Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

(±)-Hypandrone A, a Pair of Polycyclic Polyprenylated Acylphloroglucinol Enantiomers with a Caged 7/6/5/6/6 Pentacyclic Skeleton from *Hypericum androsaemum*

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Contents

Experimental section

General experimental procedures

Optical rotations and UV spectra were recorded on a PerkinElmer 341 polarimeter (PerkinElmer Inc., Fremont, California, USA) and a Lambda 35 instrument (PerkinElmer Inc., Fremont, California, USA), respectively. IR spectra were obtained using a Bruker Vertex 70 FT-IR spectrophotometer (Bruker, Karlsruhe, Germany). Experimental ECD data were collected on a JASCO J-810 spectrometer (JASCO, Tokyo, Japan). The NMR spectra were recorded on a Bruker AM-400 spectrometer with TMS as the internal standard. All chemical shifts (δ) were expressed in ppm relative to the solvent signal (methanol-d_4: δ_H 3.31, δ_C 49.0). HRESIMS data were recorded in the positive-ion mode on a Bruker micrOTOF-Q II spectrometer (Bruker, Karlsruhe, Germany). Column chromatography (CC) was performed with silica gel (200–300 mesh, Qingdao Marine Chemical, Inc., Qingdao, China), Sephadex LH-20 (40–70 μm, Amersham Pharmacia Biotech AB, Uppsala, Sweden), and octadecylsilyl (ODS, 50 μm, YMC Co. Ltd., Japan). Semi-preparative HPLC separations were conducted on an Agilent 1100 liquid chromatograph with a reversed-phase (RP) C_{18} column (5 μm, 10 × 250 mm, Welch Materials, Inc.) and a CHIRALPAK IG preparative column (10 × 250 mm, 5 μm particles, Daicel, China). Thin-layer chromatography (TLC) was carried out with silica gel 60 F_{254} (Yantai Chemical Industry Research Institute). Fractions were monitored by TLC, and spots were visualized by heating silica gel plates sprayed with 10% H_2SO_4 in EtOH.

Plant material

The fruit parts of *Hypericum androsaemum* were collected from Shennongjia Forestry, Hubei Province, People's Republic of China, in October 2022. The plant was identified by Professor Jingming Jia of Shenyang Pharmaceutical University. A voucher specimen (No. HB20221011) has been deposited in the herbarium of School of Pharmacy, Tongji Medical College, Huazhong University of Science and Technology.

Exaction and isolation

The air-dried fruit parts of *H. androsaemum* (10 kg) were percolated with 95% EtOH three times at room temperature. The combined EtOH extract was concentrated under vacuum (water-bath temperature for evaporation was maintained below 50 °C) to yield a residue (860 g). Then, the resulting residue was suspended in H_2O and extracted three times with petroleum ether to afford a crude extract.

The petroleum ether extract (170 g) was subjected to silica gel column chromatography, eluted with petroleum ether/acetate extract (50:1–1:1, v/v) to afford eight main fractions (A–H). Fr. E (12 g) was chromatographed on an MCI gel column (6 × 80 cm) and eluted with CH_3OH/H_2O (10:90–100:0, v/v) to get six subfractions (Fr. E1–Fr. E6). Fraction E5 (3.2 g) was further purified on Sephadex LH-20 eluted with CH_3OH to give nine subfractions (Fr. E5-1–Fr. E5-9). Fr. E5-4 (1.4 g) was separated by MPLC over octadecylsilane (ODS) and eluted with a step gradient of CH_3OH/H_2O (60:40–90:10, v/v, flow rate: 25 mL/min) to give seven subfractions (Fr. E5-4A–Fr. E5-4G) and Fr. E5-4E (18 mg) purified by preparative HPLC (CH_3CN/H_2O, 60/40, v/v, flow rate: 8 mL/min) to yield **1** (5-4E1A, 5.8 mg, t_R 33.6 min). Then, **1** was further separated using a CHIRALPAK IG preparative column (2.0 mL/min; CH_3CN/H_2O = 55:45, v/v) to obtain (+)-**1** (2.9 mg, t_R =20.1 min) and (–)-**1** (2.3 mg, t_R = 22.5 min).

Hypandrone A (**1**): colorless crystals, m.p. 236–238 °C; UV (MeOH) λ_{max} (log ε): 201 (3.74), 229 (3.26), 275 (2.78) nm; IR (KBr) ν_{max}: 3436, 2924, 2854, 1732, 1711, 1667, 1645, 1465, 1377, 1237, 1206, 1163, 1080 cm^{-1}; for ^1H and ^{13}C NMR data, see Table 1; HRMS (ESI-TOF) *m/z* 529.1840 ([M + Na]$^+$, calcd 529.1838); (+)-**1**: white powder, $[\alpha]_D^{25}$: +33.8 (MeOH, *c* 0.1); ECD (MeOH) λ_{max} ($\Delta\varepsilon$): 210 (+4.68), 235 (–9.77), 295 (+3.94); (–)-**1**: white powder, $[\alpha]_D^{25}$: –33.8 (MeOH, *c* 0.1); ECD (MeOH) λ_{max} ($\Delta\varepsilon$): 210 (–4.27), 235 (+8.14), 296 (–4.09).

Single-crystal X-ray diffraction analysis

Crystal data for hypandrone A (**1**) (CCDC No. 2310824): M = 506.53, a = 13.5043(4) Å, b = 14.0510(4) Å, c = 26.6409(8) Å, α = 90°, β = 90°, γ = 90°, V = 5055.1(3) Å^3, T = 150(2) K, space group *Pbca*, Z = 8, μ(Cu Kα) = 0.801 mm^{-1}, 27819 reflections measured, 4615 independent reflections (R_{int} = 0.0794). The final R_1 values were 0.0486 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.1185 ($I > 2\sigma(I)$). The final R_1 values were 0.0601 (all data). The final $wR(F^2)$ values were 0.1249 (all data). The goodness of fit on F^2 was 1.095.

ECD calculation details

(1) Methods

In general, conformational analyses were carried out via random searching in the Sybyl-X 2.0 using the MMFF94S force field with an energy cutoff of 5 kcal/mol.[1] The results showed eight lowest energy conformers. Subsequently, geometry optimizations and frequency analyses were implemented at the B3LYP-D3(BJ)/6-31G* level in CPCM methanol using ORCA5.0.1[2] All conformers used for property calculations in this work were characterized to be stable point on potential energy surface (PES) with no imaginary frequencies. The excitation energies, oscillator strengths, and rotational strengths (velocity) of the first 60 excited states were calculated using the TD-DFT methodology at the PBE0/def2-TZVP level in CPCM methanol using ORCA5.0.1.[2] The ECD spectra were simulated by the overlapping Gaussian function (half the bandwidth at 1/e peak height, sigma = 0.30 for all).[3] Gibbs free energies for conformers were determined by using thermal correction at B3LYP-D3(BJ)/6-31G* level and electronic energies evaluated at the wB97M-V/def2-TZVP level in CPCM methanol using ORCA5.0.1[2] To get the final spectra, the simulated spectra of the conformers were averaged according to the boltzmann distribution theory and their relative Gibbs free energy (ΔG). By comparing the experiment spectra with the calculated model molecules, the absolute configuration of the chiral center was determined.

[1]. Sybyl Software, version X 2.0; Tripos Associates Inc.: St. Louis, MO, **2013**.

[2]. Neese, F. The ORCA program system, Wiley Interdiscip. Rev.: Comput. Mol. Sci. **2012**, *2*, 73–78.

[3]. Stephens, P. J.; Harada, N. ECD cotton effect approximated by the Gaussian curve and other methods. Chirality **2010**, *22*, 229–233.

(2) Results

Table S1.2.1.Gibbs free energies[a] and equilibrium populations[b] of low-energy conformers of (+)-**1**.

Conformers	ΔG(a.u.)	P(%)/100	G(a.u.)
(+)-**1** 000001_tddft_	0.00245	1.91	-1576.450721
(+)-**1** 000002_tddft_	0.00052	14.82	-1576.452655
(+)-**1** 000003_tddft_	0.00058	13.93	-1576.452596
(+)-**1** 000004_tddft_	0.00053	14.72	-1576.452648
(+)-**1** 000005_tddft_	0.0	25.71	-1576.453175
(+)-**1** 000006_tddft_	0.00837	0.0	-1576.444804
(+)-**1** 000007_tddft_	0.00055	14.44	-1576.45263
(+)-**1** 000009_tddft_	0.00054	14.46	-1576.452631

[a]wB97M-V/def2-TZVP, in a.u.

[b]From ΔG values at 298.15 K.

Table S1.2.2.Cartesian coordinates for the low-energy reoptimized random reseach conformers of (+)-**1** at B3LYP-D3(BJ)/6-31G* level of theory in methanol.

(+)-**1** 000001_en_		Standard Orientation (A.U.)			
Center number	Atomic number	Atomic Type	X	Y	Z
1	6	C	-8.529836	2.430752	-1.932522
2	6	C	-11.997414	0.362102	-4.289843
3	6	C	-10.478585	0.332591	-1.783674
4	6	C	-12.373161	1.390948	0.205293
5	6	C	-11.728216	4.1695	0.783407
6	6	C	-9.270535	4.508691	-0.602371
7	6	C	-6.47538	2.147748	-3.751002
8	8	O	-6.534335	0.461028	-5.342752
9	6	C	-11.450798	4.64307	3.662271
10	6	C	-13.814698	5.880096	-0.324314
11	6	C	-9.315098	3.196598	4.838808
12	6	C	-9.489264	1.091301	6.247314
13	6	C	-7.151172	-0.231392	7.180784
14	8	O	-14.165843	0.287175	1.058445
15	8	O	-8.191774	6.771657	-0.399729
16	8	O	-12.809064	-1.794565	-5.288952
17	6	C	-12.319557	-4.285766	-4.305023
18	6	C	-9.845531	-4.510292	-2.797427
19	6	C	-9.246793	-2.23279	-1.073745
20	6	C	-14.357915	-5.1001	-2.412223
21	6	C	-13.146332	-7.379102	-1.109953
22	6	C	-10.291521	-6.733562	-0.912896
23	6	C	-4.270221	3.934079	-3.681252
24	6	C	-3.103358	4.601915	-1.390272
25	6	C	-0.991128	6.18953	-1.389212
26	6	C	-0.043515	7.124805	-3.669592
27	6	C	-1.182681	6.44055	-5.957336
28	6	C	-3.268746	4.831434	-5.967267
29	6	C	-12.256734	-5.949354	-6.659538
30	6	C	-9.37111	-5.627491	1.64809
31	8	O	-12.537878	2.339711	-5.286105
32	8	O	-9.885898	-2.975986	1.41658
33	6	C	-6.517813	-6.08165	1.943621
34	6	C	-10.75968	-6.570345	3.984774
35	1	H	-9.143763	-8.396813	-1.389643
36	1	H	-8.252048	-4.811753	-4.088713
37	6	C	-11.940078	-0.169099	6.94682
38	1	H	-11.156354	6.689711	3.916062

39	1	H	-13.275659	4.168411	4.531935
40	1	H	-13.334409	7.874401	0.009792
41	1	H	-14.018869	5.557727	-2.363853
42	1	H	-15.617353	5.448604	0.615718
43	1	H	-7.419631	3.920978	4.417395
44	1	H	-5.411762	0.738132	6.584303
45	1	H	-7.145015	-0.376418	9.262206
46	1	H	-7.089877	-2.180619	6.445394
47	1	H	-6.614602	6.82515	-1.345554
48	1	H	-7.194633	-1.914624	-1.165273
49	1	H	-16.169307	-5.522994	-3.34138
50	1	H	-14.67077	-3.559221	-1.050441
51	1	H	-14.017549	-7.802483	0.722546
52	1	H	-13.383334	-9.085902	-2.274865
53	1	H	-3.826231	3.830388	0.384383
54	1	H	-0.077001	6.682437	0.394749
55	1	H	1.596935	8.378256	-3.667881
56	1	H	-0.430532	7.160581	-7.73994
57	1	H	-4.157623	4.245312	-7.733956
58	1	H	-14.071931	-5.82573	-7.663855
59	1	H	-10.750234	-5.30085	-7.935608
60	1	H	-11.896479	-7.934701	-6.167126
61	1	H	-5.777572	-4.965138	3.532715
62	1	H	-6.140616	-8.092221	2.319634
63	1	H	-5.460356	-5.556136	0.232335
64	1	H	-12.740821	-5.956563	3.965521
65	1	H	-10.696693	-8.646831	4.0862
66	1	H	-9.872168	-5.813534	5.704523
67	1	H	-13.601001	1.029359	6.628317
68	1	H	-12.191186	-1.875022	5.785651
69	1	H	-11.922871	-0.76037	8.945401

(+)-**1** 000002_en_		Standard Orientation (A.U.)			
Center number	Atomic number	Atomic Type	X	Y	Z
1	6	C	-7.708278	3.331418	-1.04422
2	6	C	-11.420239	1.704439	-3.553567
3	6	C	-9.703067	1.286349	-1.248467
4	6	C	-11.485417	1.958506	1.038751
5	6	C	-10.444416	4.243191	2.496344
6	6	C	-8.089785	4.839676	1.036602
7	6	C	-5.425231	3.645568	-2.50601
8	8	O	-3.806889	5.235627	-1.863057
9	6	C	-9.763562	3.508243	5.276715
10	6	C	-12.34579	6.440212	2.34201
11	6	C	-11.973674	3.37324	7.047485
12	6	C	-13.176251	1.289159	7.861229
13	6	C	-15.38073	1.48166	9.651096
14	8	O	-13.446026	0.908331	1.486262
15	8	O	-6.559046	6.631233	1.789358
16	8	O	-12.298218	-0.274049	-4.837896
17	6	C	-11.782419	-2.90101	-4.299957
18	6	C	-9.231026	-3.371839	-2.986073
19	6	C	-8.502579	-1.375657	-0.994463
20	6	C	-13.727071	-4.009318	-2.457185
21	6	C	-12.460979	-6.457203	-1.581359
22	6	C	-9.598959	-5.840001	-1.412672
23	6	C	-4.909682	1.970634	-4.729949
24	6	C	-2.691616	0.516716	-4.74875
25	6	C	-2.194351	-1.11836	-6.756957
26	6	C	-3.875394	-1.264075	-8.793455
27	6	C	-6.047383	0.237085	-8.815326
28	6	C	-6.580536	1.836665	-6.782394
29	6	C	-11.856092	-4.156015	-6.8942
30	6	C	-8.560598	-5.10628	1.240857
31	8	O	-12.01238	3.814231	-4.187691
32	8	O	-9.058424	-2.441312	1.396915
33	6	C	-5.699061	-5.584035	1.353208
34	6	C	-9.855907	-6.354011	3.484014
35	1	H	-8.475136	-7.413963	-2.167064
36	1	H	-7.715328	-3.501873	-4.396539
37	6	C	-12.503495	-1.355316	7.072444
38	1	H	-8.709484	1.717478	5.224691
39	1	H	-8.436565	4.968754	5.942875
40	1	H	-14.146068	5.863637	3.198467

41	1	H	-11.602007	8.098708	3.351123
42	1	H	-12.684635	6.9517	0.356405
43	1	H	-12.669932	5.200179	7.729449
44	1	H	-15.024405	0.391792	11.395354
45	1	H	-15.789745	3.448534	10.184131
46	1	H	-17.09901	0.667477	8.790073
47	1	H	-5.101842	6.569893	0.547897
48	1	H	-6.448859	-1.089771	-1.130311
49	1	H	-15.581771	-4.29336	-3.352625
50	1	H	-13.970094	-2.69003	-0.869925
51	1	H	-13.249376	-7.166954	0.199591
52	1	H	-12.75391	-7.963313	-2.986203
53	1	H	-1.374776	0.670549	-3.167176
54	1	H	-0.480193	-2.269161	-6.745495
55	1	H	-3.477086	-2.532545	-10.373149
56	1	H	-7.339848	0.170733	-10.423531
57	1	H	-8.261521	3.026406	-6.820783
58	1	H	-10.393507	-3.326903	-8.114972
59	1	H	-11.505021	-6.197622	-6.74484
60	1	H	-13.711778	-3.858252	-7.780802
61	1	H	-4.896569	-4.662629	3.035889
62	1	H	-5.30647	-7.6235	1.465046
63	1	H	-4.714578	-4.849213	-0.324654
64	1	H	-11.839194	-5.767139	3.622445
65	1	H	-9.772442	-8.425189	3.314922
66	1	H	-8.909122	-5.80802	5.251566
67	1	H	-10.917515	-1.440837	5.747328
68	1	H	-12.060494	-2.532124	8.738664
69	1	H	-14.135082	-2.243886	6.126062

(+)-**1** 000003_en_		Standard Orientation (A.U.)			
Center number	Atomic number	Atomic Type	X	Y	Z
1	6	C	-7.662824	3.283908	-1.080774
2	6	C	-11.473447	1.882102	-3.576741
3	6	C	-9.735264	1.321577	-1.317544
4	6	C	-11.456566	1.983787	1.019013
5	6	C	-10.309725	4.180662	2.530557
6	6	C	-7.959062	4.740261	1.050939
7	6	C	-5.393799	3.568022	-2.570101
8	8	O	-3.715693	5.086769	-1.906651
9	6	C	-9.610564	3.33286	5.273774
10	6	C	-12.134174	6.446677	2.479585
11	6	C	-11.795814	3.217781	7.076673
12	6	C	-13.06282	1.152244	7.838311
13	6	C	-15.230215	1.363115	9.670725
14	8	O	-13.449645	0.994801	1.462716
15	8	O	-6.355802	6.454548	1.831446
16	8	O	-12.457695	-0.017486	-4.902442
17	6	C	-12.030996	-2.678867	-4.466343
18	6	C	-9.477609	-3.290138	-3.214093
19	6	C	-8.636219	-1.391941	-1.172011
20	6	C	-13.987096	-3.780463	-2.631864
21	6	C	-12.799069	-6.301975	-1.861457
22	6	C	-9.914562	-5.794387	-1.717248
23	6	C	-4.964516	1.946713	-4.851071
24	6	C	-2.78737	0.435399	-4.953901
25	6	C	-2.368606	-1.148639	-7.020035
26	6	C	-4.087299	-1.185699	-9.0298
27	6	C	-6.217545	0.37294	-8.96715
28	6	C	-6.672688	1.921628	-6.876774
29	6	C	-12.193594	-3.836259	-7.101788
30	6	C	-8.809326	-5.190193	0.941918
31	8	O	-11.989316	4.033321	-4.133809
32	8	O	-9.19402	-2.514012	1.192863
33	6	C	-5.968561	-5.787769	0.99435
34	6	C	-10.123878	-6.457718	3.162654
35	1	H	-8.861274	-7.382399	-2.540958
36	1	H	-7.993059	-3.432012	-4.656245
37	6	C	-12.502436	-1.485638	6.946155
38	1	H	-8.620485	1.509525	5.147216
39	1	H	-8.22283	4.724414	5.963303
40	1	H	-13.940792	5.903142	3.344049

41	1	H	-11.318786	8.043148	3.532484
42	1	H	-12.483074	7.037128	0.517777
43	1	H	-12.412643	5.044084	7.832557
44	1	H	-14.885704	0.203379	11.371718
45	1	H	-15.559039	3.32441	10.275048
46	1	H	-16.990353	0.640225	8.812705
47	1	H	-4.922558	6.381534	0.56158
48	1	H	-6.575204	-1.18147	-1.336814
49	1	H	-15.864091	-3.964871	-3.50663
50	1	H	-14.158295	-2.510416	-0.995763
51	1	H	-13.586446	-7.044331	-0.093418
52	1	H	-13.167578	-7.746398	-3.312512
53	1	H	-1.440585	0.505465	-3.39182
54	1	H	-0.686868	-2.345173	-7.074369
55	1	H	-3.750585	-2.41436	-10.654635
56	1	H	-7.537506	0.392284	-10.554164
57	1	H	-8.318483	3.159683	-6.849943
58	1	H	-10.719585	-3.01995	-8.317407
59	1	H	-11.920337	-5.89398	-7.031868
60	1	H	-14.050111	-3.434717	-7.944466
61	1	H	-5.659367	-7.844171	1.031033
62	1	H	-4.978695	-5.0354	-0.672574
63	1	H	-5.106045	-4.958112	2.694956
64	1	H	-9.129365	-6.012534	4.932214
65	1	H	-12.078304	-5.792879	3.350781
66	1	H	-10.130358	-8.523736	2.923994
67	1	H	-12.099381	-2.74214	8.563403
68	1	H	-14.17288	-2.269494	5.975482
69	1	H	-10.927344	-1.584391	5.608889

(+)-**1** 000004_en_		Standard Orientation (A.U.)			
Center number	Atomic number	Atomic Type	X	Y	Z
1	6	C	-7.567852	3.373303	-1.17485
2	6	C	-11.071521	2.267808	-4.234514
3	6	C	-9.809705	1.665495	-1.696734
4	6	C	-11.754731	2.621302	0.340963
5	6	C	-10.443635	4.38423	2.232368
6	6	C	-7.934632	4.797195	0.972447
7	6	C	-5.083075	3.3472	-2.312415
8	8	O	-3.361199	4.695909	-1.424588
9	6	C	-10.005012	3.003449	4.794038
10	6	C	-11.938567	6.851574	2.544409
11	6	C	-12.367279	1.997272	6.01672
12	6	C	-12.446875	0.236633	7.843742
13	6	C	-14.922164	-0.653398	8.929363
14	8	O	-13.976143	2.153336	0.3352
15	8	O	-6.25476	6.298827	1.989255
16	8	O	-12.131627	0.410143	-5.569044
17	6	C	-12.277109	-2.219102	-4.84952
18	6	C	-10.094712	-3.114795	-3.141297
19	6	C	-9.137365	-1.149912	-1.220545
20	6	C	-14.667436	-2.766702	-3.30114
21	6	C	-14.088369	-5.31571	-2.064938
22	6	C	-11.216668	-5.27631	-1.477219
23	6	C	-4.459863	1.545639	-4.40401
24	6	C	-2.36625	-0.052917	-4.080663
25	6	C	-1.753264	-1.831667	-5.926705
26	6	C	-3.189972	-1.989147	-8.141457
27	6	C	-5.226153	-0.34775	-8.506283
28	6	C	-5.872985	1.408163	-6.642741
29	6	C	-12.24808	-3.618736	-7.369575
30	6	C	-10.399831	-4.549429	1.25988
31	8	O	-11.135645	4.403703	-5.026398
32	8	O	-10.106712	-1.856927	1.169206
33	6	C	-7.846393	-5.772705	1.885873
34	6	C	-12.318575	-5.08656	3.334317
35	1	H	-10.375829	-7.113993	-1.950077
36	1	H	-8.496925	-3.730204	-4.312379
37	6	C	-10.127753	-0.959077	8.982731
38	1	H	-8.67443	1.441204	4.459601
39	1	H	-9.026719	4.369832	6.032551
40	1	H	-10.901594	8.146019	3.796296

41	1	H	-12.208562	7.778088	0.703337
42	1	H	-13.808998	6.468088	3.356318
43	1	H	-14.166355	2.743078	5.326105
44	1	H	-14.991757	-0.355443	10.994491
45	1	H	-16.543457	0.327637	8.076392
46	1	H	-15.168662	-2.704406	8.623378
47	1	H	-4.705848	6.102522	0.871191
48	1	H	-7.060571	-1.26818	-1.181868
49	1	H	-16.374128	-2.781287	-4.488578
50	1	H	-14.900314	-1.275922	-1.874054
51	1	H	-15.259757	-5.670523	-0.391703
52	1	H	-14.484865	-6.866276	-3.394194
53	1	H	-1.24239	0.110006	-2.358103
54	1	H	-0.141157	-3.090708	-5.646152
55	1	H	-2.703995	-3.375863	-9.592046
56	1	H	-6.318796	-0.419387	-10.256554
57	1	H	-7.421433	2.724455	-6.965554
58	1	H	-10.477242	-3.21651	-8.380931
59	1	H	-12.388127	-5.671545	-7.081222
60	1	H	-13.842798	-2.998541	-8.548409
61	1	H	-6.444298	-5.426769	0.387576
62	1	H	-7.102601	-4.995118	3.665231
63	1	H	-8.04916	-7.832306	2.09774
64	1	H	-12.828607	-7.102215	3.372498
65	1	H	-11.514667	-4.574835	5.17833
66	1	H	-14.030453	-3.947363	3.062487
67	1	H	-9.802123	-0.239036	10.915527
68	1	H	-10.366593	-3.022819	9.164142
69	1	H	-8.404526	-0.603731	7.881144

(+)-**1** 000005_en_		Standard Orientation (A.U.)			
Center number	Atomic number	Atomic Type	X	Y	Z
1	6	C	-7.676377	3.215859	-0.850121
2	6	C	-11.281656	1.89979	-3.697304
3	6	C	-9.693186	1.243613	-1.362306
4	6	C	-11.535712	1.689303	0.929249
5	6	C	-10.311672	3.450702	2.873465
6	6	C	-8.033857	4.366261	1.457164
7	6	C	-5.348764	3.686789	-2.198699
8	8	O	-3.759323	5.199975	-1.33006
9	6	C	-9.412788	1.904721	5.239642
10	6	C	-12.124024	5.586747	3.611952
11	6	C	-11.512562	0.619909	6.638651
12	6	C	-12.541673	1.317819	8.855481
13	6	C	-14.661683	-0.188687	10.014756
14	8	O	-13.647667	0.868771	1.070484
15	8	O	-6.497496	6.012711	2.478348
16	8	O	-12.180625	0.048519	-5.154799
17	6	C	-11.860467	-2.629969	-4.743419
18	6	C	-9.406679	-3.34059	-3.344557
19	6	C	-8.581519	-1.469617	-1.273877
20	6	C	-13.967256	-3.708093	-3.065966
21	6	C	-12.897171	-6.25979	-2.227438
22	6	C	-10.018596	-5.828063	-1.878083
23	6	C	-4.704298	2.209372	-4.524892
24	6	C	-2.416411	0.865408	-4.556346
25	6	C	-1.775372	-0.618418	-6.638822
26	6	C	-3.384138	-0.723142	-8.735035
27	6	C	-5.62383	0.675492	-8.743383
28	6	C	-6.295809	2.128266	-6.642641
29	6	C	-11.886467	-3.738079	-7.405062
30	6	C	-9.054091	-5.279454	0.851934
31	8	O	-11.743931	4.069338	-4.218437
32	8	O	-9.219318	-2.583235	1.074869
33	6	C	-6.285058	-6.105553	1.103885
34	6	C	-10.631594	-6.364746	2.998773
35	1	H	-8.962566	-7.443286	-2.642127
36	1	H	-7.85622	-3.553448	-4.706077
37	6	C	-11.745026	3.599375	10.359862
38	1	H	-8.065587	0.468965	4.569733
39	1	H	-8.366532	3.235678	6.442817
40	1	H	-13.794629	4.784524	4.545485

41	1	H	-11.175408	6.900831	4.912363
42	1	H	-12.739045	6.640861	1.929321
43	1	H	-12.28766	-1.052396	5.702125
44	1	H	-16.356696	0.999707	10.28281
45	1	H	-15.19379	-1.81665	8.83783
46	1	H	-14.132842	-0.891812	11.907876
47	1	H	-5.058011	6.164768	1.21775
48	1	H	-6.514774	-1.269544	-1.393356
49	1	H	-15.776825	-3.847059	-4.080108
50	1	H	-14.238992	-2.443339	-1.441622
51	1	H	-13.826449	-6.991151	-0.524414
52	1	H	-13.194534	-7.689524	-3.709275
53	1	H	-1.161367	0.986916	-2.92294
54	1	H	-0.00738	-1.68477	-6.636131
55	1	H	-2.876308	-1.875482	-10.371335
56	1	H	-6.858565	0.64937	-10.397571
57	1	H	-8.016768	3.25672	-6.681377
58	1	H	-10.312702	-2.952656	-8.512033
59	1	H	-11.685958	-5.805152	-7.354216
60	1	H	-13.670938	-3.262339	-8.357402
61	1	H	-5.120339	-5.370053	-0.455442
62	1	H	-5.493596	-5.404801	2.894173
63	1	H	-6.133384	-8.180076	1.079998
64	1	H	-10.767287	-8.43479	2.853207
65	1	H	-9.754472	-5.893685	4.824033
66	1	H	-12.543302	-5.557805	2.987957
67	1	H	-11.24302	3.058176	12.311137
68	1	H	-10.130623	4.606021	9.53459
69	1	H	-13.326131	4.952452	10.514205

(+)-**1** 000006_en_		Standard Orientation (A.U.)			
Center number	Atomic number	Atomic Type	X	Y	Z
1	6	C	-8.563632	1.764785	-1.202284
2	6	C	-11.082754	-0.134706	-4.651484
3	6	C	-10.443695	-0.319266	-1.805646
4	6	C	-12.848256	0.581184	-0.369285
5	6	C	-12.34029	3.128318	0.919939
6	6	C	-9.606793	3.576822	0.295924
7	6	C	-6.026097	1.738772	-2.313231
8	8	O	-5.030411	-0.202368	-3.090807
9	6	C	-12.861935	3.026212	3.805055
10	6	C	-14.024295	5.141593	-0.353442
11	6	C	-11.105291	1.275819	5.175817
12	6	C	-9.175168	1.897193	6.705139
13	6	C	-7.510322	-0.136868	7.805218
14	8	O	-14.864781	-0.468915	-0.35801
15	8	O	-8.586168	5.677213	1.238302
16	8	O	-11.828946	-2.186421	-5.899213
17	6	C	-12.102993	-4.712802	-4.866442
18	6	C	-10.337208	-5.238206	-2.617594
19	6	C	-9.545723	-2.970945	-0.948155
20	6	C	-14.834911	-5.174078	-3.906088
21	6	C	-14.626374	-6.294066	-1.229115
22	6	C	-11.817346	-6.956403	-0.7841
23	6	C	-4.647208	4.210308	-2.58192
24	6	C	-2.093732	4.383482	-1.88698
25	6	C	-0.778673	6.640173	-2.243552
26	6	C	-1.986506	8.714649	-3.354397
27	6	C	-4.512328	8.532262	-4.107312
28	6	C	-5.850289	6.290453	-3.715048
29	6	C	-11.460992	-6.432865	-7.087872
30	6	C	-10.757914	-6.174253	1.825163
31	8	O	-10.966942	1.869771	-5.737396
32	8	O	-10.429431	-3.495173	1.536745
33	6	C	-8.195682	-7.434934	2.332227
34	6	C	-12.52214	-6.589046	4.061552
35	1	H	-11.453341	-8.969042	-1.159255
36	1	H	-8.60628	-6.138872	-3.320504
37	6	C	-8.461281	4.552017	7.438553
38	1	H	-12.759342	4.967263	4.537636
39	1	H	-14.834597	2.388162	4.021111
40	1	H	-13.586348	7.019	0.422259

41	1	H	-13.711426	5.171618	-2.408382
42	1	H	-16.021305	4.69765	0.009751
43	1	H	-11.363845	-0.724727	4.737335
44	1	H	-7.580735	-0.12977	9.891922
45	1	H	-8.060916	-2.023734	7.130704
46	1	H	-5.513759	0.179879	7.283462
47	1	H	-6.890601	5.91869	0.5682
48	1	H	-7.476468	-2.880886	-0.94923
49	1	H	-15.830527	-6.442653	-5.217902
50	1	H	-15.869976	-3.379264	-3.875296
51	1	H	-15.218521	-4.844528	0.125781
52	1	H	-15.853023	-7.948737	-0.952447
53	1	H	-1.165002	2.730214	-1.073333
54	1	H	1.200122	6.782176	-1.672074
55	1	H	-0.948311	10.475137	-3.648022
56	1	H	-5.440988	10.136169	-5.016437
57	1	H	-7.811446	6.097415	-4.331792
58	1	H	-12.76474	-6.080036	-8.667674
59	1	H	-9.517088	-6.087294	-7.738218
60	1	H	-11.634836	-8.425141	-6.515983
61	1	H	-7.332965	-6.619028	4.039112
62	1	H	-8.428861	-9.481279	2.625865
63	1	H	-6.870637	-7.164194	0.753377
64	1	H	-14.288332	-5.527165	3.83316
65	1	H	-12.975769	-8.608633	4.266109
66	1	H	-11.609073	-5.947625	5.816614
67	1	H	-8.515622	4.781462	9.512282
68	1	H	-6.50148	4.961377	6.850777
69	1	H	-9.679395	5.996512	6.586452

(+)-**1** 000007_en_		Standard Orientation (A.U.)			
Center number	Atomic number	Atomic Type	X	Y	Z
1	6	C	-7.451072	3.244835	-0.838984
2	6	C	-11.561173	2.333054	-3.060112
3	6	C	-9.645258	1.419874	-1.076467
4	6	C	-11.084052	1.875137	1.491612
5	6	C	-9.663166	3.815528	3.116248
6	6	C	-7.456272	4.458154	1.459386
7	6	C	-5.329917	3.608806	-2.518107
8	8	O	-3.524858	4.98433	-1.874179
9	6	C	-8.717564	2.595379	5.63879
10	6	C	-11.352104	6.14397	3.550242
11	6	C	-10.686531	2.376831	7.666894
12	6	C	-11.991037	0.30445	8.341744
13	6	C	-13.90936	0.409431	10.441536
14	8	O	-13.078014	0.935626	2.030001
15	8	O	-5.701868	6.014007	2.24675
16	8	O	-12.803253	0.65584	-4.466927
17	6	C	-12.501606	-2.05682	-4.381794
18	6	C	-9.874084	-2.941096	-3.499821
19	6	C	-8.704855	-1.341979	-1.364579
20	6	C	-14.318772	-3.267308	-2.475299
21	6	C	-13.220633	-5.920732	-2.136448
22	6	C	-10.310495	-5.57961	-2.253308
23	6	C	-5.190604	2.22256	-4.982857
24	6	C	-3.080856	0.685547	-5.453875
25	6	C	-2.917129	-0.694452	-7.694513
26	6	C	-4.82704	-0.496732	-9.513184
27	6	C	-6.892243	1.091388	-9.083322
28	6	C	-7.090546	2.434994	-6.818168
29	6	C	-13.015986	-2.885821	-7.094928
30	6	C	-8.901146	-5.35232	0.319319
31	8	O	-11.980349	4.559639	-3.325233
32	8	O	-9.08083	-2.707115	0.9063
33	6	C	-6.116516	-6.105457	-0.004889
34	6	C	-10.064541	-6.797445	2.516116
35	1	H	-9.449337	-7.109143	-3.361489
36	1	H	-8.560282	-2.992611	-5.104148
37	6	C	-11.71567	-2.233683	7.097546
38	1	H	-7.874069	0.752181	5.179263
39	1	H	-7.170531	3.815032	6.314588
40	1	H	-10.340694	7.556733	4.691517

41	1	H	-11.87471	6.9959	1.728129
42	1	H	-13.083785	5.570886	4.539756
43	1	H	-11.089055	4.128048	8.695702
44	1	H	-13.440957	-0.955225	11.950186
45	1	H	-14.038372	2.301361	11.292239
46	1	H	-15.801317	-0.119991	9.736773
47	1	H	-4.412247	6.035112	0.828695
48	1	H	-6.663964	-1.214365	-1.734711
49	1	H	-16.286022	-3.249286	-3.147757
50	1	H	-14.233002	-2.195797	-0.696649
51	1	H	-13.867592	-6.832617	-0.390835
52	1	H	-13.825943	-7.156648	-3.696291
53	1	H	-1.583882	0.574151	-4.037888
54	1	H	-1.286015	-1.913836	-8.034391
55	1	H	-4.690669	-1.564311	-11.275153
56	1	H	-8.361535	1.295769	-10.518987
57	1	H	-8.684891	3.701153	-6.507114
58	1	H	-12.869814	-4.948963	-7.284165
59	1	H	-14.921907	-2.293103	-7.67324
60	1	H	-11.630355	-2.010695	-8.372181
61	1	H	-5.249949	-5.211329	-1.670874
62	1	H	-5.03144	-5.540176	1.676546
63	1	H	-5.945099	-8.164895	-0.240346
64	1	H	-10.224147	-8.819506	2.057241
65	1	H	-8.873538	-6.605579	4.207977
66	1	H	-11.944877	-6.058019	2.977474
67	1	H	-11.201184	-3.69196	8.499686
68	1	H	-13.538909	-2.812664	6.268632
69	1	H	-10.322762	-2.252367	5.568308

(+)-**1** 000009_en_		Standard Orientation (A.U.)			
Center number	Atomic number	Atomic Type	X	Y	Z
1	6	C	-7.517621	3.394769	-1.088376
2	6	C	-11.014644	2.321328	-4.167842
3	6	C	-9.77039	1.705674	-1.624598
4	6	C	-11.717808	2.673018	0.404926
5	6	C	-10.402207	4.421169	2.306802
6	6	C	-7.883272	4.816132	1.060963
7	6	C	-5.027264	3.349797	-2.212822
8	8	O	-3.298154	4.680718	-1.311949
9	6	C	-9.988587	3.032646	4.868475
10	6	C	-11.878422	6.900046	2.615859
11	6	C	-12.365323	2.041637	6.075461
12	6	C	-12.468025	0.279682	7.900012
13	6	C	-14.955634	-0.594992	8.969645
14	8	O	-13.942997	2.22347	0.386852
15	8	O	-6.195542	6.300057	2.09033
16	8	O	-12.076874	0.472981	-5.513696
17	6	C	-12.248834	-2.155471	-4.797258
18	6	C	-10.084219	-3.070774	-3.076852
19	6	C	-9.121595	-1.115476	-1.149
20	6	C	-14.652854	-2.684066	-3.263357
21	6	C	-14.102631	-5.238427	-2.025117
22	6	C	-11.2341	-5.224055	-1.421195
23	6	C	-4.408422	1.549162	-4.306371
24	6	C	-2.327612	-0.065098	-3.978287
25	6	C	-1.719051	-1.842897	-5.826617
26	6	C	-3.147246	-1.984098	-8.048028
27	6	C	-5.170109	-0.327357	-8.417104
28	6	C	-5.812556	1.428131	-6.551616
29	6	C	-12.216884	-3.553423	-7.318126
30	6	C	-10.425565	-4.507511	1.321054
31	8	O	-11.061947	4.459487	-4.954666
32	8	O	-10.107593	-1.817544	1.235448
33	6	C	-7.886359	-5.753672	1.959396
34	6	C	-12.360523	-5.030024	3.384081
35	1	H	-10.406496	-7.06838	-1.891523
36	1	H	-8.484827	-3.699769	-4.238404
37	6	C	-10.163224	-0.932309	9.050913
38	1	H	-8.666893	1.461798	4.539704
39	1	H	-9.008245	4.390545	6.11471
40	1	H	-10.838611	8.182979	3.877185

41	1	H	-12.129831	7.833319	0.775551
42	1	H	-13.756953	6.530173	3.41543
43	1	H	-14.154993	2.800166	5.374334
44	1	H	-15.036583	-0.297698	11.034436
45	1	H	-16.565133	0.396786	8.106799
46	1	H	-15.213306	-2.644213	8.660875
47	1	H	-4.642635	6.093108	0.97934
48	1	H	-7.045958	-1.249309	-1.100504
49	1	H	-16.3526	-2.683435	-4.460797
50	1	H	-14.881861	-1.192299	-1.836706
51	1	H	-15.286491	-5.584325	-0.358823
52	1	H	-14.504664	-6.784838	-3.357557
53	1	H	-1.21025	0.085328	-2.250375
54	1	H	-0.117014	-3.113964	-5.542672
55	1	H	-2.66475	-3.370124	-9.500429
56	1	H	-6.255749	-0.386526	-10.17219
57	1	H	-7.349934	2.756471	-6.87793
58	1	H	-10.436724	-3.166042	-8.318838
59	1	H	-12.37629	-5.605141	-7.032056
60	1	H	-13.799306	-2.918984	-8.505901
61	1	H	-6.473172	-5.417687	0.469199
62	1	H	-7.145454	-4.984544	3.743631
63	1	H	-8.107266	-7.811788	2.167464
64	1	H	-12.88848	-7.041143	3.417131
65	1	H	-11.562675	-4.527448	5.233176
66	1	H	-14.060771	-3.875557	3.103759
67	1	H	-9.844169	-0.217027	10.986576
68	1	H	-10.415394	-2.994862	9.227682
69	1	H	-8.431579	-0.585738	7.959816

Anti-Inflammatory Effect Assay

Cell Culture. RAW264.7 macrophages were obtained from American Type Cell Collection (ATCC, America), cultured in DMEM with 10% heat-inactivated FBS and maintained in a humidifed incubator with 5% CO_2 at 37 °C. THP-1 cells were obtained from ATCC and maintained in RPMI-1640 medium with 10% heat-inactivated FBS. In order to differentiate into macrophages, THP-1 cells were stimulated by phorbol 12-myristate 13-acetate (PMA, 100 ng/mL, Sigma Aldrich) for 10 h.

Cell Viability Assay. The compounds were dissolved in dimethyl sulfoxide (DMSO) at a concentration of 40 mM as the stock solution and stored at –20 °C. Cell Counting Kit-8 (CCK-8, Beyotime), LPS, dexamethasone (Dex), nigericin, the Griess reagent and DMSO were purchased from Sigma-Aldrich (America). Briefly, RAW264.7 cells (10000 cells/well) were seeded into a 96-well plate and incubated overnight at 37 °C. The tested compounds were added to the cells. Dimethyl sulfoxide (DMSO) was used as the vehicle control. Following incubation for 24h, 10 µL of the Cell Counting Kit-8 agent was added to cells and then incubated for 1.5 h at 37 °C. Finally, the absorbance at 450 nm was recorded using a microplate reader (Thermo Fisher, Waltham, MA, USA).

ELISA: Detection of NO and IL-1*β* cytokines by means of ELISA. RAW264.7 cells were seeded into 96-well plates (4×10^4 cells per well) and incubated to adhere for 24 h. The cells were then treated with different concentrations of compounds or vehicles (DMSO), followed by stimulation with 1 µg/mL LPS. Dex was used as the positive control. After 18 h, the supernatant was collected to detect the NO content using the Griess reagent. THP-1 cells culture medium was collected and centrifuged at 15,000 × g for 10 min at 4 °C. Supernatant (700 uL) were transferred to a new 2 ml tube, and mixed thoroughly with 700 ul methanol and 175 uL chloroform, after sit at room temperature for 10 min, the mixture was centrifuged at the same condition, and the white intermediate layer was collected. After washed with methanol, the protein sample in culture medium was dissolved in 2% SDS sample buffer for Western blotting analysis. The rest of supernatant was collected in another new tube and stored in -20 °C for ELISA kit detection. The level of IL-1*β* in cell culture medium was determined by ELISA kit (Neobioscience, China), according to the manufacturer's instruction.

Western Blotting. Western blotting was performed as described previously. For samples' preparation, THP-1 cells were fully lysed with RIPA buffer. Then, the protein concentration was determined using a BCA Protein Assay Kit and all samples were diluted into the same concentration. Equal number of proteins (20−30 µg) were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), transferred to polyvinylidene fluoride (PVDF) membranes, and then blocked with 5% nonfat milk in TBST buffer (100 mM NaCl, 10 mM Tris-HCl, pH 7.5 and 0.1% Tween-20) for 2 h at room temperature and incubated with relevant primary antibodies overnight at 4 °C. After washing with TBST three times, a horseradish peroxidase-conjugated secondary antibody was added and incubated for 2 h at room temperature. Signals were developed using a SuperSignal West Femto Maximum Sensitivity Substrate kit (Thermo, America). Finally, specific protein bands were visualized using the ChemiDoc MP Imaging System (Bio-Rad, Hercules, America) and quantitated using Image Lab 5.1.

Figure S1. The raw images for all Western blot.

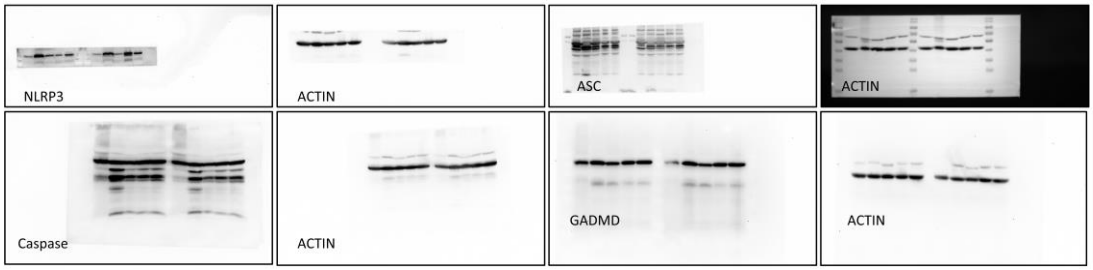

Figure S2. ^{1}H NMR spectrum of compound **1** (recorded in methanol-d_4)

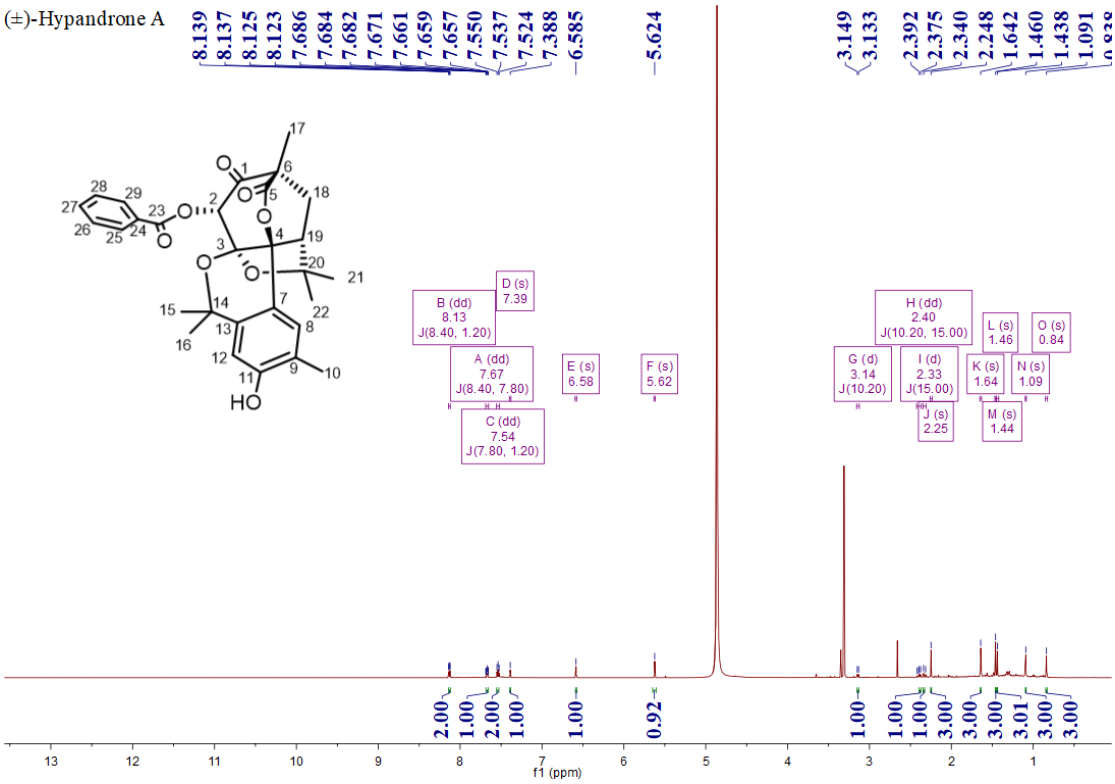

Figure S3. ^{13}C NMR spectrum of compound **1** (recorded in methanol-d_4)

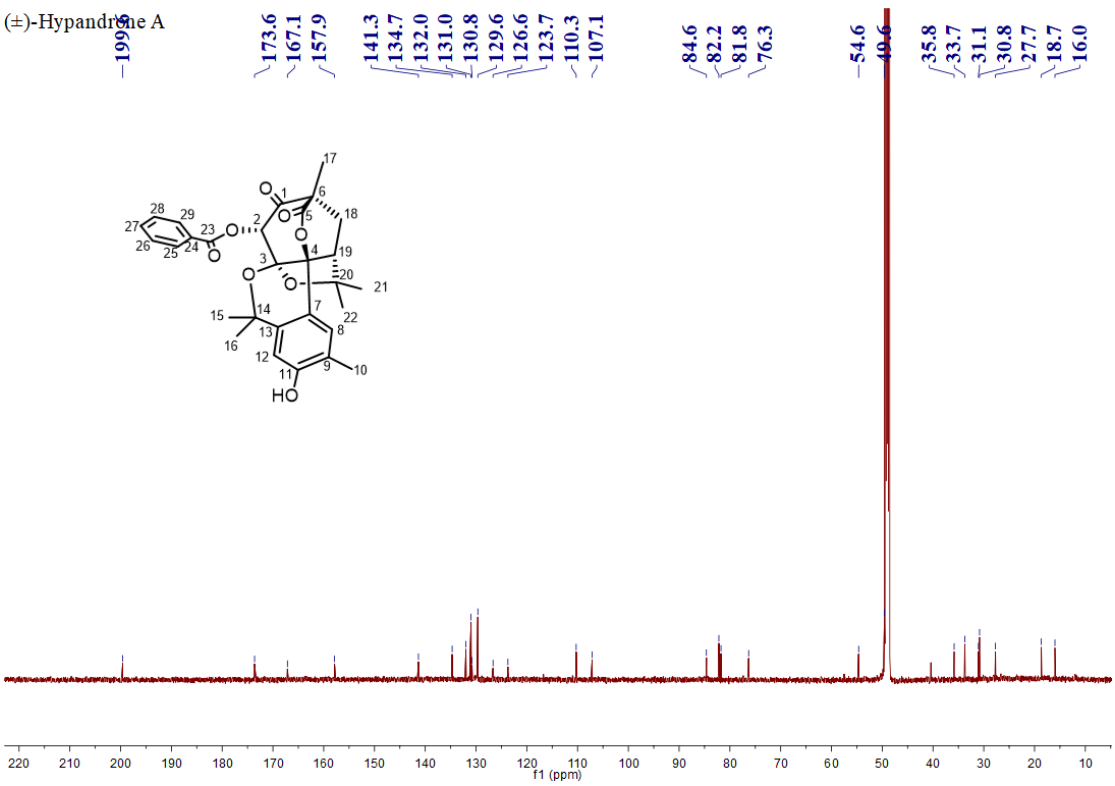

Figure S4. DEPT spectrum of compound **1** (recorded in methanol-d_4)

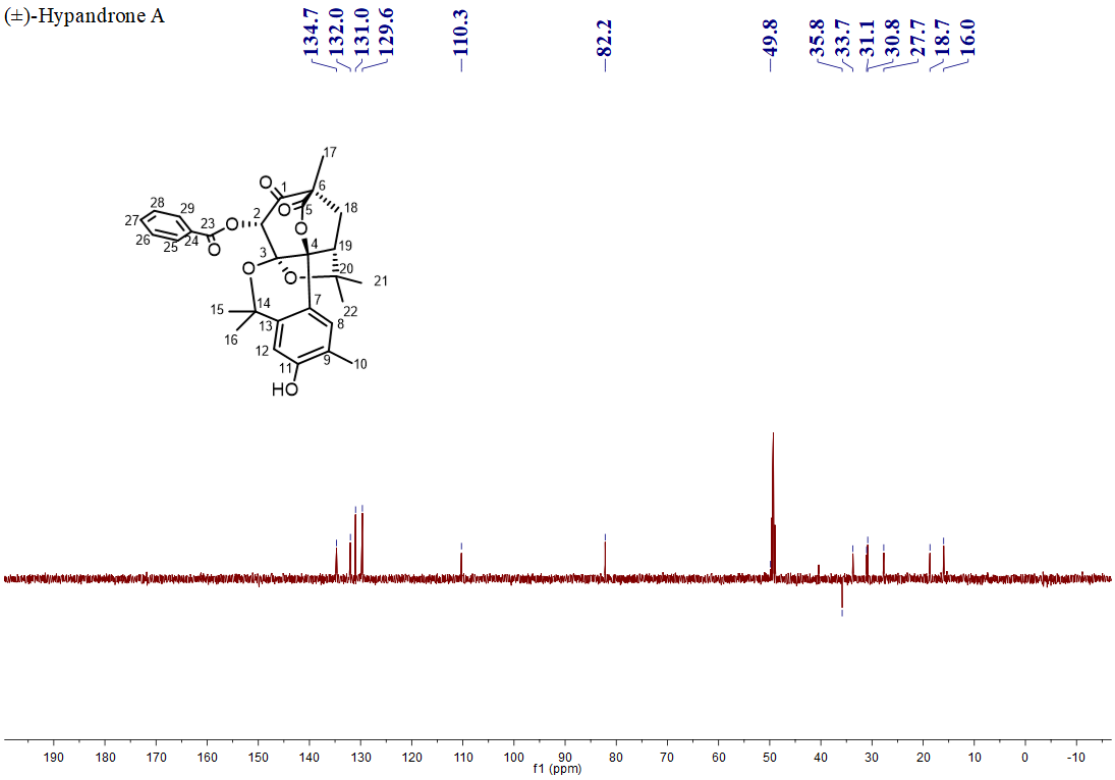

Figure S5. HSQC spectrum of compound **1** (recorded in methanol-d_4)

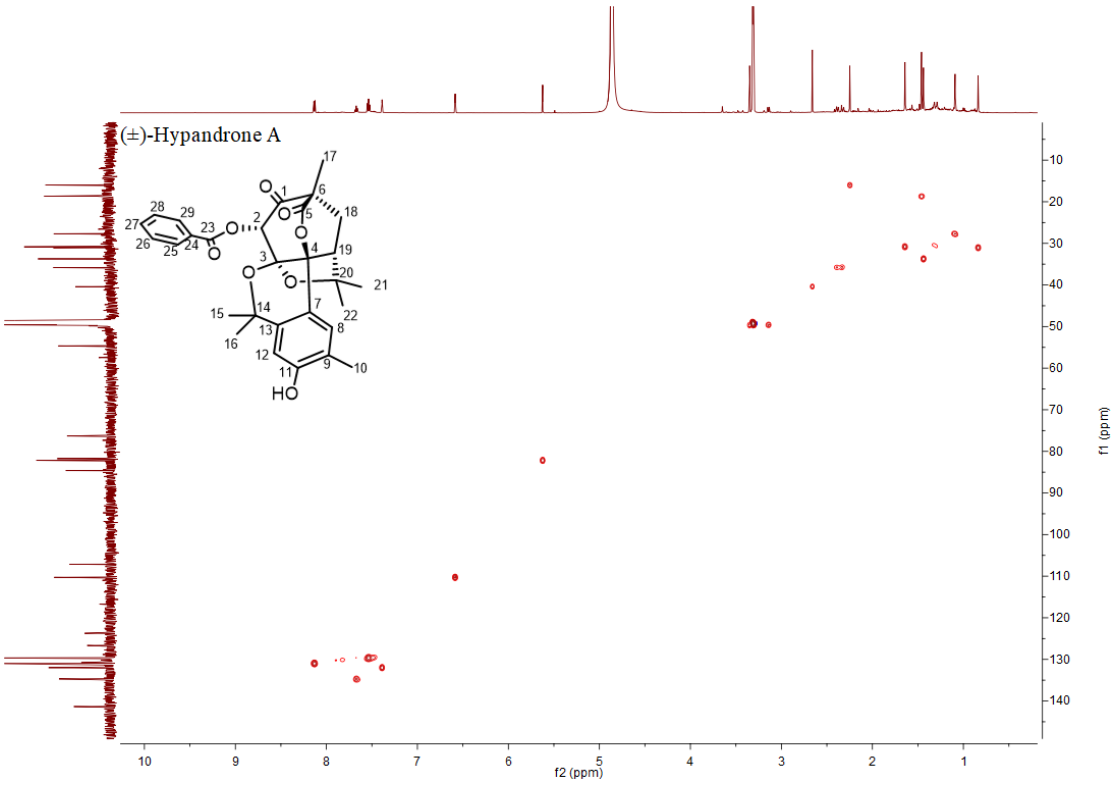

Figure S6. HMBC spectrum of compound **1** (recorded in methanol-d_4)

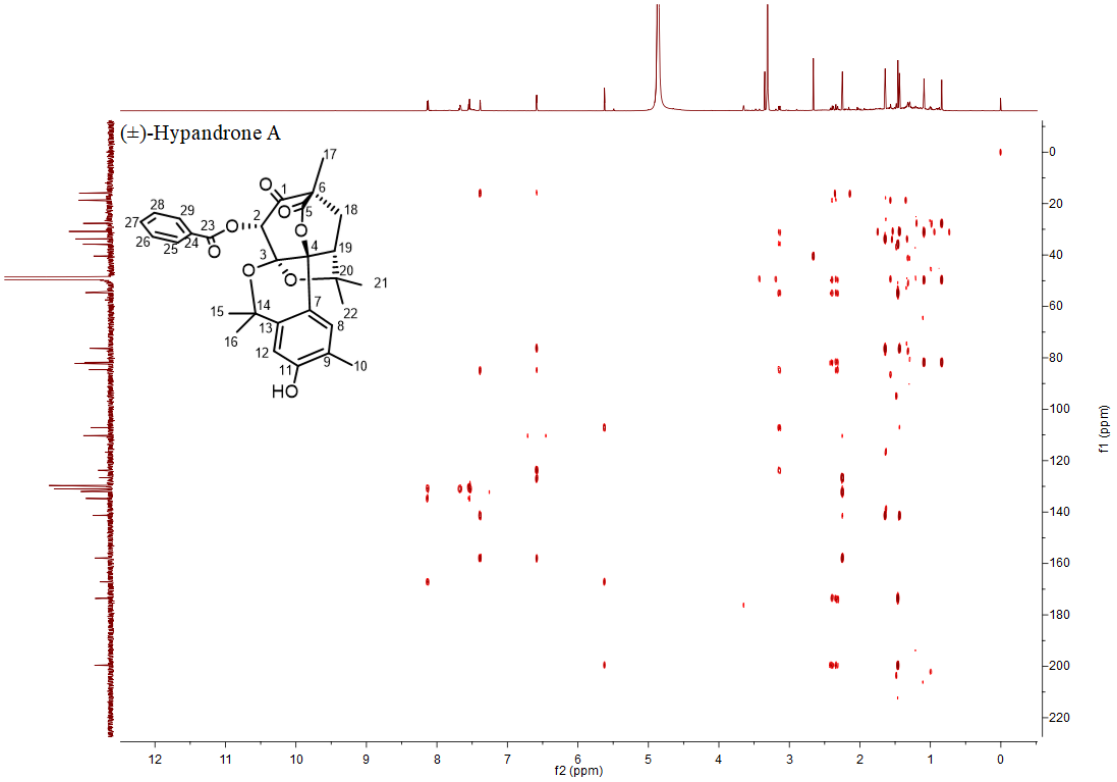

Figure S7. $^{1}H–^{1}H$ COSY spectrum of compound 1 (recorded in methanol-d_4)

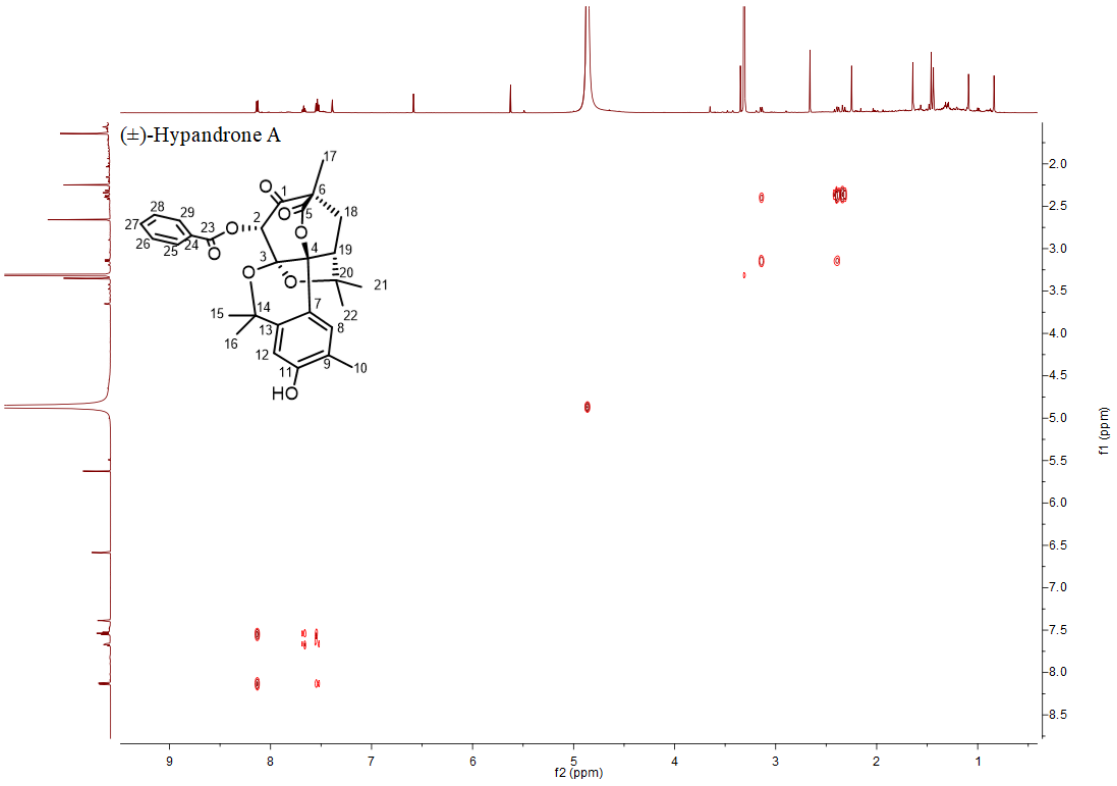

Figure S8. NOESY spectrum of compound 1 (recorded in methanol-d_4)

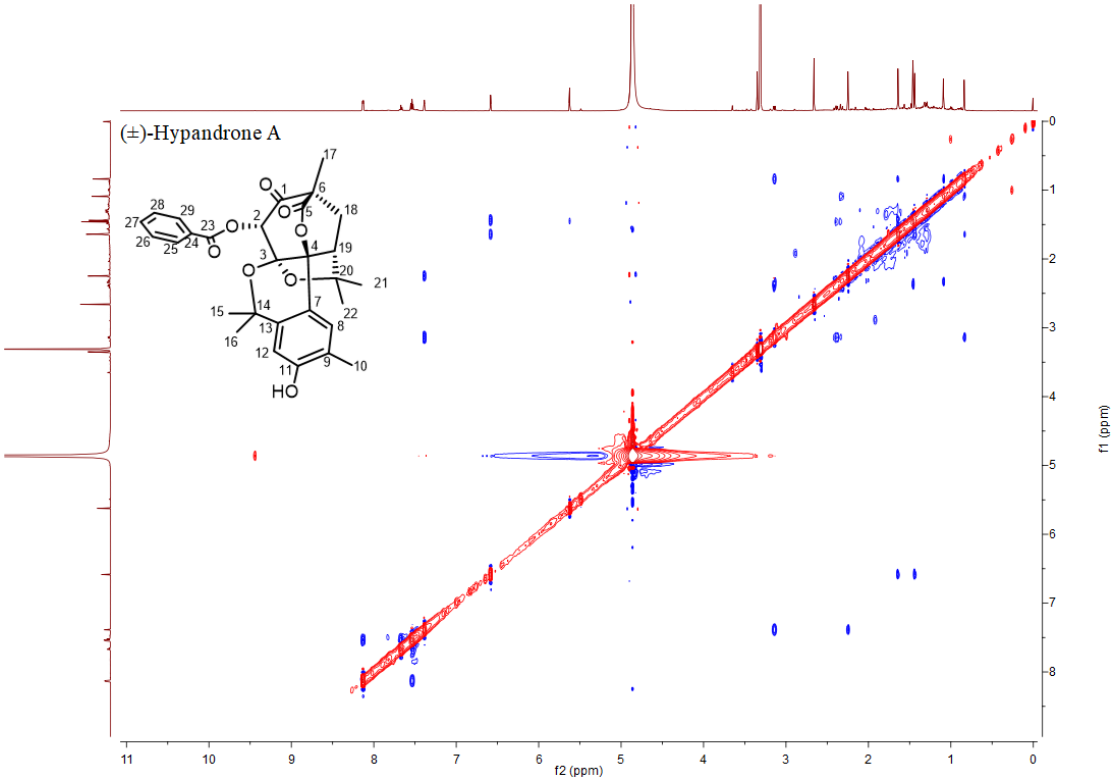

Figure S9. HRESIMS spectrum of compound (±)-**1**

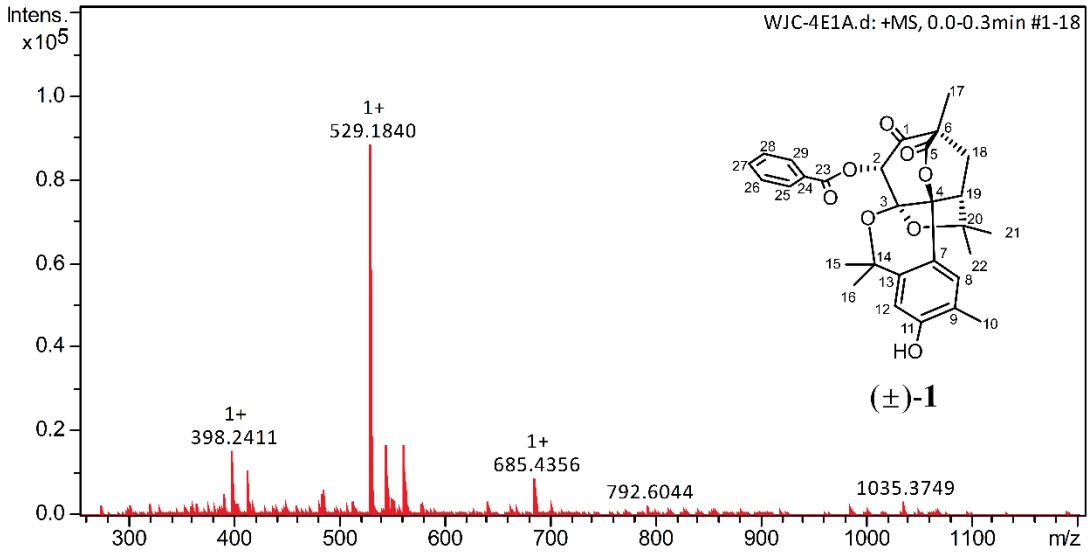

Figure S10. IR spectrum of compound (±)-**1**

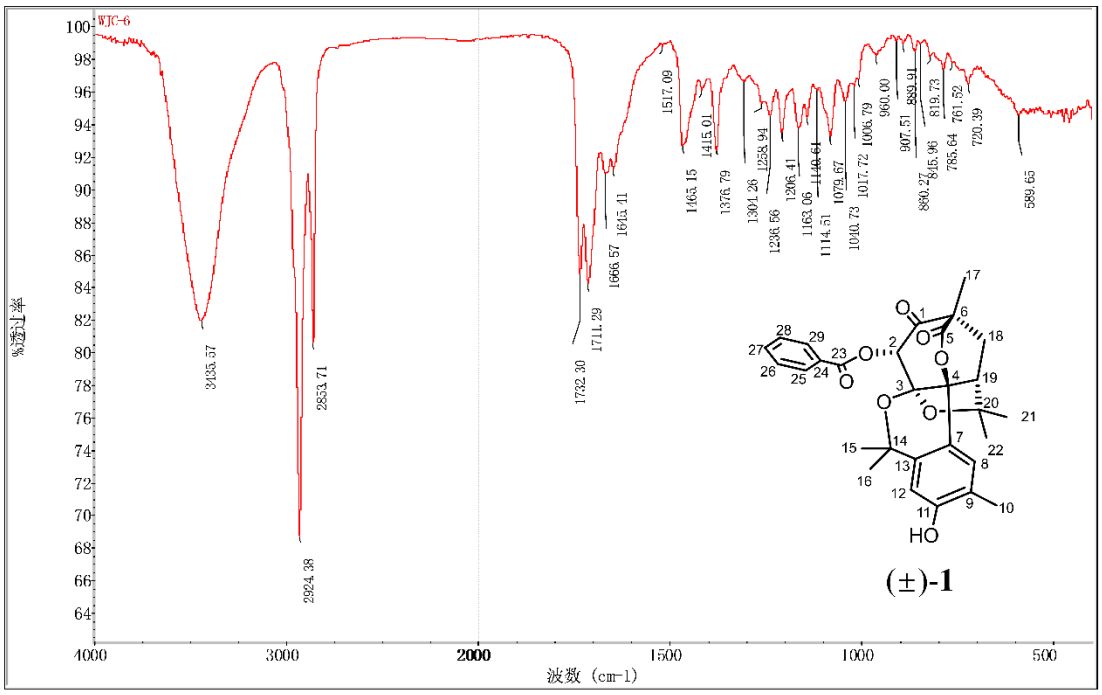

Figure S11. UV spectrum of compound (±)-**1**

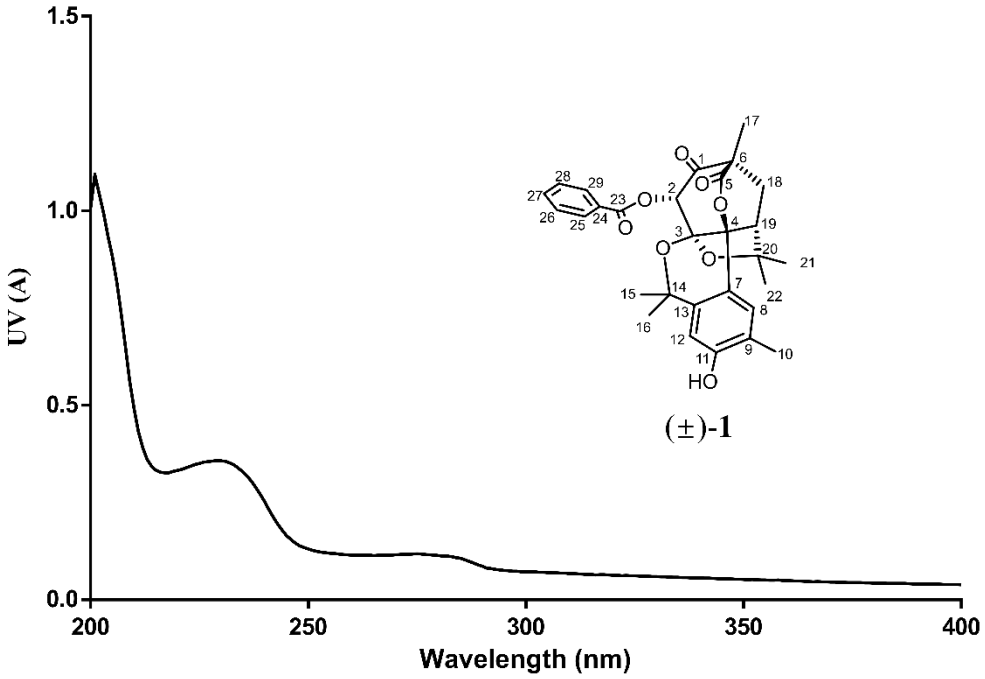

Figure S12. Chiral HPLC separation chromatogram of (±)-**1**

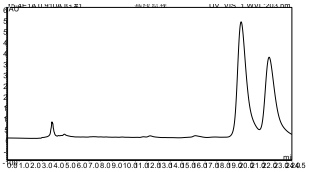

Figure S13. CD spectrum of (±)-**1** in MeOH

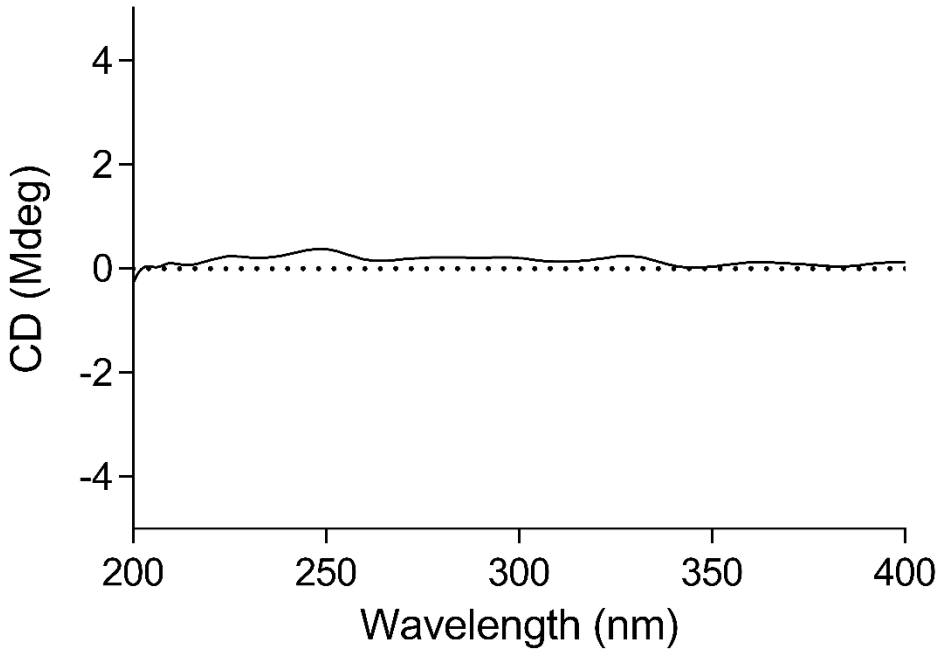

Figure S14. CD spectrum of (+)-**1** in MeOH

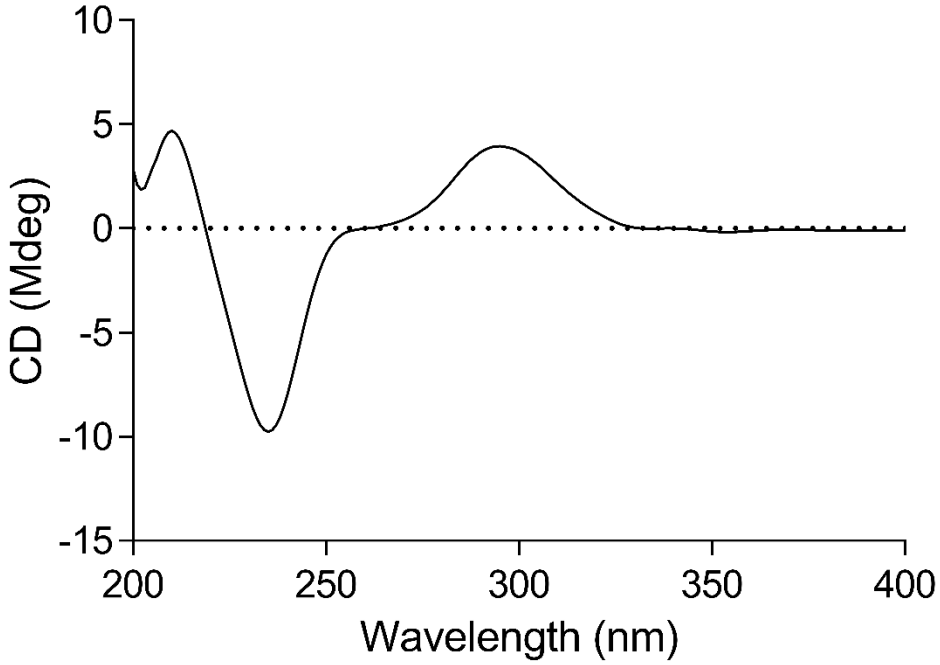

Figure S15. CD spectrum of (–)-**1** in MeOH