17665
Independent reflections	5074 [R_{int} = 0.0328, R_{sigma} = 0.0627]	7070 [R_{int} = 0.0437, R_{sigma} = 0.0765]
Data/restraints/parameters	5074/4/384	7070/0/400

Goodness-of-fit on F^2	1.026	1.026
Final R indexes [I>=2σ (I)]	R_1 = 0.0548, wR_2 = 0.1073	R_1 = 0.0833, wR_2 = 0.2061
Final R indexes [all data]	R_1 = 0.0886, wR_2 = 0.1250	R_1 = 0.1504, wR_2 = 0.2450
Largest diff. peak/hole / e $Å^{-3}$	0.19/-0.13	0.31/-0.22
Flack parameter	-0.3(10)	-0.1(8)
CCDC	2254435	2254434

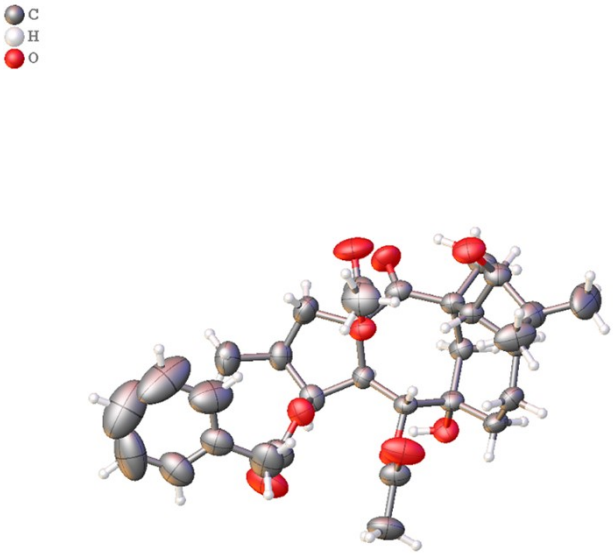


Figure S4. Single-crystal X-ray structure of **1** (with thermal ellipsoils shown at the 30% probability level)

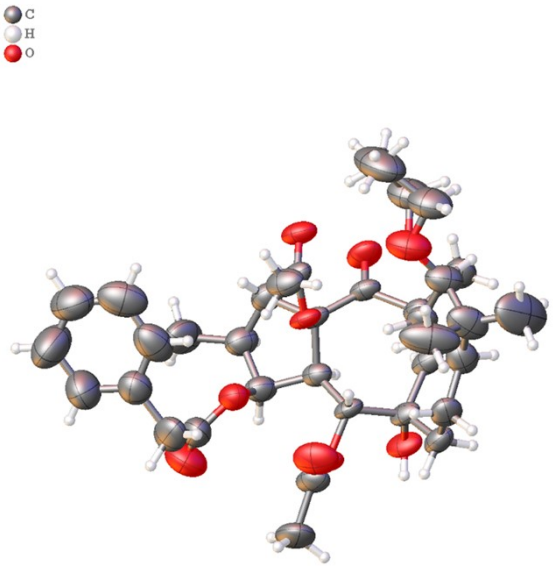


Figure S5. Single-crystal X-ray structure of **3** (with thermal ellipsoils shown at the 30% probability level)

5. Anti-HIV assays

The CD4 cell line MT-4 was obtained from the American Type Culture Collection (Rockville, MD, USA) and cultured in RPMI 1640 medium (Gibco BRL, Gaithersburg, MD, USA) with 10% heat-inactivated fetal calf serum (Biowhittaker Europe, Verviers, Belgium) and 2 mmol/L L-glutamine (Gibco BRL). The HIV-1 molecular clone NL4.3 was obtained from the NIAID AIDS Reagent Program (National Institutes of Health, Bethesda, MD, USA).

The anti-HIV-1 activity in MT4 cells was determined using a tetrazolium-based colorimetric assay. The assay was performed according to our previous report.[2] Threefold dilutions of the drugs in 100 μL medium were added to duplicate wells of 96-well flat bottom plates (Iwaki Glass). Then, MT-4 cells were seeded in the tissue culture plates (7.5×10^4 cells in 50 μL medium), and finally 50 μL diluted HIV-1 NL 4.3 stock (20× the median tissue culture infective dose) was added to each well, resulting in a final volume of 200 μL. The cytopathic effect induced by the virus was checked regularly microscopically. After 4 d of infection, when a strong cytopathic effect was observed in the positive control (i.e., untreated, HIV-infected cells), the cell viability was assessed spectrophotometrically via the in-situ reduction of the tetrazolium compound 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium inner salt, using the CellTiter 96 AQueous One Solution Cell Proliferation Assay (Promega, Fitchburg, WI, USA). The absorbance was then recorded at 490 nm with a 96-well plate reader and compared with four cell control replicates (cells without virus and drugs) and four virus control wells (cells with virus but without drug). Each assay was performed at least three times. The median inhibitory concentration (EC_{50}), or the concentration that inhibited HIV-induced cell death by 50%, was calculated from each dose–response curve. Absorbance was recorded using the VersaMax ELISA™ microplate reader (Molecular Devices) and analyzed with the Softmax Pro® software (Molecular Devices, Version 4.0). Using mock-infected cells, the 50% cytotoxic concentration (CC_{50}) of each compound was investigated.

Table S2. Anti-HIV-1 activity and cellular cytotoxicity of compounds **1-3** evaluated in MT-4 cells

Compound	HIV-1 NL 4.3	
	EC_{50} (μM) [a]	CC_{50} (μM) [b]
1	21.7	61.6
2	>100	>100
3	>100	>100
Euphorbia factor L_1	>100	>100

[a] Concentration required to achieve 50% protection of MT-4 cells against HIV-induced cytopathicity; [b] Concentration required to reduce the viability of mock-infected MT4 cells by 50%.

6. Reference

(1) N. Wang, J. B. Xu, X. H. Li, X. L. Zhou and F. Gao, *Org. Lett.*, 2022, **24**, 8598–8602.

(2) N. Wang, H. Wang, L. X. Wan, X. H. Li, X. L. Zhou, J. H. Li, S. De Jonghe, D. Schols, J. B. Xu and F. Gao, *Org. Lett.*, 2023, **25**, 597–602.

(3) G. Appendino, E. Belloro, G. C. Tron, J. Jakupovic and M. Ballero, *J. Nat. Prod.* 1999, **62**, 1399–1404.

(4) Q. Zuo, H. Y. Mu, Q. Gong, X. Ding, W. Wang, H. Y. Zhang and W. M. Zhao, *Fitoterapia*, 2021, **150**, 104834.

7. Copies of NMR spectra

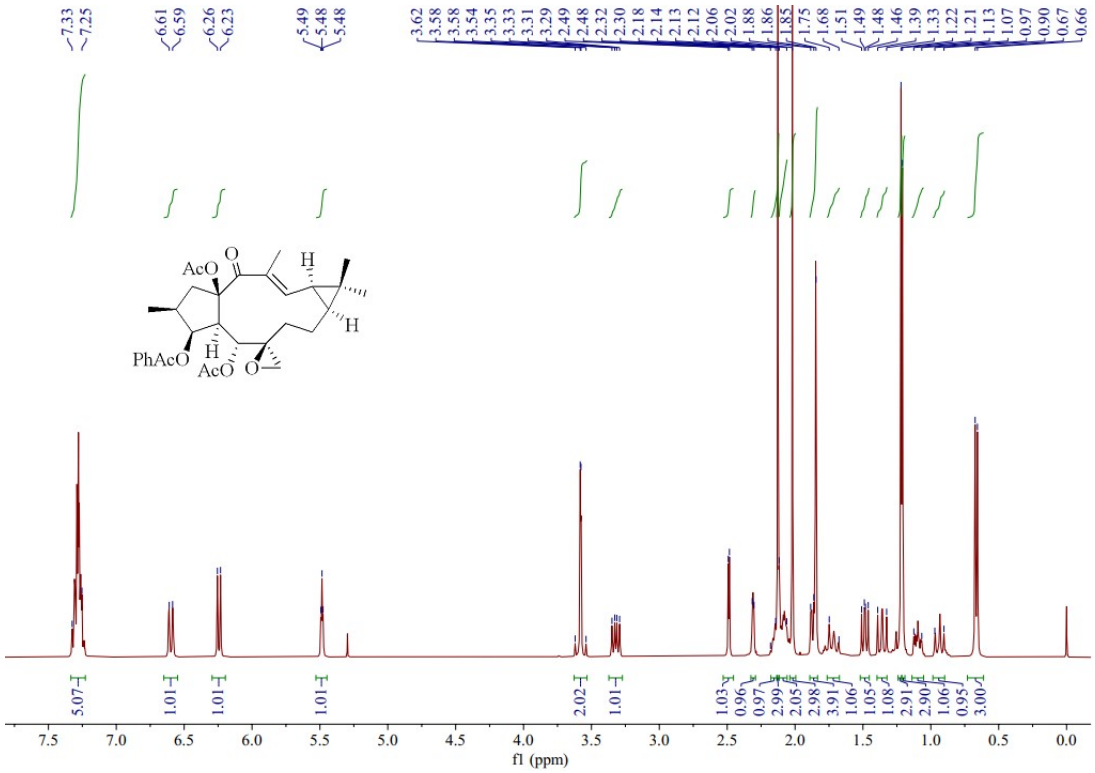


Figure S6. ^{1}H NMR spectrum of *Euphorbia* factor L_1 (400 MHz, $CDCl_3$)

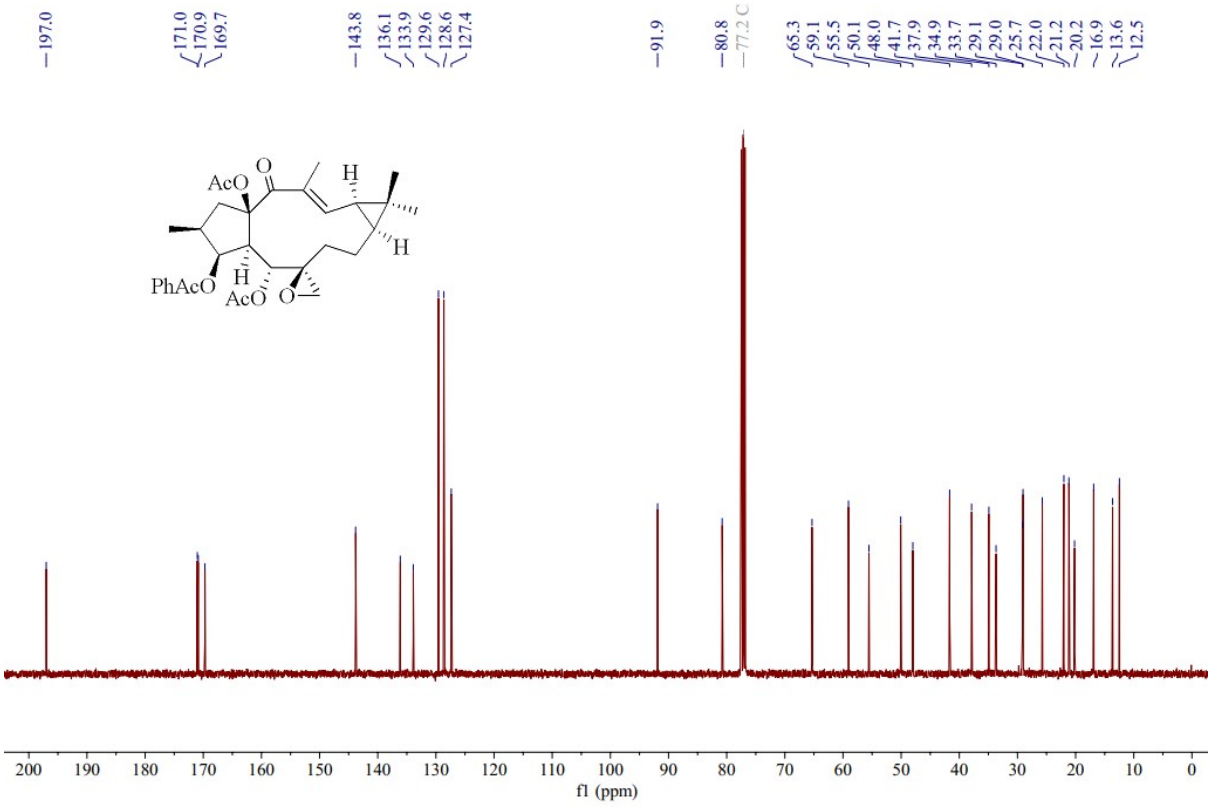


Figure S7. ^{13}C NMR spectrum of *Euphorbia* factor L_1 (100 MHz, $CDCl_3$)

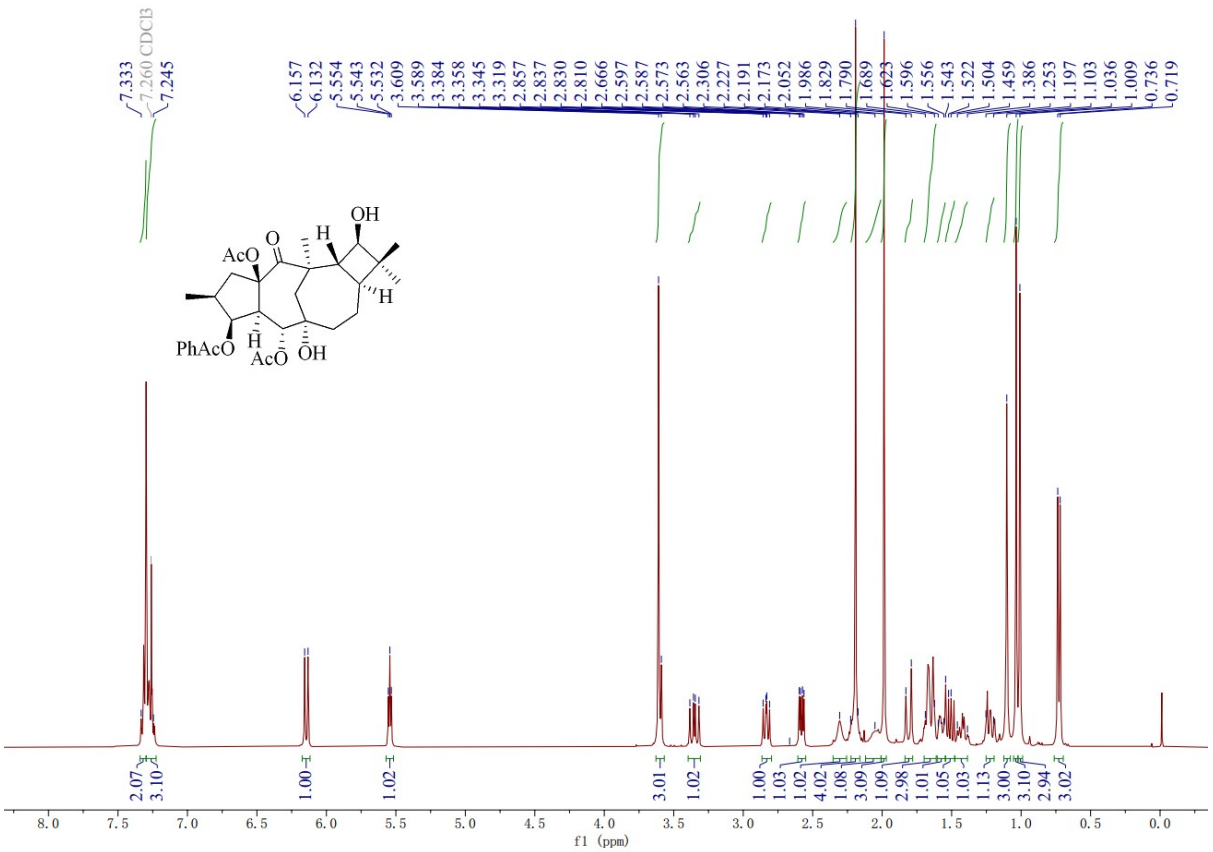


Figure S8. ^{1}H NMR spectrum of compound **1** (400 MHz, $CDCl_3$)

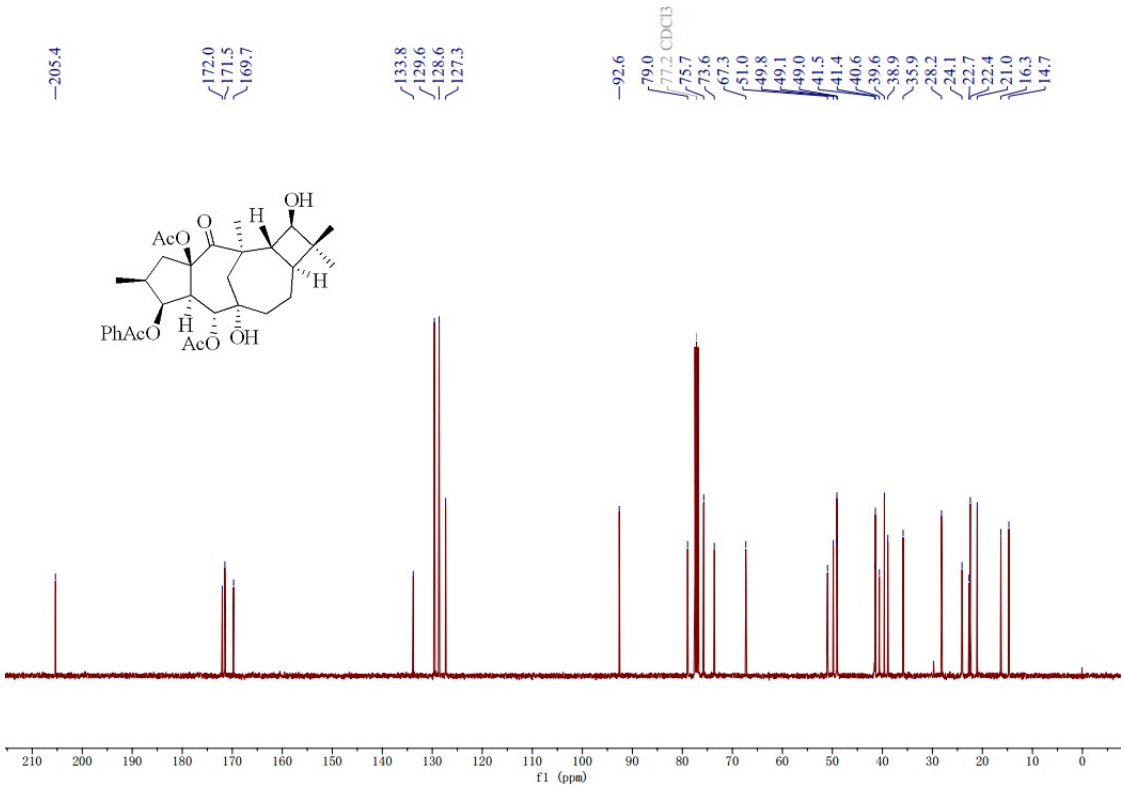


Figure S9. ^{13}C NMR spectrum of compound **1** (100 MHz, $CDCl_3$)

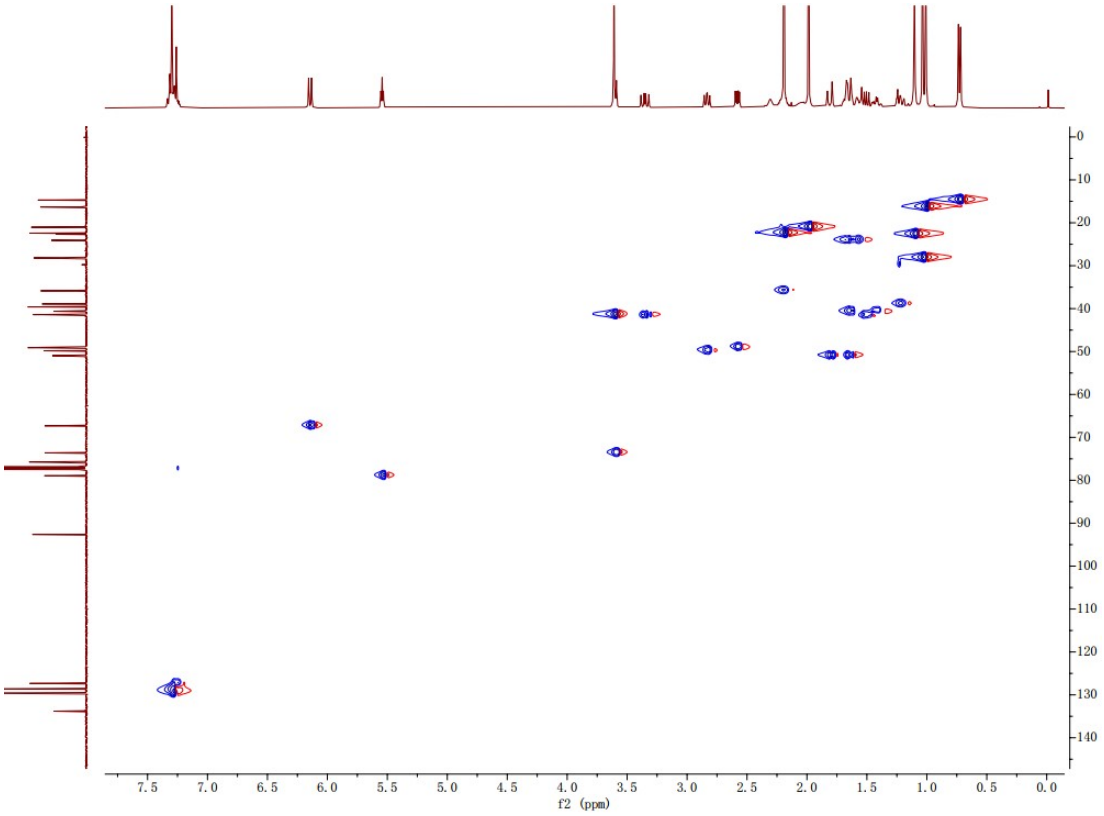


Figure S10. HSQC spectrum of compound **1** (400 MHz, $CDCl_3$)

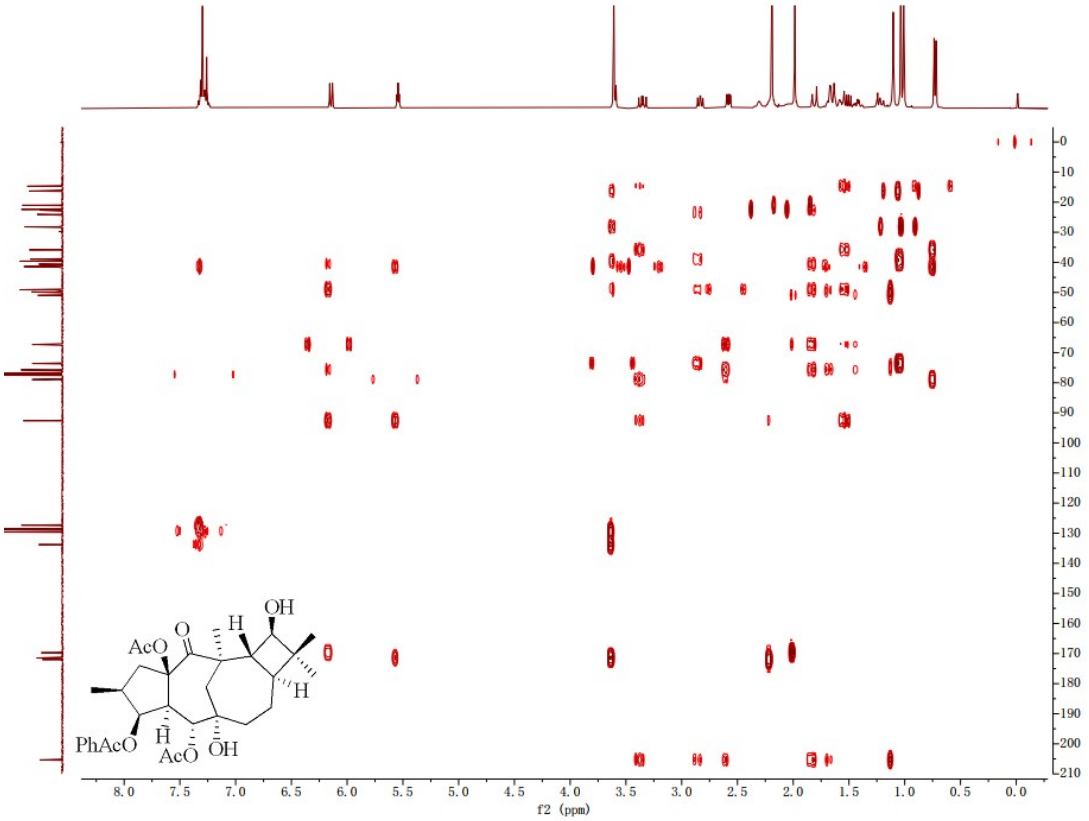


Figure S11. HMBC spectrum of compound **1** (400 MHz, $CDCl_3$)

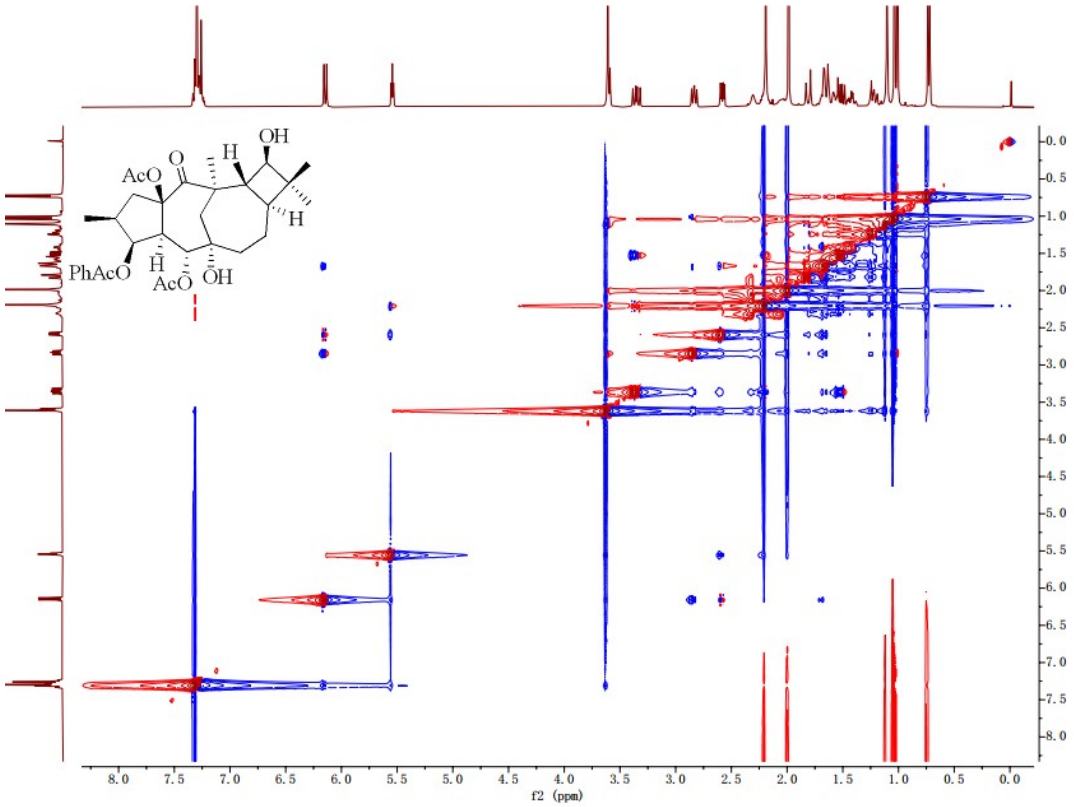


Figure S12. NOESY spectrum of compound **1** (400 MHz, $CDCl_3$)

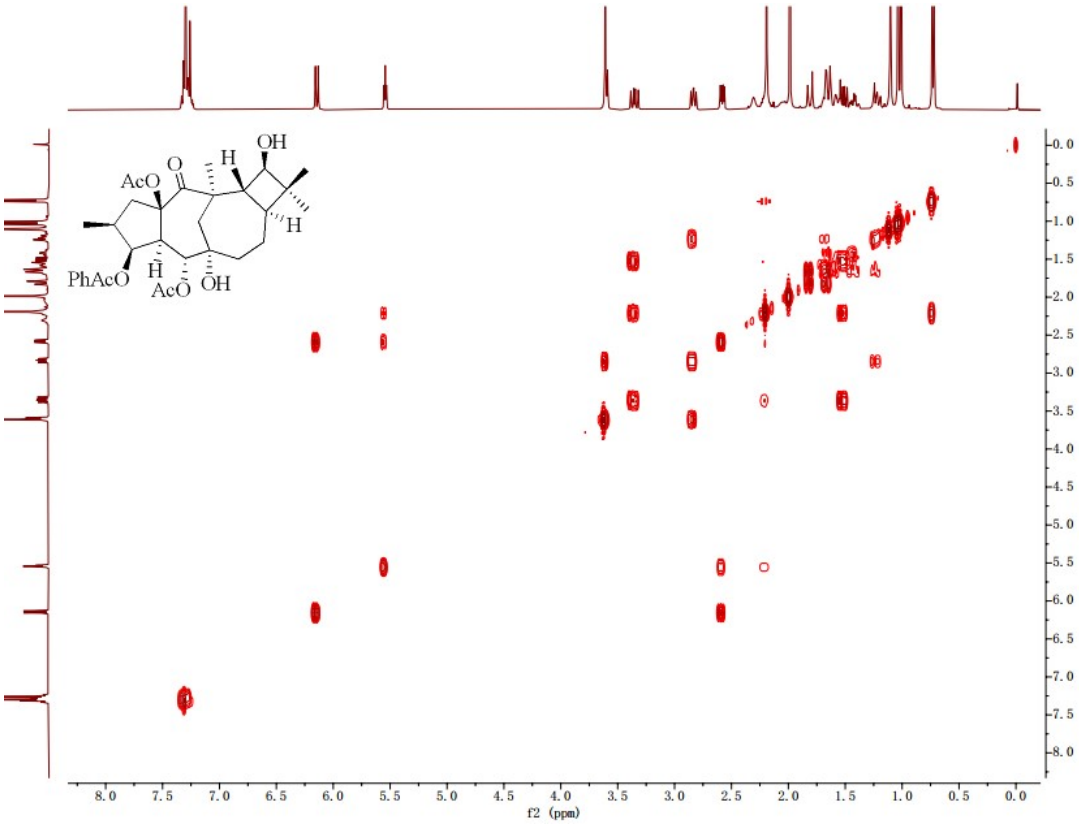


Figure S13. ^1H-^1H COSY spectrum of compound **1** (400 MHz, $CDCl_3$)

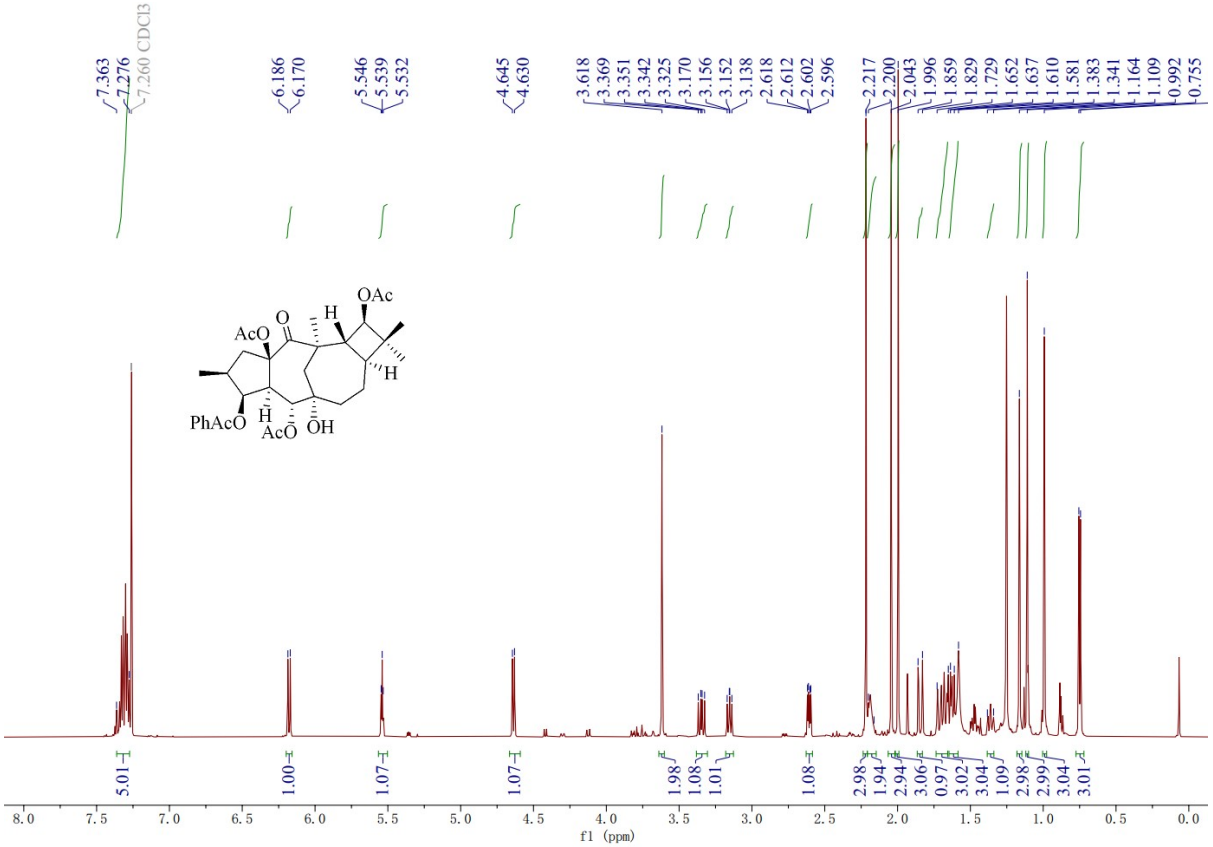


Figure S14. ^{1}H NMR spectrum of compound **2** (600 MHz, $CDCl_3$)

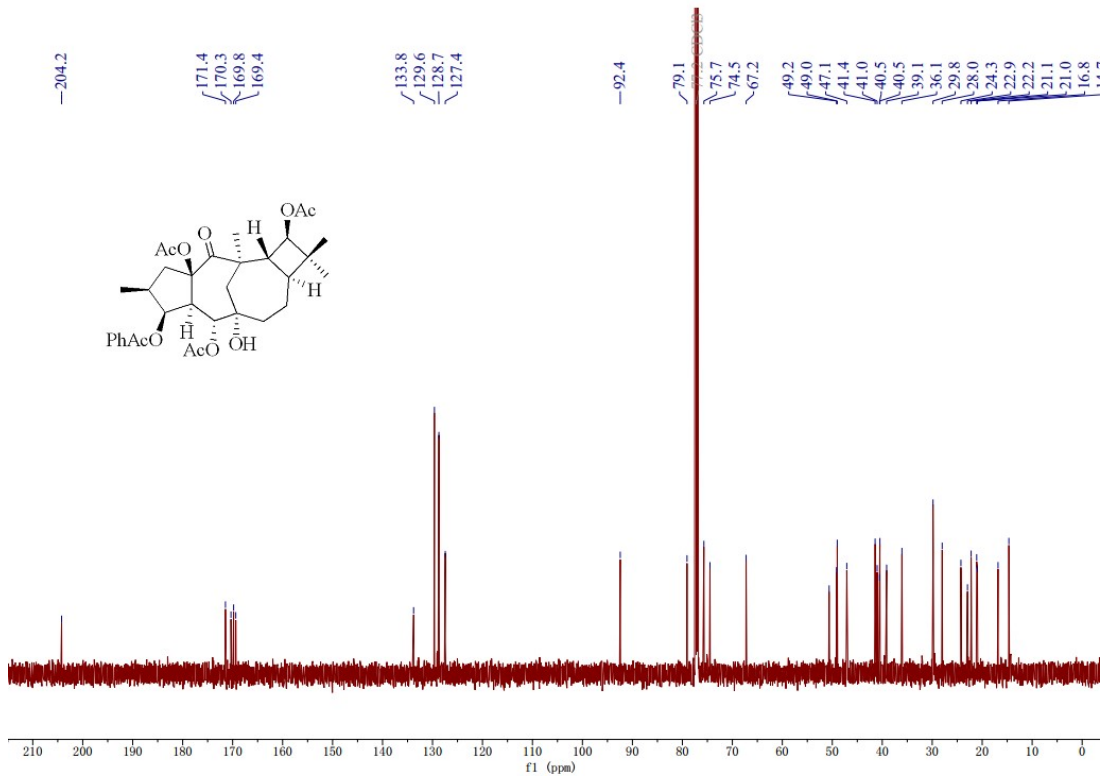


Figure S15. ^{13}C NMR spectrum of compound **2** (150 MHz, $CDCl_3$)

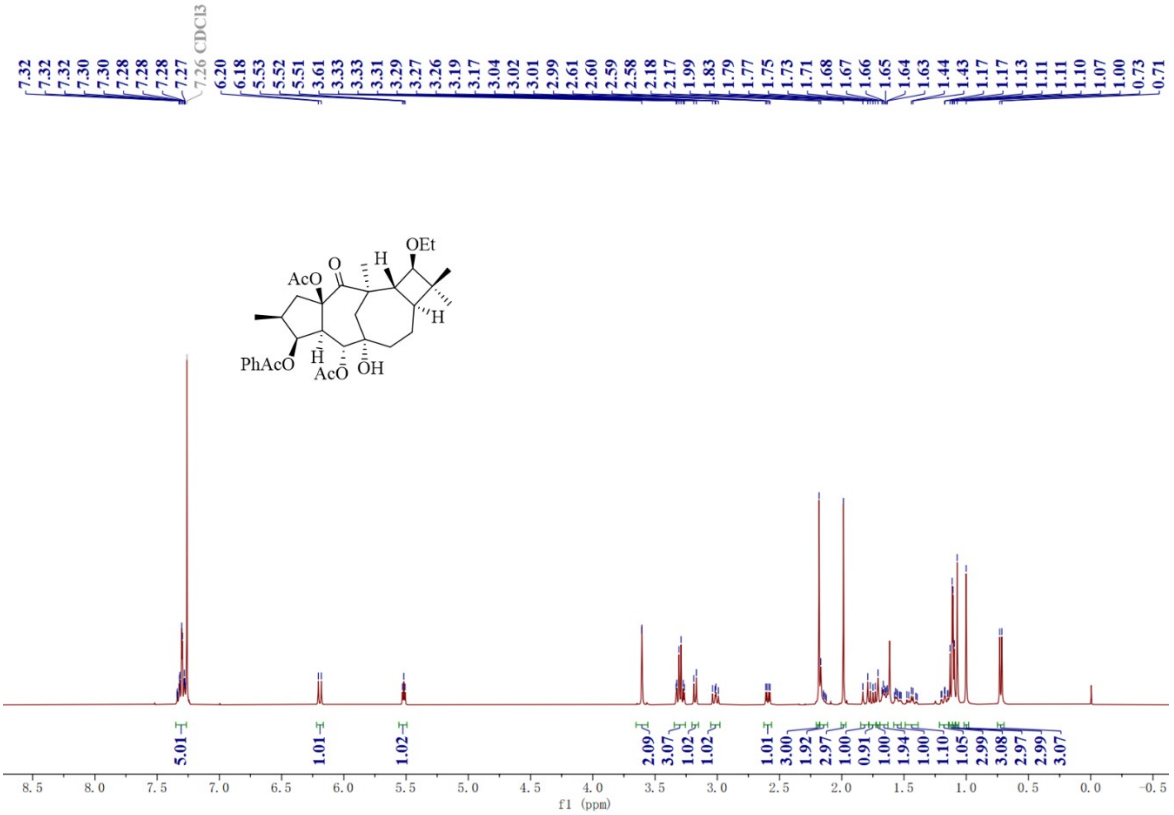


Figure S16. ^{1}H NMR spectrum of compound **3** (600 MHz, $CDCl_3$)

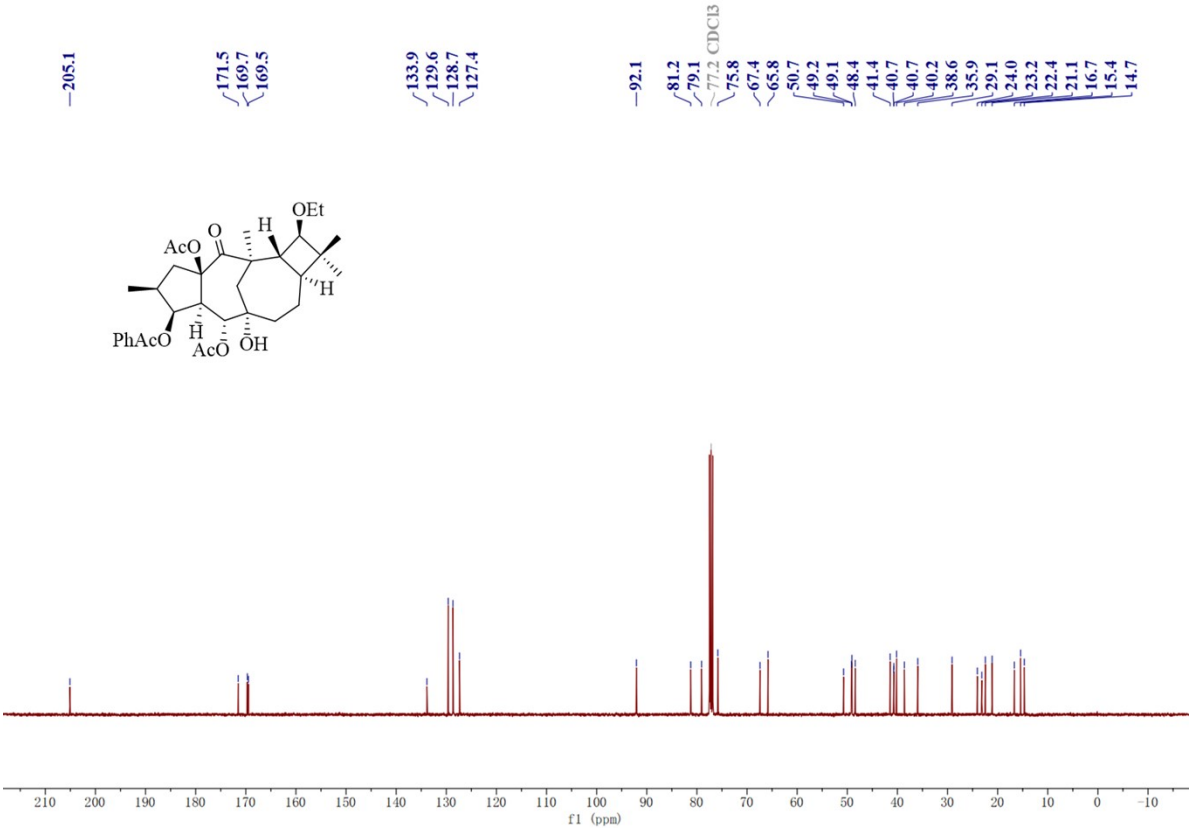


Figure S17. ^{13}C NMR spectrum of compound **3** (100 MHz, $CDCl_3$)