Supporting information

Rapid screening of unprecedented sesquiterpenes with distinctive ring skeletons from *Daphne aurantiaca* employing an integrated strategy

Shu-Hui Dong[a], Jin-Ling Han[a], Xin-Yu Chang[b], Mei-Ya Lian[a], Xin Zhang[a], Xiao-Ling Liu[b], Ming Bai[a], Xiao-Xiao Huang[a,] *, Shao-Jiang Song[a,] *

a Engineering Research Center of Natural Medicine Active Molecule Research & Development, Liaoning Province; Key Laboratory of Computational Chemistry-Based Natural Antitumor Drug Research & Development, Liaoning Province; Key Laboratory of Natural Bioactive Compounds Discovery & Modification, Shenyang; School of Traditional Chinese Materia Medica, Shenyang Pharmaceutical University, Shenyang, Liaoning 110016, China

b Shenyang Pharmaceutical University Wuya College of Innovation, Shenyang, Liaoning 110016, China

*Corresponding author.

E-mail addresses: songsj99@163.com (Shao-Jiang Song).
xiaoxiao270@163.com (Xiao-Xiao Huang).

List of Supporting Information

Experimental Section

General Experimental Procedures

Optical rotations were tested by an Anton Paar MCP 200 digital polarimeter (Anton Paar GmbH, Graz, Austria). The UV spectra were recorded on a Shimadzu UV-2600i spectrophotometer (Shimadzu, Kyoto, Japan). NMR spectra were performed on Bruker AVANCE III HD 600 MHz spectrometer using tetramethylchlorosilane (TMS) as the internal standard. HRESIMS experiments of **1**, **4** and **5** were performed using the Thermo Q EXACTIVE mass spectrometer. HRESIMS data of **2** and **6** were carried out by a Bruker COMPACT spectrometer. HRESIMS data of **3** was taken with a Waters G2-S Qtof spectrometer. ECD spectra were measured on a Bio-Logic Science MOS-450 spectrometer (Bio-Logic Science Instruments, Seyssinet-Pariset, France). Column chromatography (CC) was carried out on silica gel (100-200 and 200-300 mesh, Qingdao, China), dianion HP-20 macroporous resin (Mitsubishi Chemical Corporation, Tokyo, Japan), and ODS gel (60–80 μm, Merck, Germany).

Extraction and Isolation

The whole plants of *D. aurantiaca* (40.0kg) were extracted with 80% aqueous ethanol (3×60L) and the residual alcohol extract was suspended in water and partitioned with petroleum ether (PE), ethyl acetate (EtOAc), and 1-butanol (*n*-BuOH), successively. The EtOAc extract (1800g) was chromatographed on silica gel with CH_2Cl_2-MeOH (1:0 to 0:1) to acquire ten fractions (Fr. A~ Fr. J). Fr. C (130 g) was separated by HP-20 and ODS column with MeOH/H_2O (20:80 to 100:0, *v*/*v*) to afford twelve fractions (Fr. C1~Fr. C12). Fr.C5 (11.7 g) was separated on a silica gel column eluted with PE-EA and a semi-preparative HPLC to get compounds **1** (1.1 mg), **2** (1.4 mg), **4** (1.5 mg), **5** (1.5 mg), **6** (1.2 mg). Fr.C6 (6.4 g) was purified by a silica gel column and RP-HPLC to obtain compounds **3** (0.5 mg).

CASE Analysis

The commercially available ACD/Labs 2020 1.1(File Version S15S41, Build 117163, 16 Jul 2020) was used for the CASE analysis. All calculations were performed on a standard 2.90 GHz PC with 16 GB of RAM.

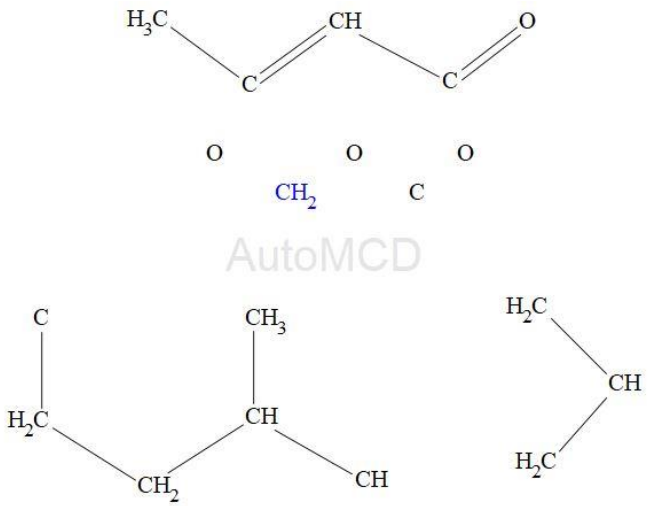


Fig. S1. The molecular connectivity diagram (MCD) for **5**

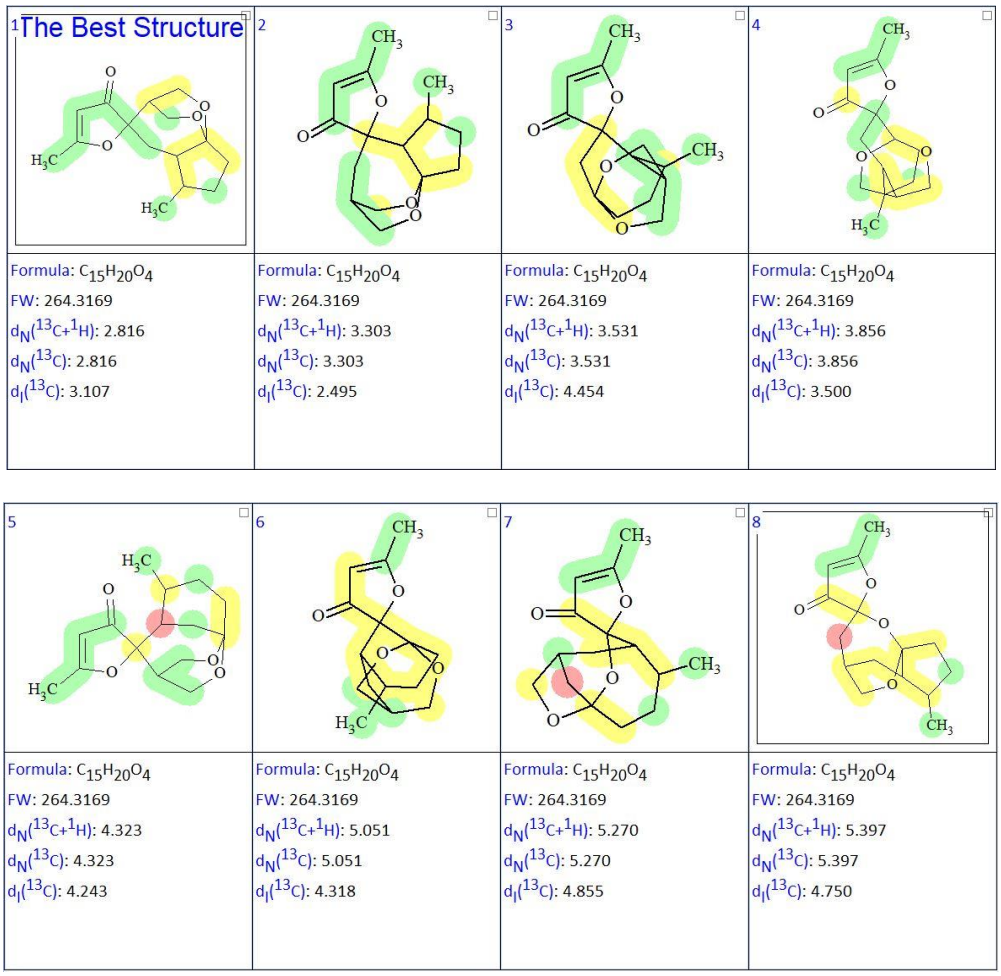


Fig. S2. Possible structures were generated by CASE (computer-assisted structure elucidation) expert systems for **5**

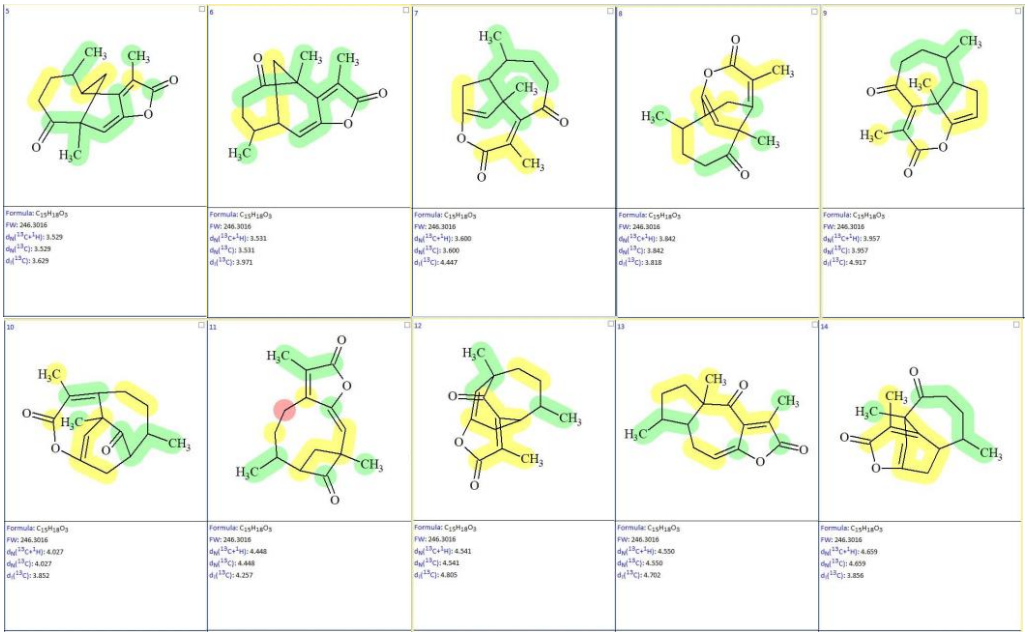


Fig. S3. Fifth to fourteenth possible structures were generated by CASE (computer-assisted structure elucidation) expert systems for **1**

Table 1. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) data for **1**–**3** (Recorded in DMSO-d_6)

No.	**1**		**2**		**3**	
	δ_H, mult (*J* in Hz)	δ_C	δ_H, mult (*J* in Hz)	δ_C	δ_H, mult (*J* in Hz)	δ_C
1		210.8	3.54, m	76.1		84.5
2	α 1.79, m	38.4	1.41, m	38.0	1.84, m	36.7
	β 1.74, m				1.79, overlap	
3	1.44, m	26.4	1.21, m	26.5	1.79, overlap	29.1
	1.20, m		0.82, m		1.14, m	
4	2.07, m	34.9	1.71, m	33.8	2.61, m	35.1
5	2.81, m	51.4	2.11, m	41.8	1.79, overlap	54.4
6	3.06, dd (18.5, 3.3)	23.2	2.76, m	20.4	1.61, m	17.9
	2.42, m		2.65, dd (18.5, 2.9)		1.30, m	
7		148.2		152.4	2.50, overlap	42.5
					2.37, m	
8		149.1		148.8		202.5
9	5.62, s	115.3	5.31, s	118.8	5.61, s	124.9
10		48.4		40.3		156.9
11		125.9		123.9		
12		169.0		169.7		
13	1.87, d (2.0)	8.8	1.82, d (2.0)	8.2		
14	1.23, s	23.7	1.21, s	28.6	1.92, s	22.6
15	0.93, d (6.9)	18.0	0.91, d (6.9)	19.4	0.95, d (7.0)	15.8
OH-1			5.01, d (4.7)			

Table 2. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) data for **4**–**6** (Recorded in DMSO-d_6)

No.	**4**		**5**		**6**	
	δ_H, mult (J in Hz)	δ_C	δ_H, mult (J in Hz)	δ_C	δ_H, mult (J in Hz)	δ_C
1		97.3		108.5		73.9
2	2.13, m	34.3	1.86, m	39.7	2.13, ddd (15.1, 10.3, 2.1)	29.4
	1.77, m		1.63, m		1.45, m	
3	2.00, overlap	31.7	1.68, m	32.0	1.81, m	30.2
	1.49, m		1.15, m		1.25, m	
4	2.40, m	34.6	1.50, m	40.3	2.27, m	37.3
5	2.60, m	43.8	1.75, overlap	53.0	1.73, dd (12.5, 6.7)	48.7
6	2.26, dd (16.2, 7.9)	28.7	1.75, overlap	32.3	α 1.98, m	21.7
	2.00, overlap		1.60, m		β 1.16, m	
7		172.2		90.6	2.66, m	50.8
8		171.4		204.8	4.05, m	79.9
9	5.88, q (1.5)	116.2	5.52, brs	102.1	α 1.87, t (12.4)	41.1
					β 2.46, dd (12.4, 1.4)	
10		170.8		188.5		59.5
11			1.97, m	35.5		140.4
12			4.30, dd (10.3, 2.8)	58.7		169.6
			3.74, dd (10.3, 3.0)			
13			4.17, dd (11.2, 2.8)	62.0	5.97, d (3.3)	118.1
			3.94, dd (11.2, 7.3)		5.63, d (3.3)	
14	2.00, d (1.5)	12.6	2.25, brs	16.6	1.29, s	21.4
15	0.91, d (7.2)	16.4	0.92, d (6.5)	18.0	1.04, d (6.8)	15.4
7-OCH_3	3.53, s	51.4				

Table 3. Calculated $^4J_{C\text{-}H}$

	$^4J_{C\text{-}H}$
δ_H 3.74/δ_C 53.0	0.164393D+01
δ_H 3.94/δ_C 53.0	0.196008D+00
δ_H 4.17/δ_C 53.0	-0.355825D+00
δ_H 4.30/δ_C 53.0	-0.164829D-01

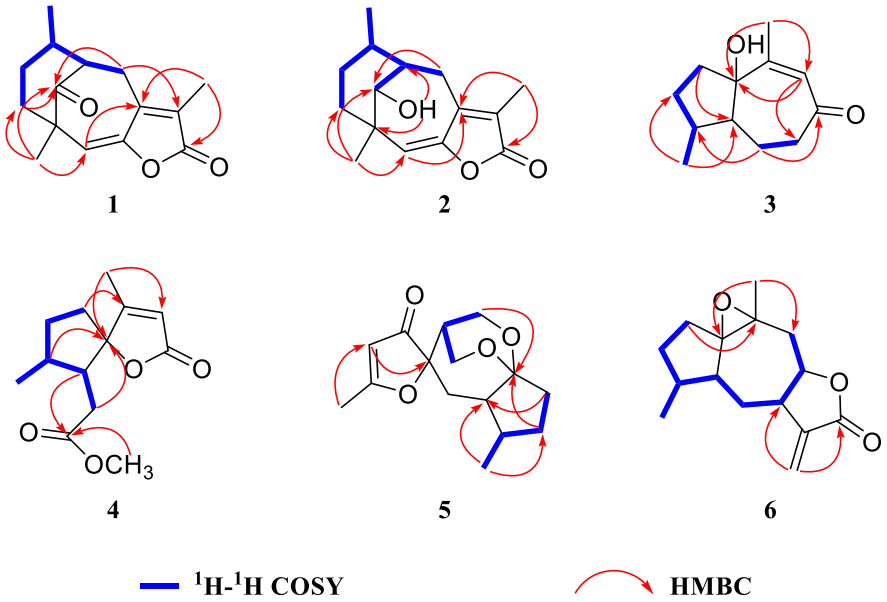


Fig. S4. Key ^{1}H-^{1}H COSY (blue line) and HMBC (red arrow) correlations for compounds **1**–**6**

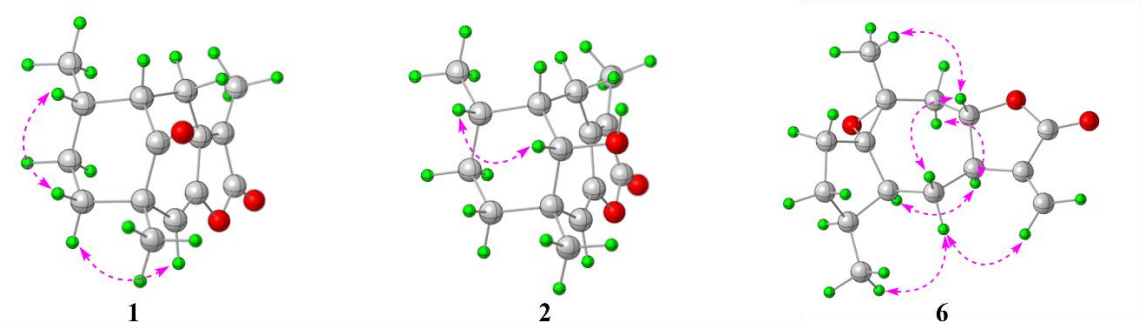


Fig. S5. Key NOE correlations for compounds **1, 2** and **6**

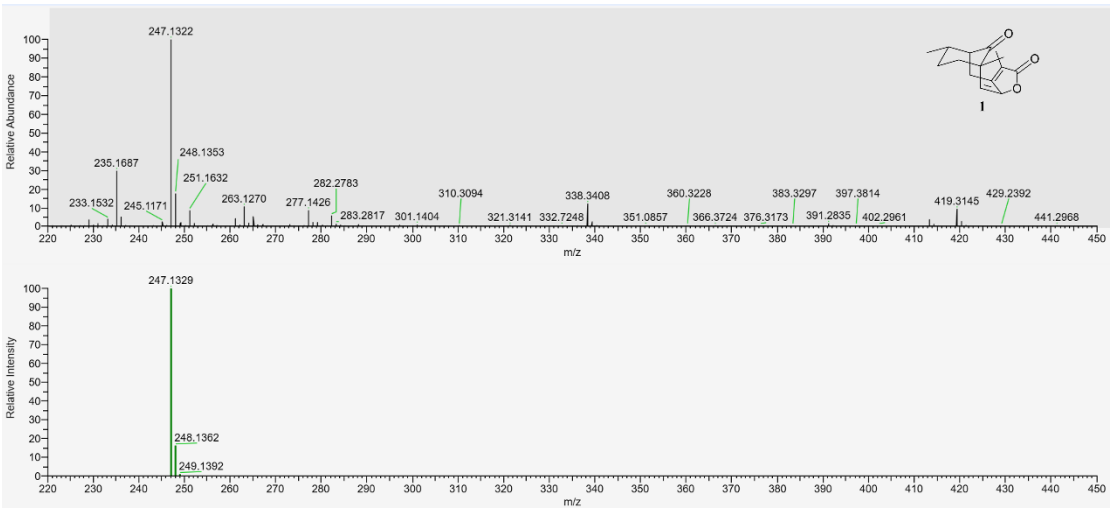


Fig. S6. The HR-ESIMS spectrum of the new compound **1**

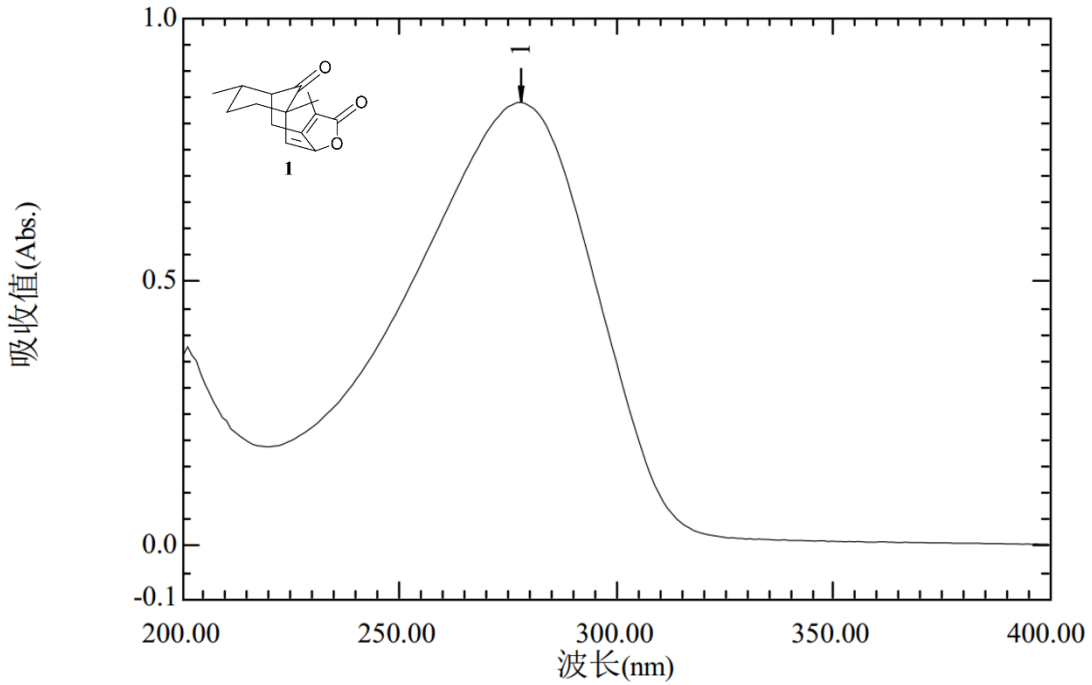


Fig. S7. The UV spectrum of the new compound **1**

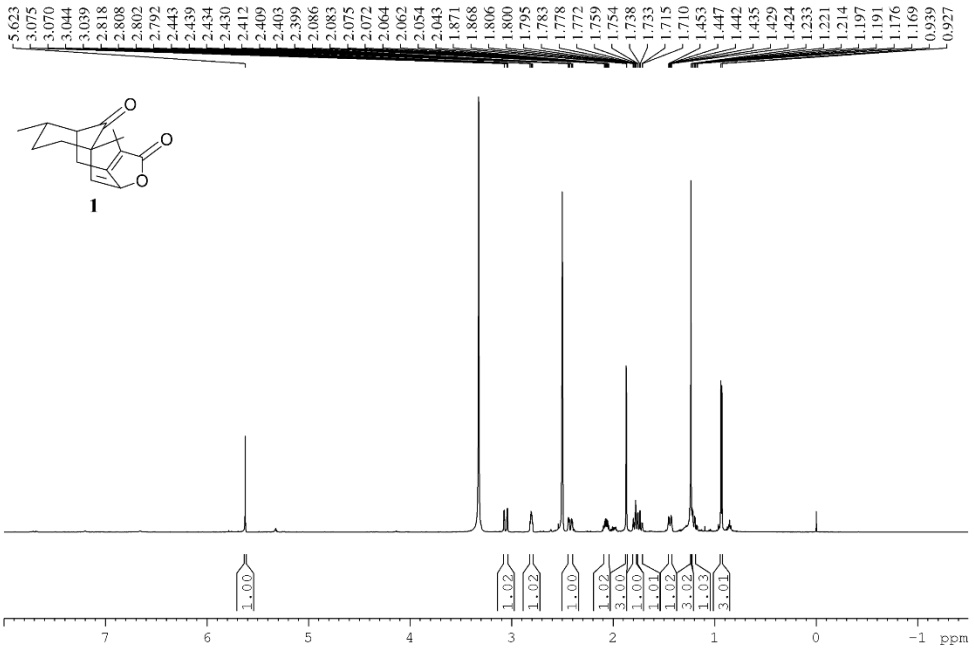


Fig. S8. ^{1}H NMR (600 MHz, DMSO-d_6) spectrum of the new compound **1**

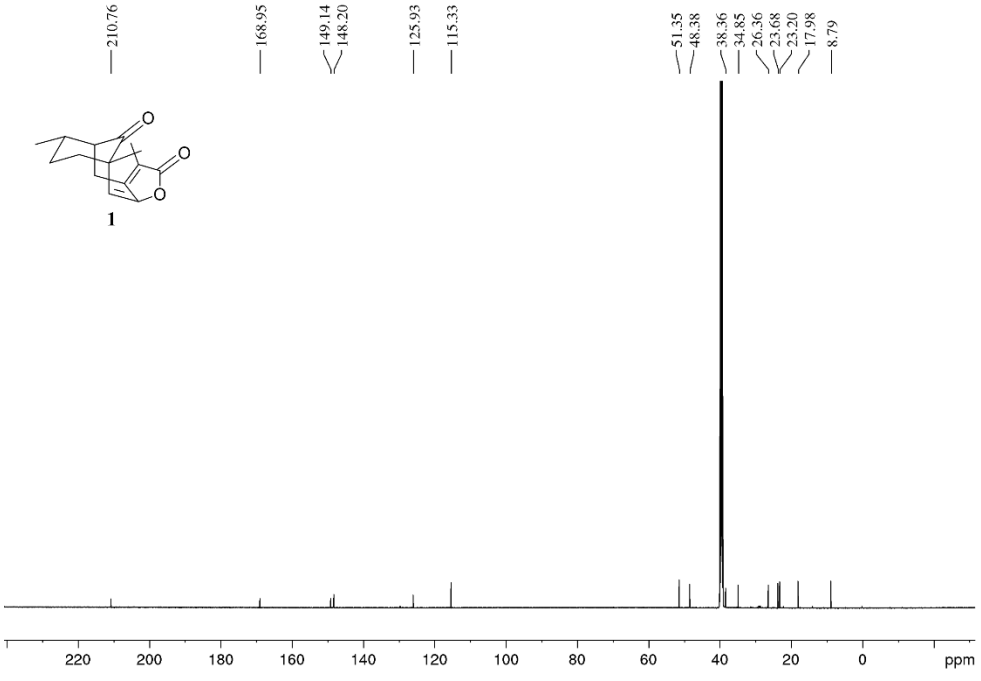


Fig. S9. ^{13}C NMR (150 MHz, DMSO-d_6) spectrum of the new compound **1**

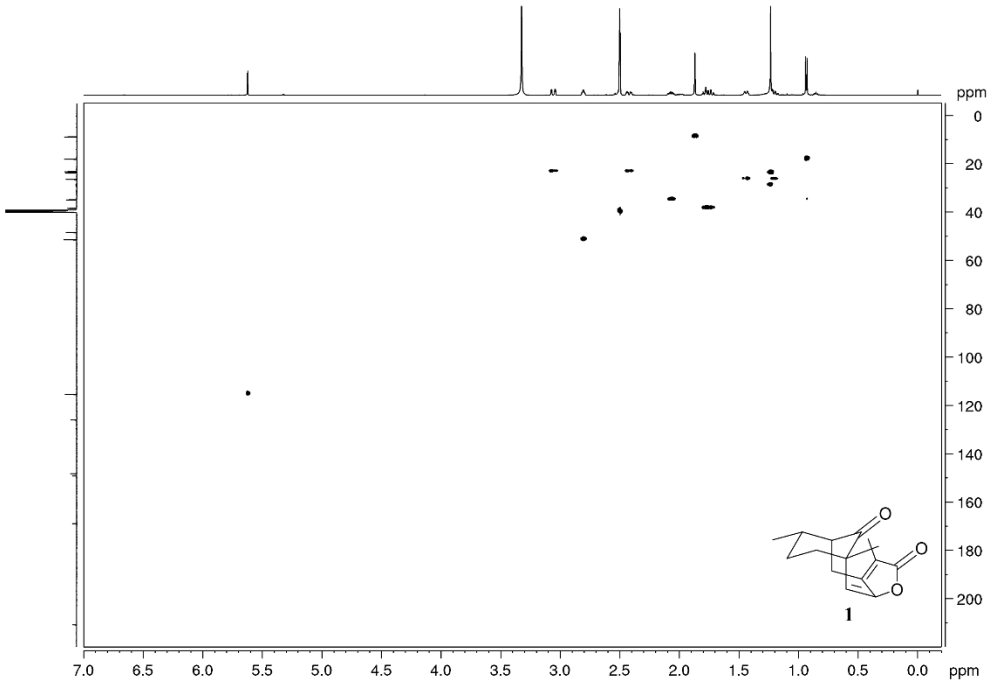


Fig. S10. HSQC (600 MHz, DMSO-d_6) spectrum of the new compound **1**

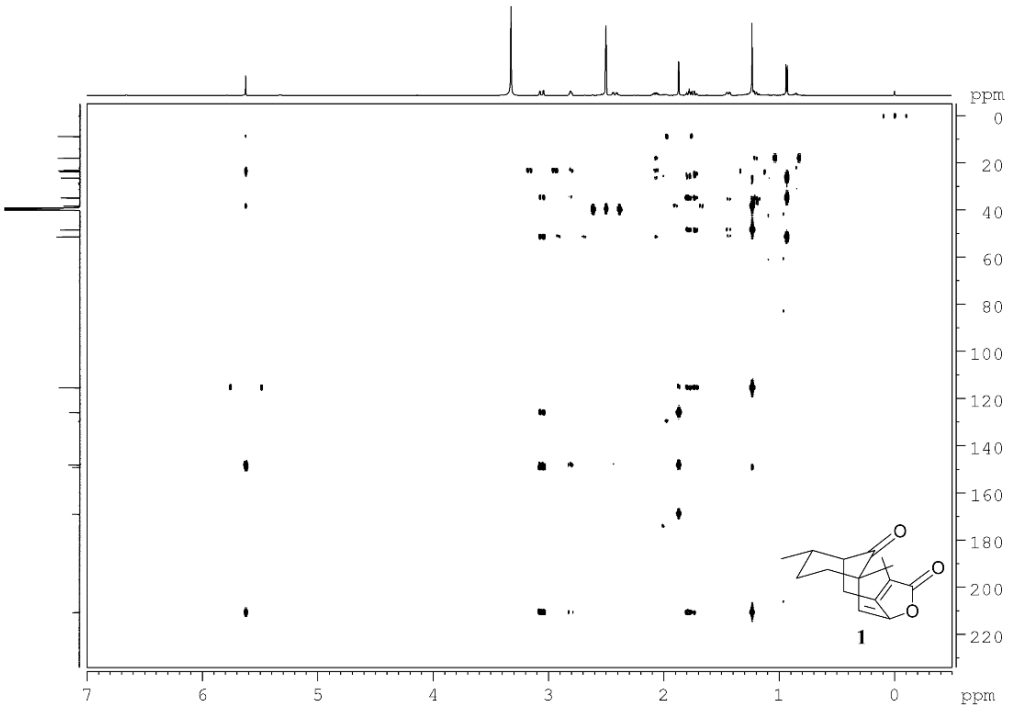


Fig. S11. HMBC (600 MHz, DMSO-d_6) spectrum of the new compound **1**

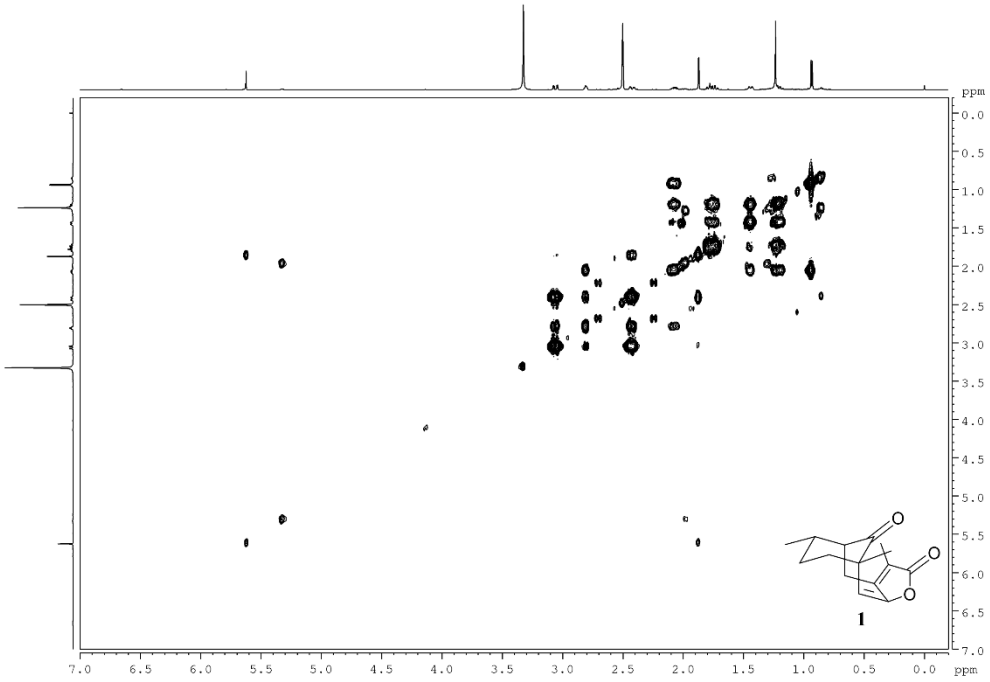


Fig. S12. ^{1}H-^{1}H COSY (600 MHz, DMSO-d_6) spectrum of the new compound **1**

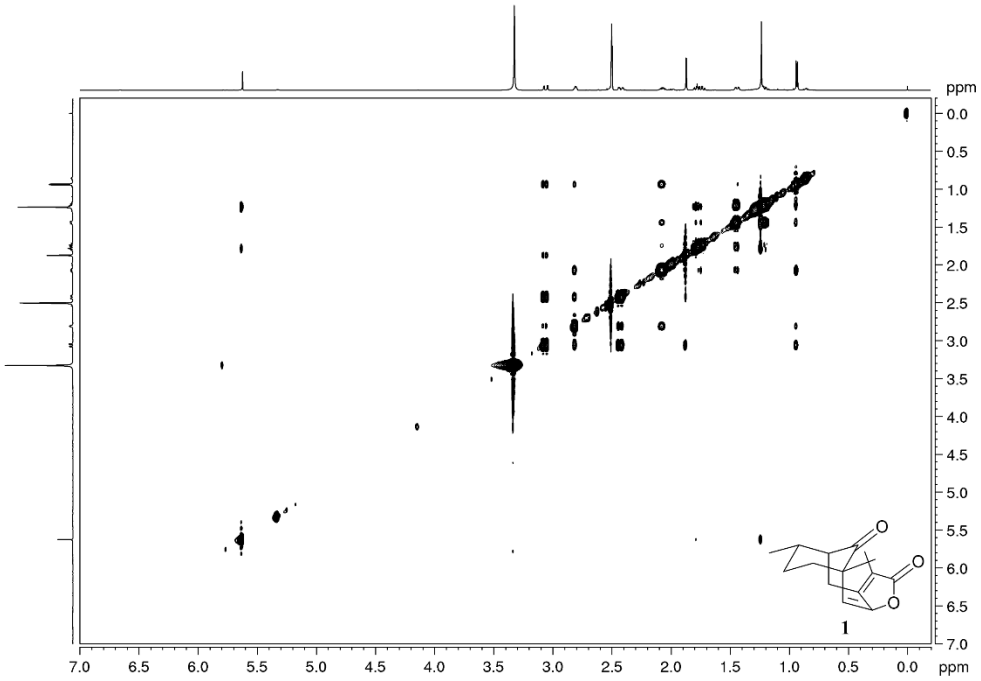


Fig. S13. NOESY (600 MHz, DMSO-d_6) spectrum of the new compound **1**

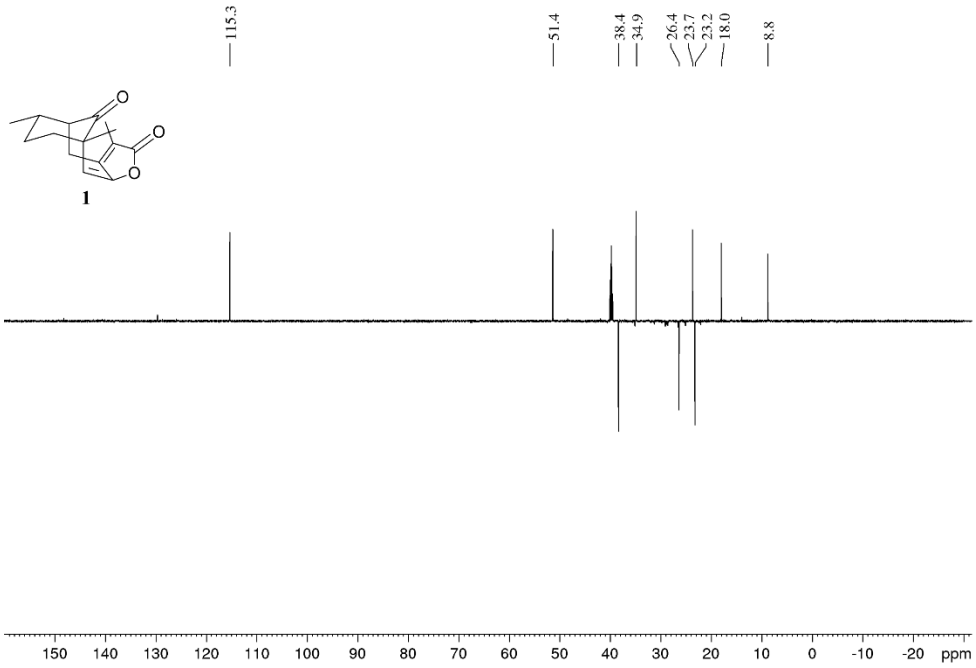
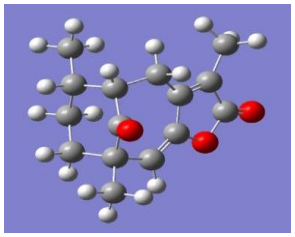


Fig. S14. DEPT (600 MHz, DMSO-d_6) spectrum of the new compound **1**



1-1 (100%)

Energy：-808.3625568 hartree

Fig. S15. Most stable conformers of the new compound **1** in solvated model calculations at the B3LYP/6-311++G (2d, p) level in ECD calculation

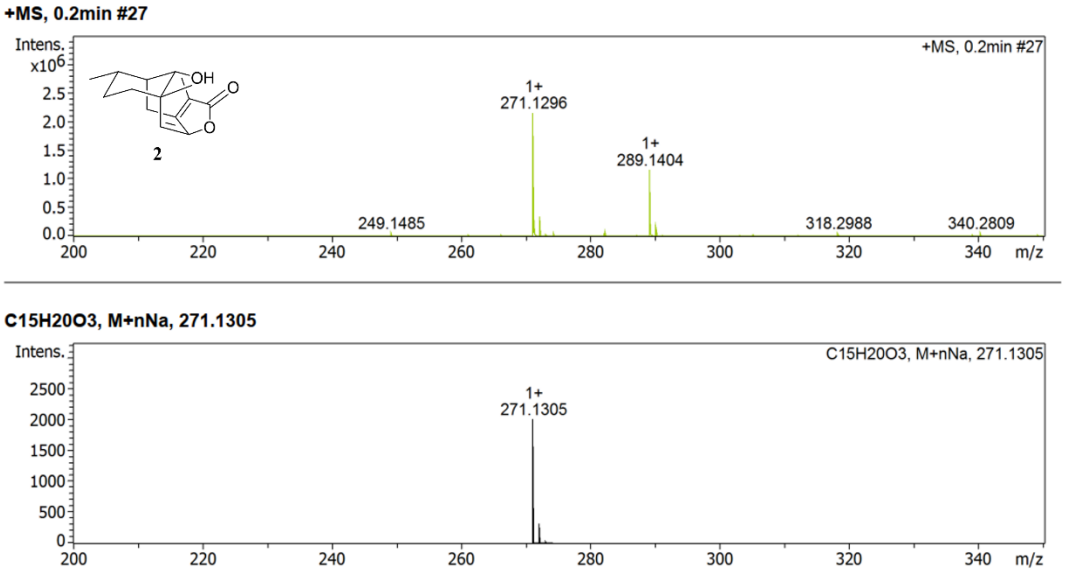


Fig. S16. The HR-ESIMS spectrum of the new compound **2**

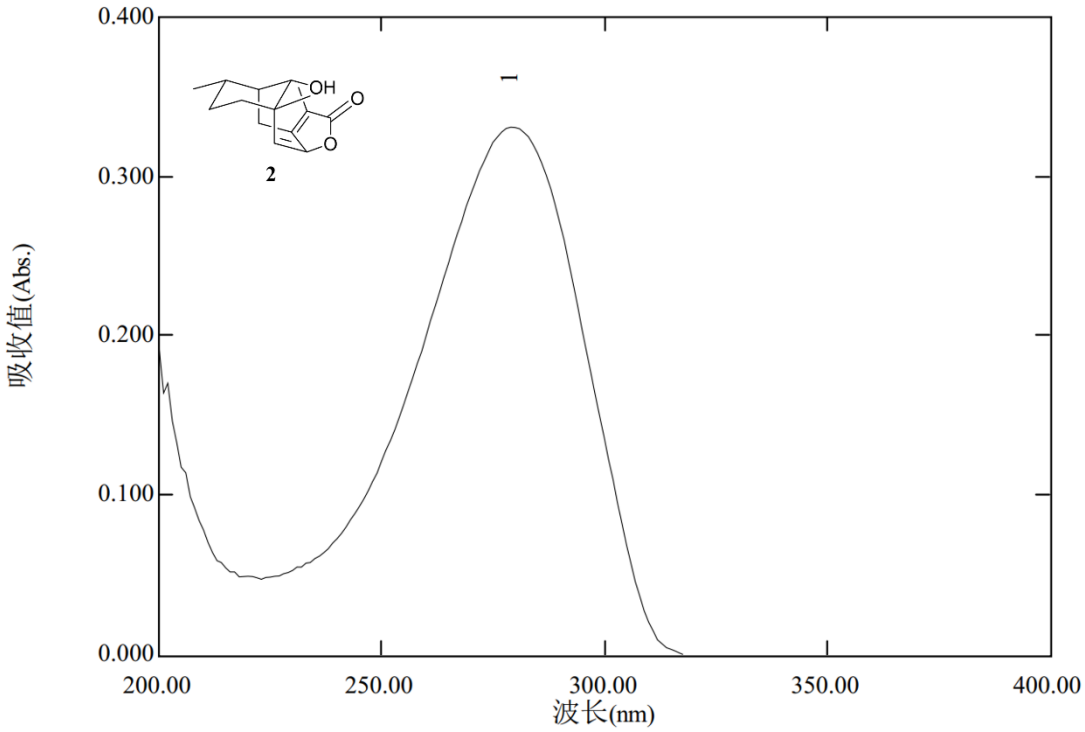


Fig. S17. The UV spectrum of the new compound **2**

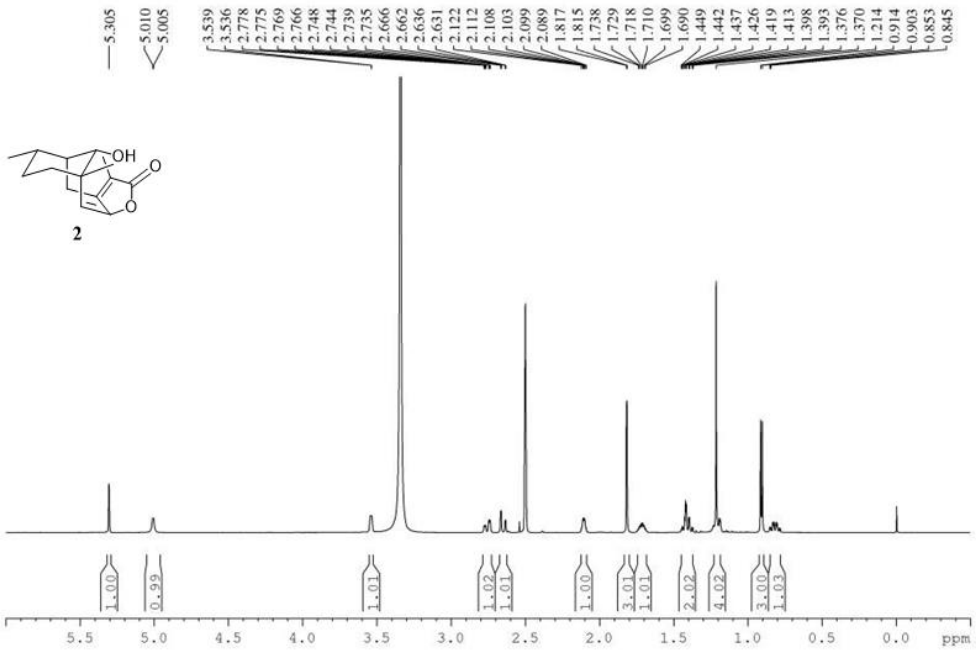


Fig. S18. ^{1}H NMR (600 MHz, DMSO-d_6) spectrum of the new compound **2**

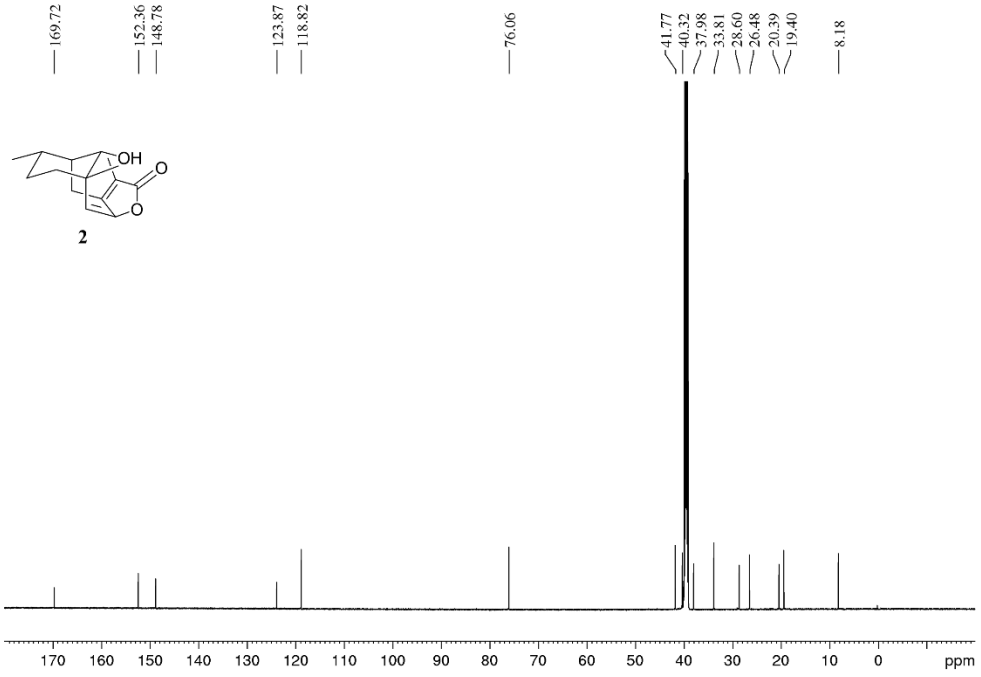


Fig. S19. ^{13}C NMR (150 MHz, DMSO-d_6) spectrum of the new compound **2**

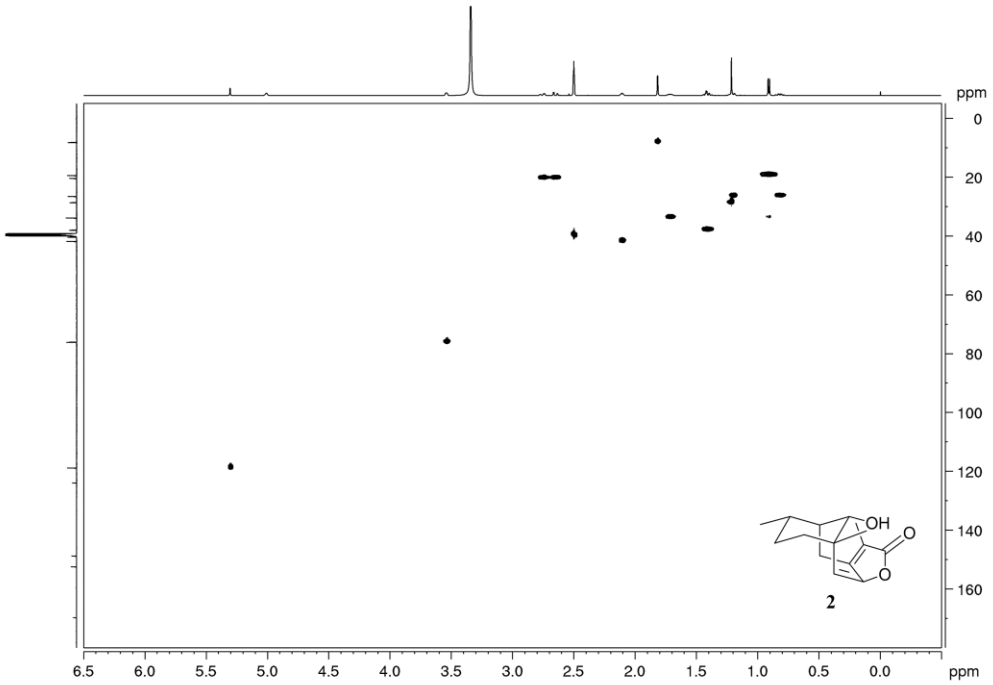


Fig. S20. HSQC (600 MHz, DMSO-d_6) spectrum of the new compound **2**

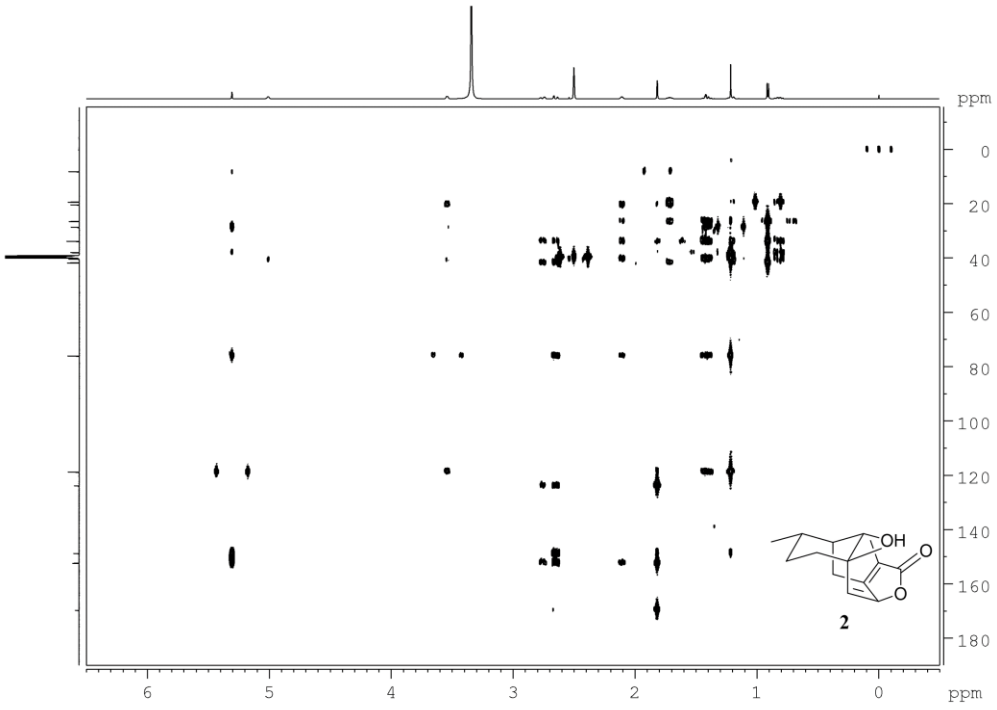


Fig. S21. HMBC (600 MHz, DMSO-d_6) spectrum of the new compound **2**

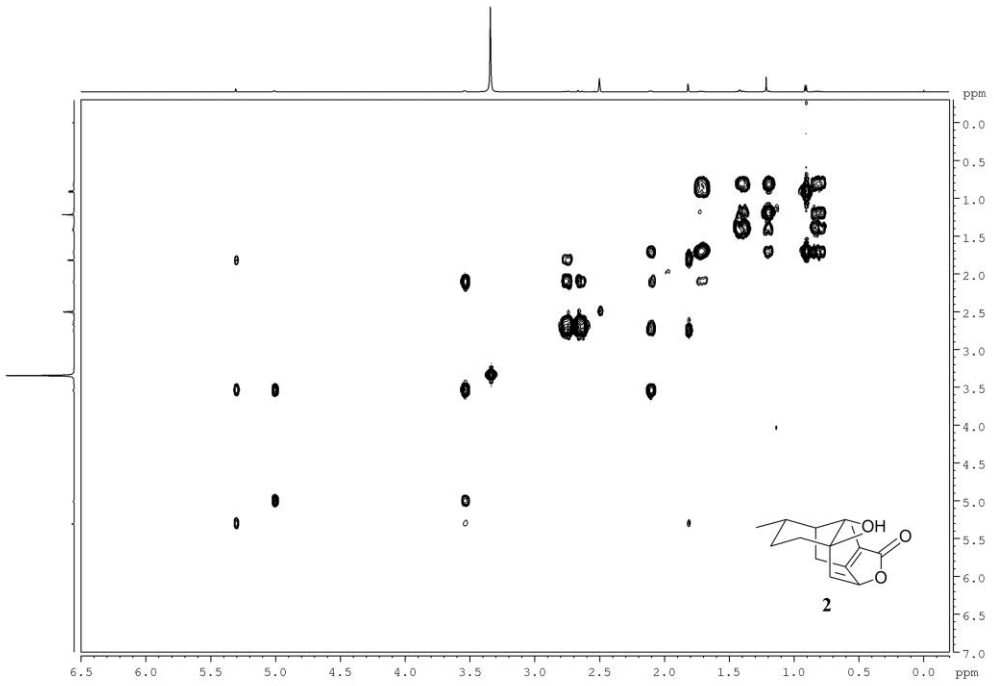


Fig. S22. ^{1}H-^{1}H COSY (600 MHz, DMSO-d_6) spectrum of the new compound **2**

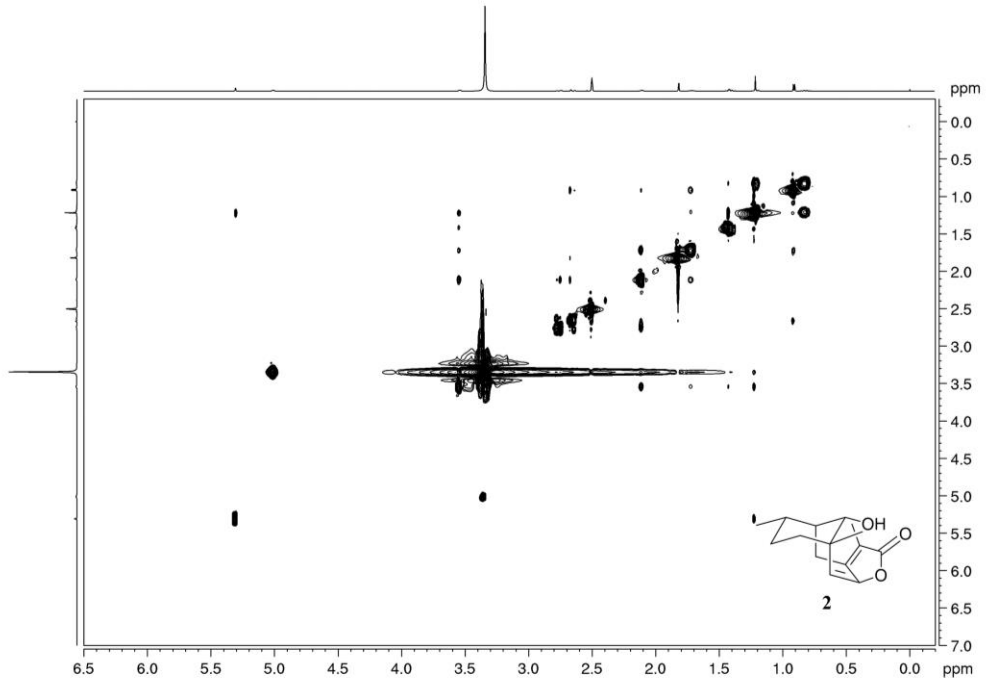


Fig. S23. NOESY (600 MHz, DMSO-d_6) spectrum of the new compound **2**

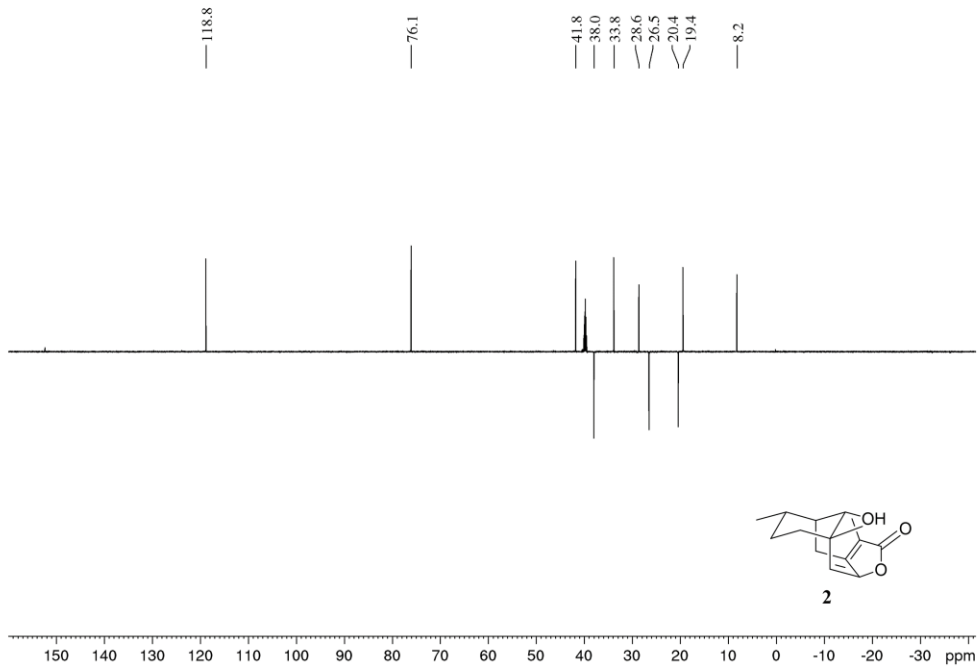


Fig. S24. DEPT (600 MHz, DMSO-d_6) spectrum of the new compound **2**

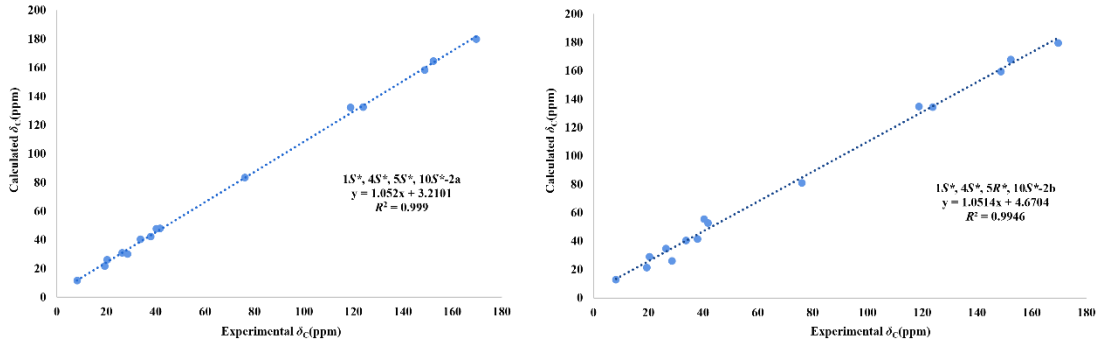
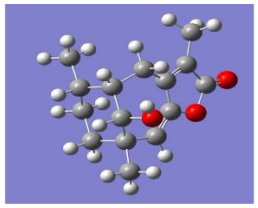


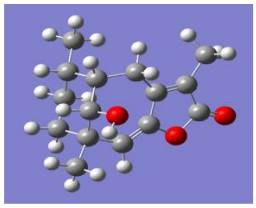
Fig. S25. Linear correlation between the experimental and calculated ^{13}C NMR chemical shifts of **2a** and **2b**

Isomer N°			1	2
DP4+ (%)		H data	100.00%	0.00%
		C data	100.00%	0.00%
		All data	100.00%	0.00%
Type	sp2?	Exp	1	2
c		41.78	47.92709338	52.7830081
c		33.82	40.32384362	40.38680259
c		26.48	30.85683922	34.69021358
c		37.98	42.23818782	41.45057004
c		40.32	47.6894924	55.43906512
c	X	188.82	132.1975	134.7038
c	X	148.78	158.2973	159.2459942
c	X	152.37	164.6176598	167.71
c		20.39	26.0523083	29.04153242
c		76.07	83.45225444	80.9226362
c	X	123.87	132.5053	134.382
c	X	169.72	179.766	179.53
c		8.18	11.63261366	12.84013954
c		19.4	21.6354636	21.28631617
c		28.61	30.01095571	25.98118273
H		2.11	2.296328295	2.21580928
H		1.71	1.895489101	2.134454369
H		0.82	1.035370094	1.345006249
H		1.21	1.34386945	2.388830746
H		1.41	1.682204054	2.188009952
H		1.41	1.653755758	1.707817718
H	X	5.31	5.886	6.1052
H		2.65	2.992609423	2.769609177
H		2.76	2.973525638	2.857430606
H		3.54	3.952846551	3.557253856
H		1.82	2.02513362	2.066246594
H		1.82	2.02513362	2.066246594
H		1.82	2.02513362	2.066246594
H		0.91	1.116983902	1.060651101
H		0.91	1.116983902	1.060651101
H		0.91	1.116983902	1.060651101
H		1.21	1.421749289	1.306702166
H		1.21	1.421749289	1.306702166
H		1.21	1.421749289	1.306702166

Fig. S26. Results of custom DP4+ analysis of **2a** and **2b**



2-1 (42.88%)
Energy: -809.5685276 hartree



2-2 (57.12%)
Energy: - 809.5687983 hartree

Fig. S27. Most stable conformers of the new compound **2** in solvated model calculations at the B3LYP/6-311++G (2d, p) level in ECD calculation

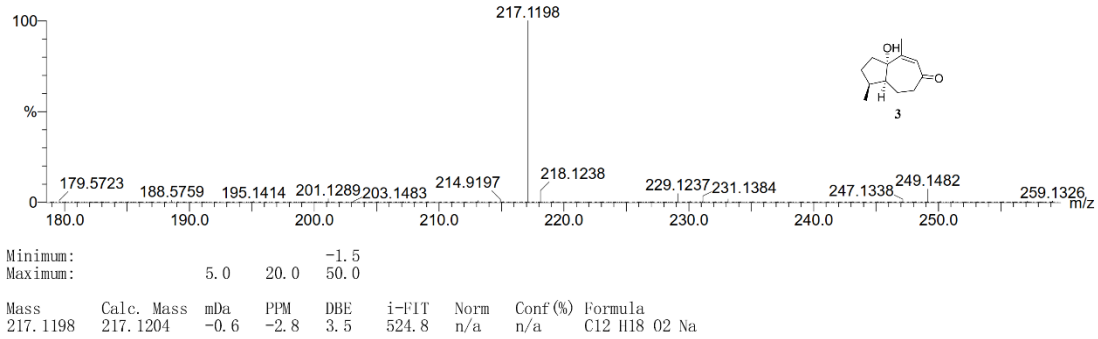


Fig. S28. The HR-ESIMS spectrum of the new compound **3**

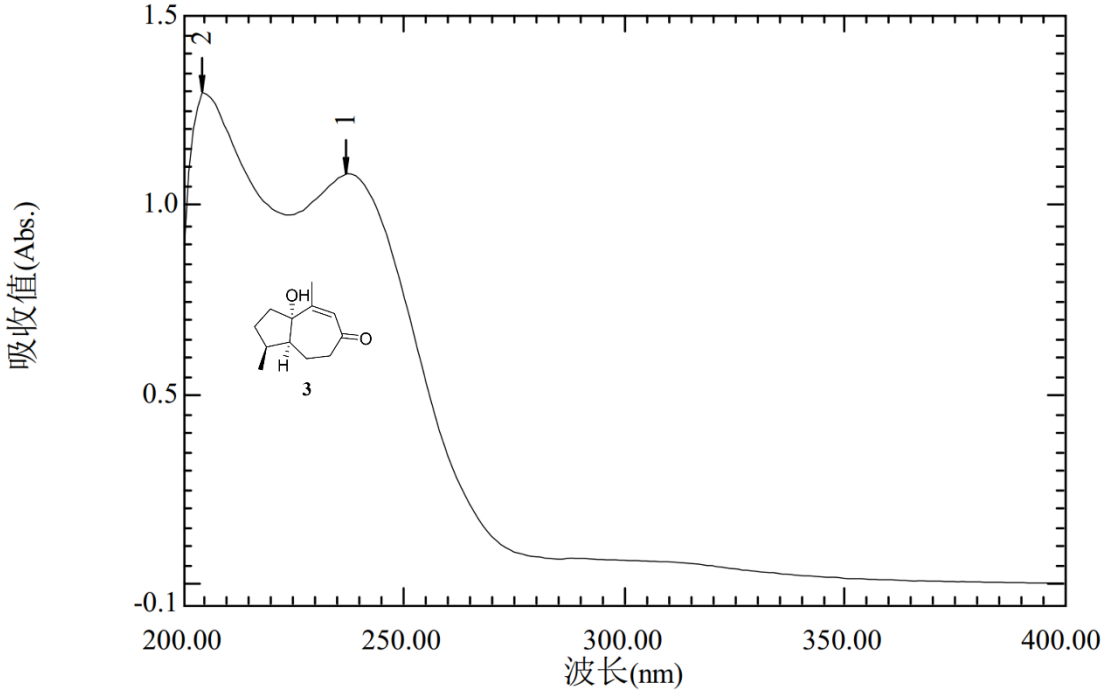


Fig. S29. The UV spectrum of the new compound **3**

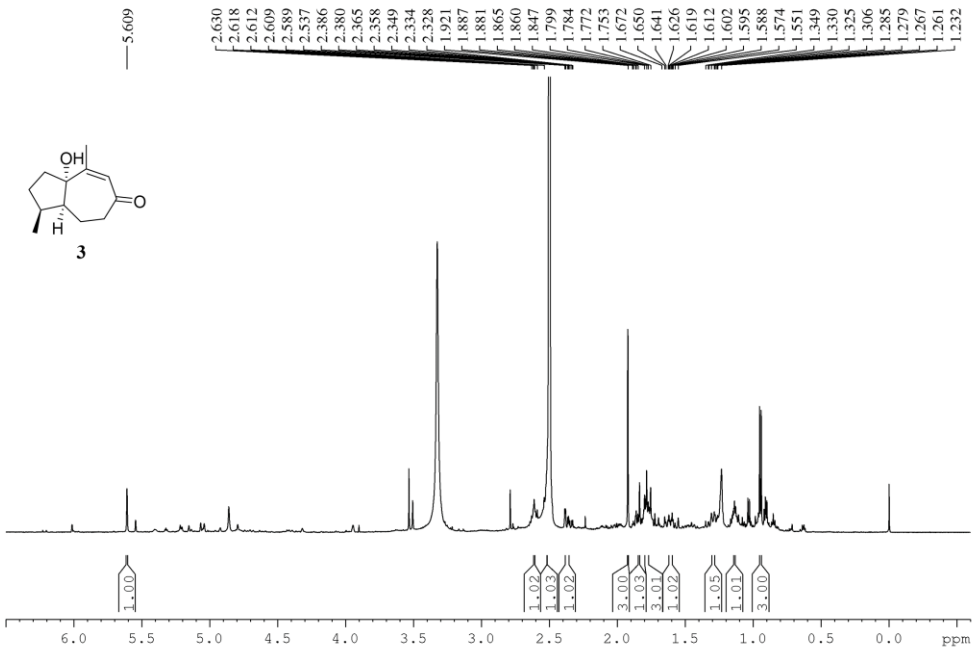


Fig. S30. ^{1}H NMR (600 MHz, DMSO-d_6) spectrum of the new compound **3**

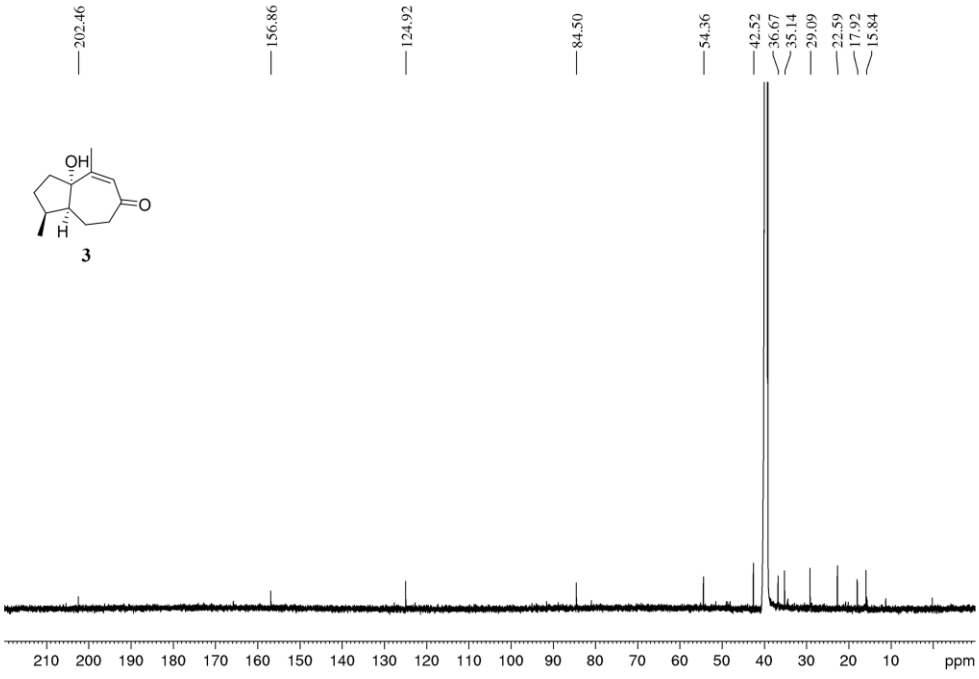


Fig. S31. ^{13}C NMR (150 MHz, DMSO-d_6) spectrum of the new compound **3**

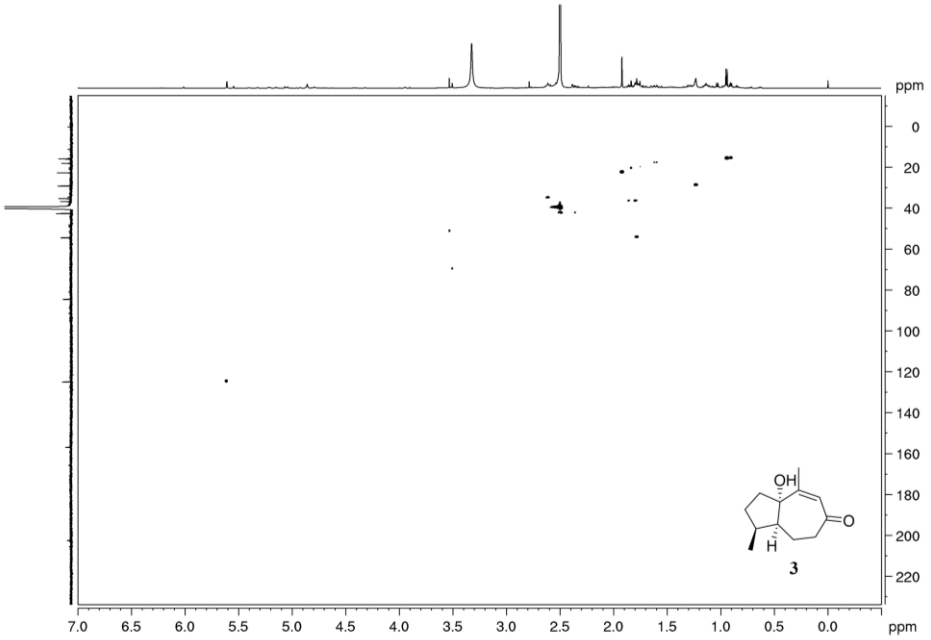


Fig. S32. HSQC (600 MHz, DMSO-d_6) spectrum of the new compound **3**

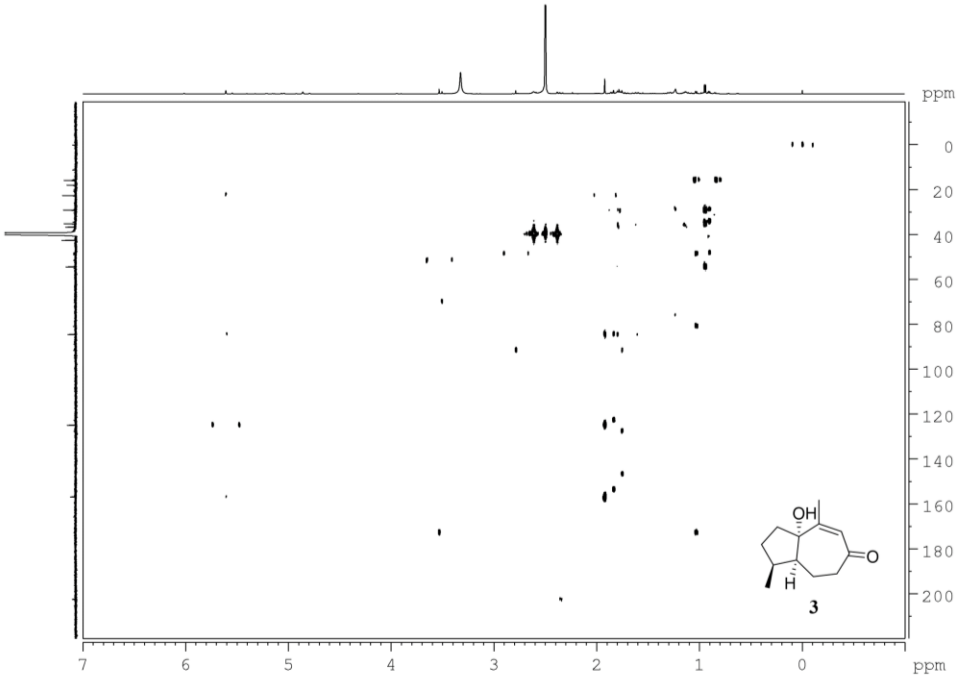


Fig. S33. HMBC (600 MHz, DMSO-d_6) spectrum of the new compound **3**

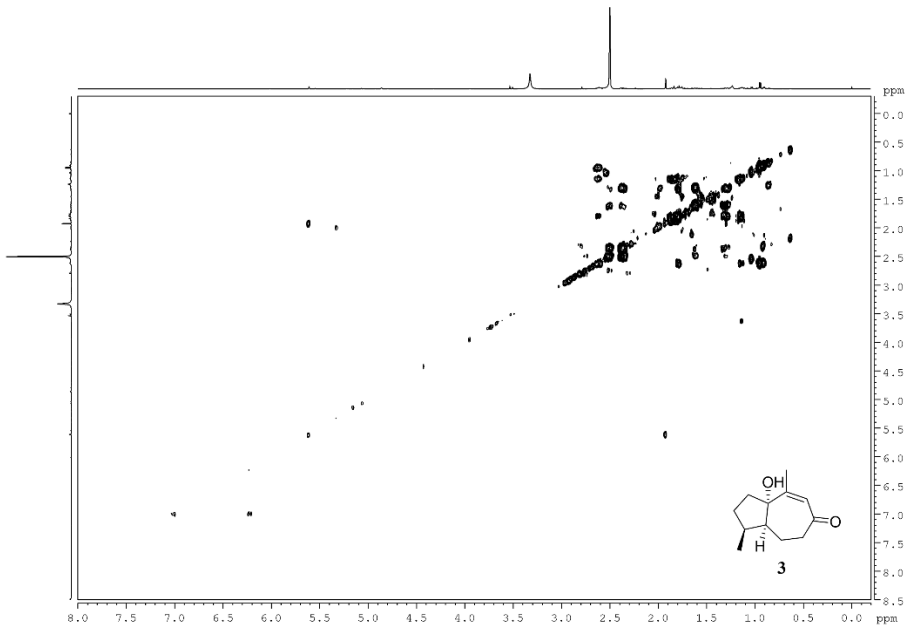


Fig. S34. ^{1}H-^{1}H COSY (600 MHz, DMSO-d_6) spectrum of the new compound **3**

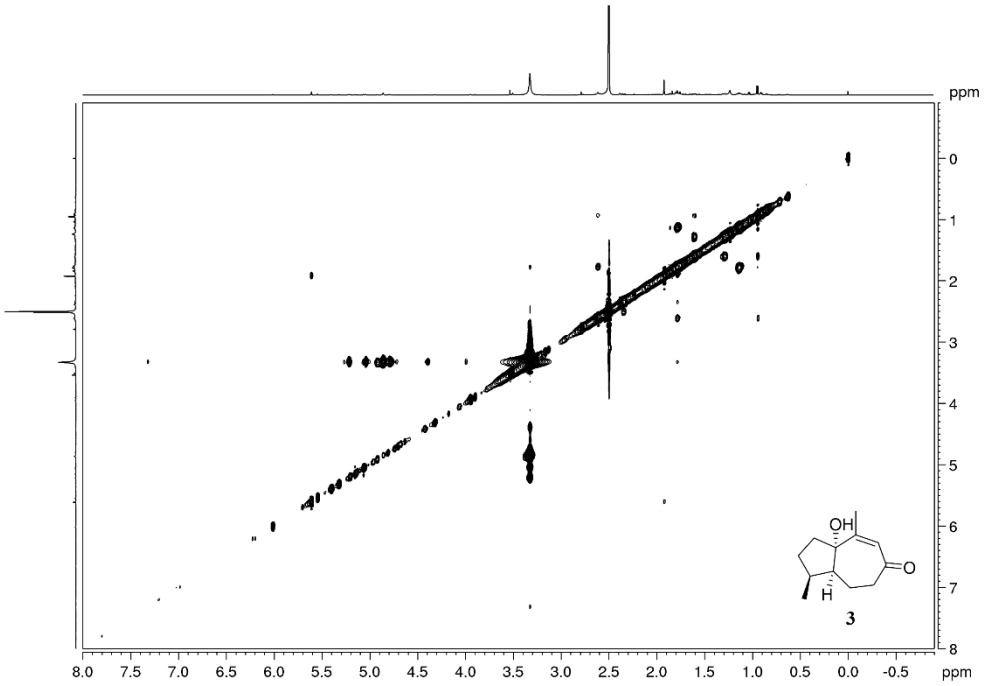


Fig. S35. NOESY (600 MHz, DMSO-d_6) spectrum of the new compound **3**

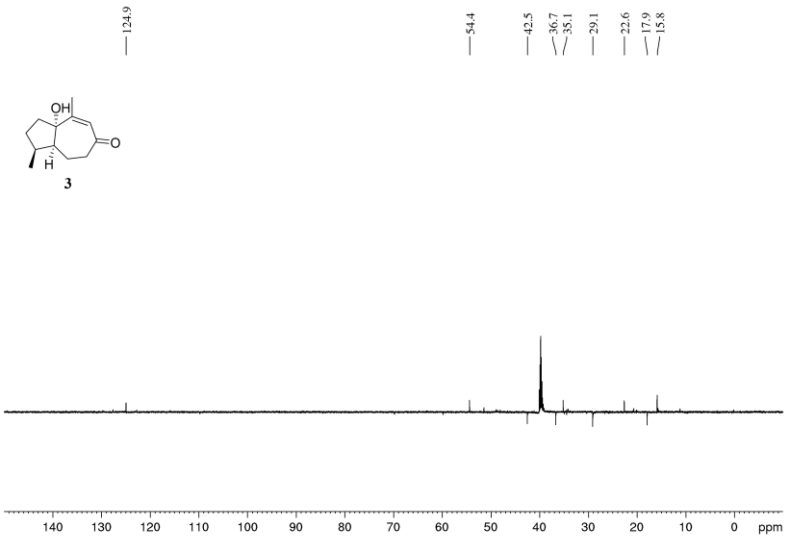


Fig. S36. DEPT (600 MHz, DMSO-d_6) spectrum of the new compound **3**

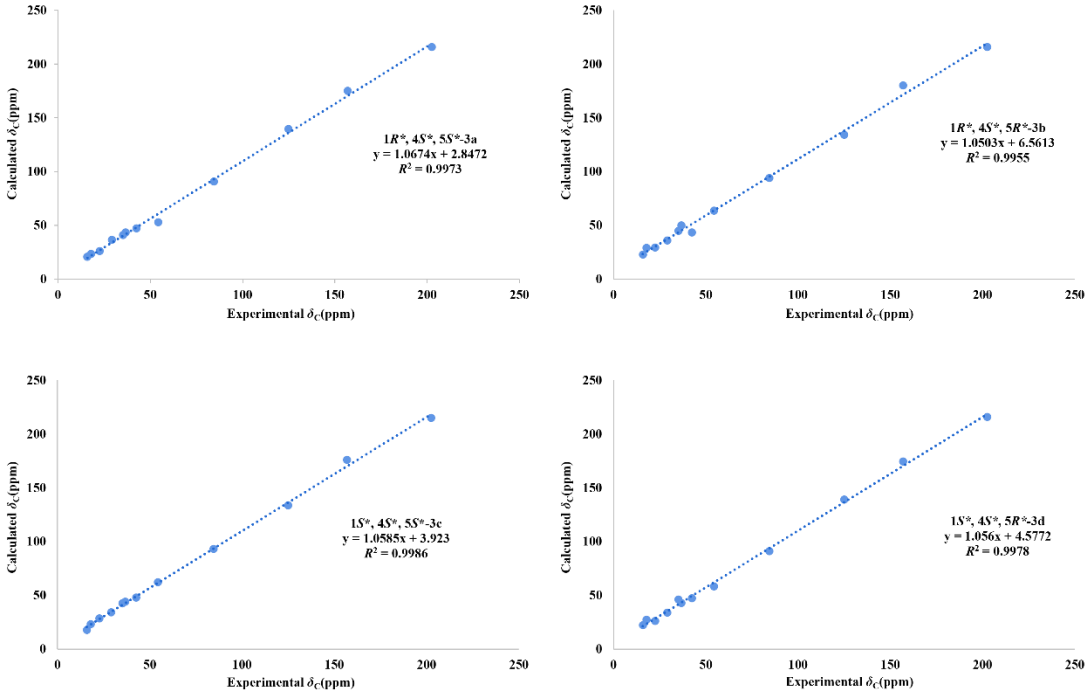


Fig. S37. Linear correlation between the experimental and calculated ^{13}C NMR chemical shifts of **3a**–**3d**

Isomer N°			1	2	3	4
DP4+ (%)		H data	0.00%	0.00%	100.00%	0.00%
		C data	0.03%	0.00%	99.97%	0.00%
		All data	0.00%	0.00%	100.00%	0.00%
Type	sp2?	Exp	1	2	3	4
c		84.5	90.88131146	93.9378265	93.1949141	91.1672993
c		36.68	43.2798552	50.06556391	43.9558827	42.9145345
c		29.09	36.47330793	35.90512107	34.1962814	33.751876
c		35.15	41.06627015	44.74938686	42.6358797	46.101396
c		54.36	52.82399538	63.74051228	62.1016622	58.1892175
c		17.92	23.45182922	29.14329313	23.2305421	27.2871102
c		42.53	47.3287964	43.41739445	47.9991086	47.1304378
c	X	202.49	215.77	215.81	215.04	215.68
c	X	124.93	139.53	134.16	133.68	138.87
c	X	156.87	174.89	179.98	175.87	174.43
c		22.6	26.22183099	29.395264	28.3922752	26.083596
c		15.85	20.90537054	22.81384225	17.8978436	22.3704216
H		1.84	2.046990346	2.147412096	2.12797037	2.0471935
H		1.79	1.846564728	1.673607917	2.14119412	2.03485025
H		1.79	2.102216087	1.943946527	2.02390403	1.39367663
H		1.14	1.641366417	1.75743988	1.47283473	2.26004802
H		2.61	2.464347339	2.094829935	3.00292808	2.12705842
H		1.79	2.226426811	1.900323047	2.02218666	1.67244366
H		1.61	2.008026475	1.754672411	1.77388049	1.74134288
H		1.3	1.81888491	1.937453489	1.58763717	2.12979107
H		2.5	3.234331526	2.66378919	2.74485241	3.23195911
H		2.37	2.539879844	2.512262398	2.61601831	2.52123313
H	X	5.61	6.3	6.25	6.15	6.28
H		1.92	2.216583821	2.310476245	2.31084197	2.21899317
H		1.92	2.216583821	2.310476245	2.31084197	2.21899317
H		1.92	2.216583821	2.310476245	2.31084197	2.21899317
H		0.95	1.116502535	1.271725273	1.14235633	1.11570546
H		0.95	1.116502535	1.271725273	1.14235633	1.11570546
H		0.95	1.116502535	1.271725273	1.14235633	1.11570546

Fig. S38. Results of custom DP4+ analysis of **3a**–**3d**

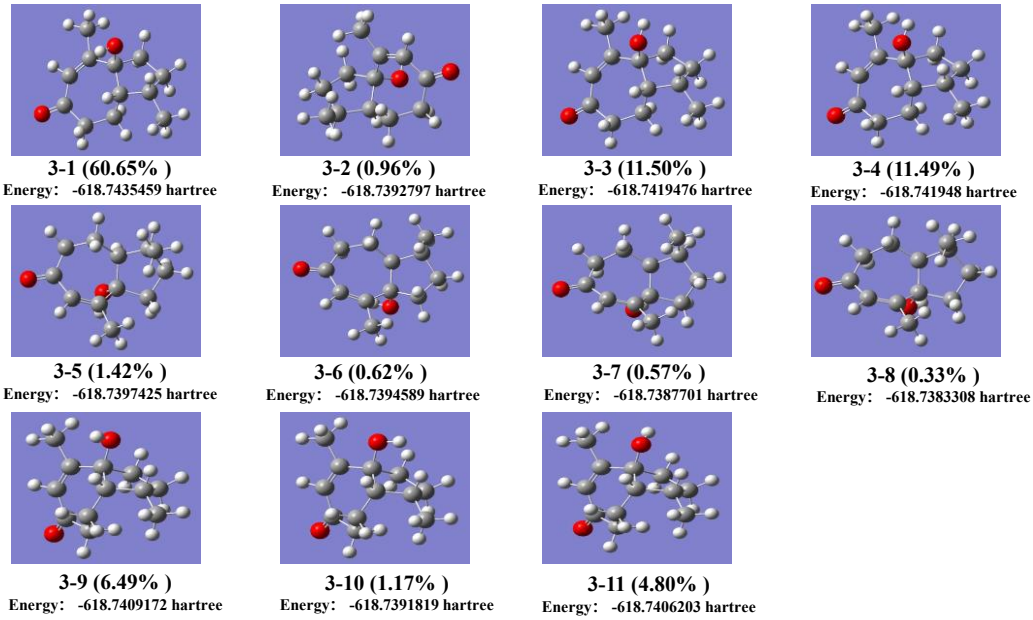


Fig. S39. Most stable conformers of the new compound **3** in solvated model calculations at the B3LYP/6-311++G (2d, p) level in ECD calculation

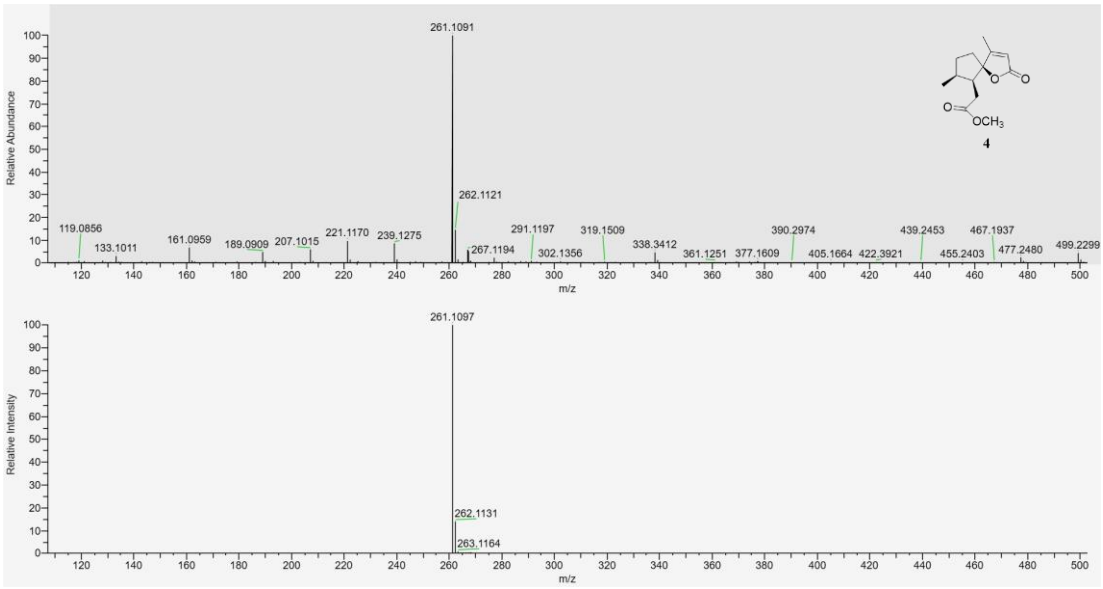


Fig. S40. The HR-ESIMS spectrum of the new compound **4**

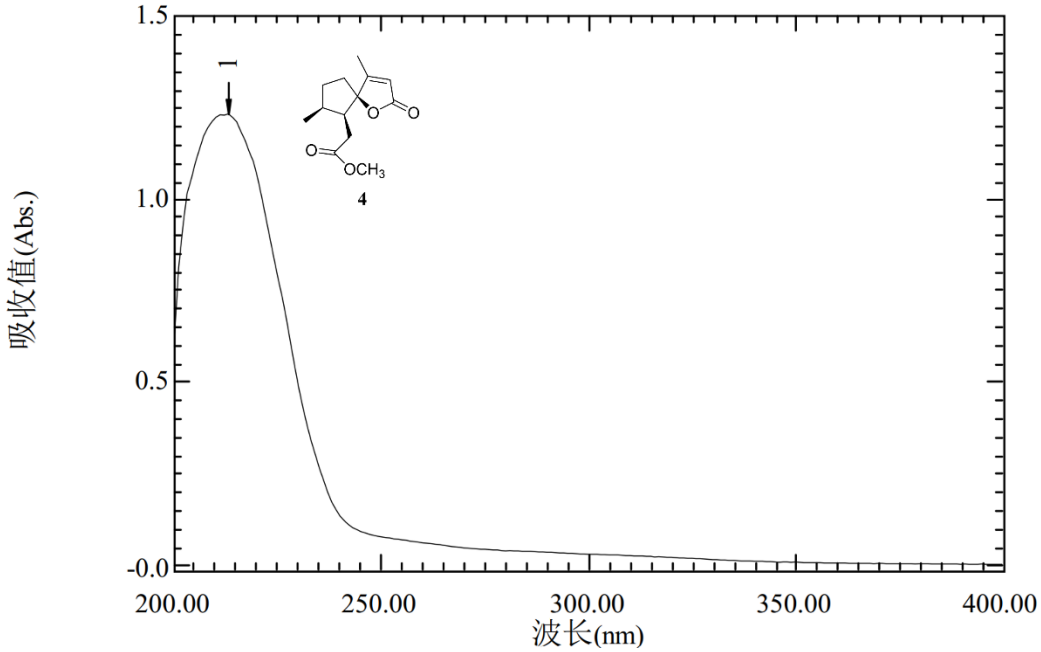


Fig. S41. The UV spectrum of the new compound **4**

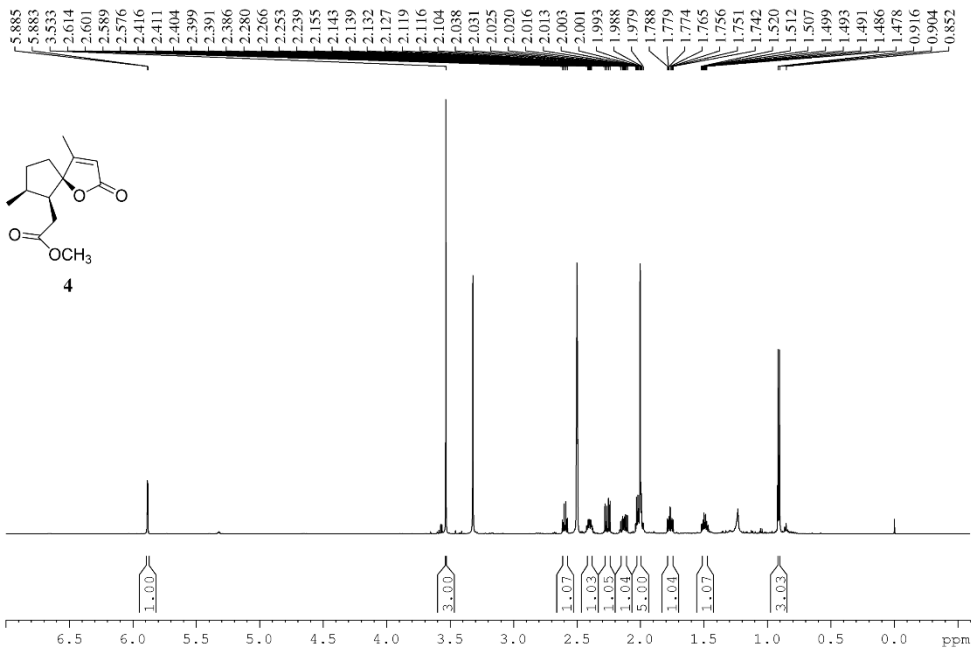


Fig. S42. ^{1}H NMR (600 MHz, DMSO-d_6) spectrum of the new compound **4**

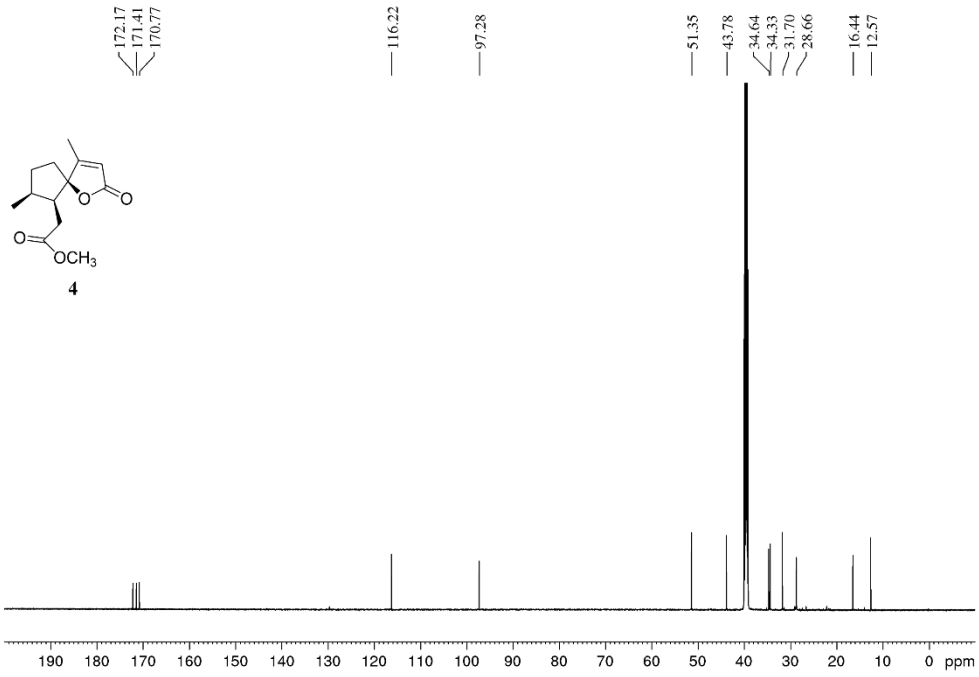


Fig. S43. ^{13}C NMR (150 MHz, DMSO-d_6) spectrum of the new compound **4**

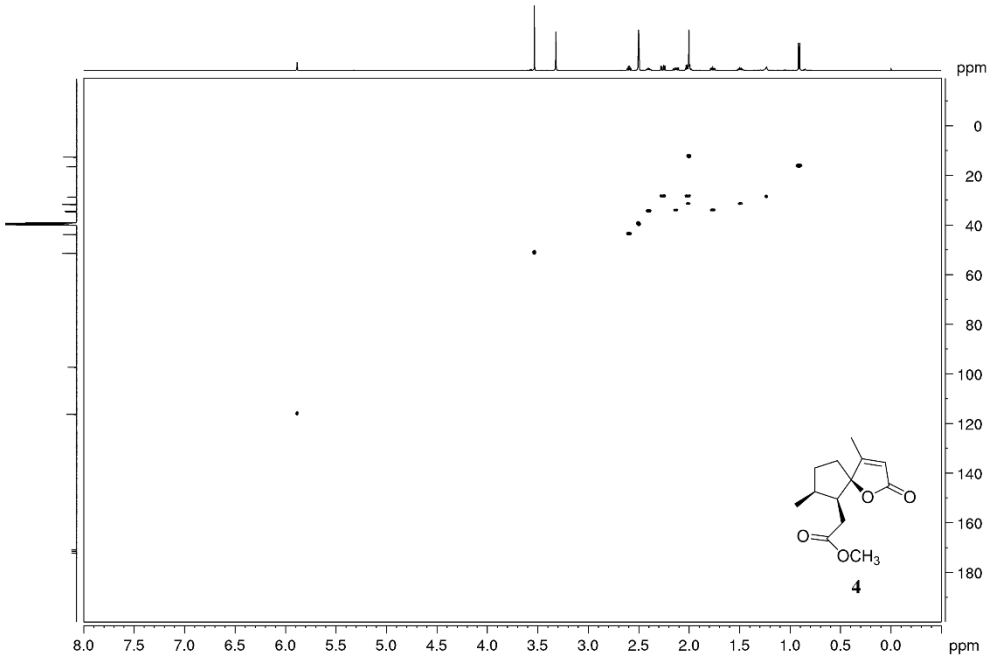


Fig. S44. HSQC (600 MHz, DMSO-d_6) spectrum of the new compound **4**

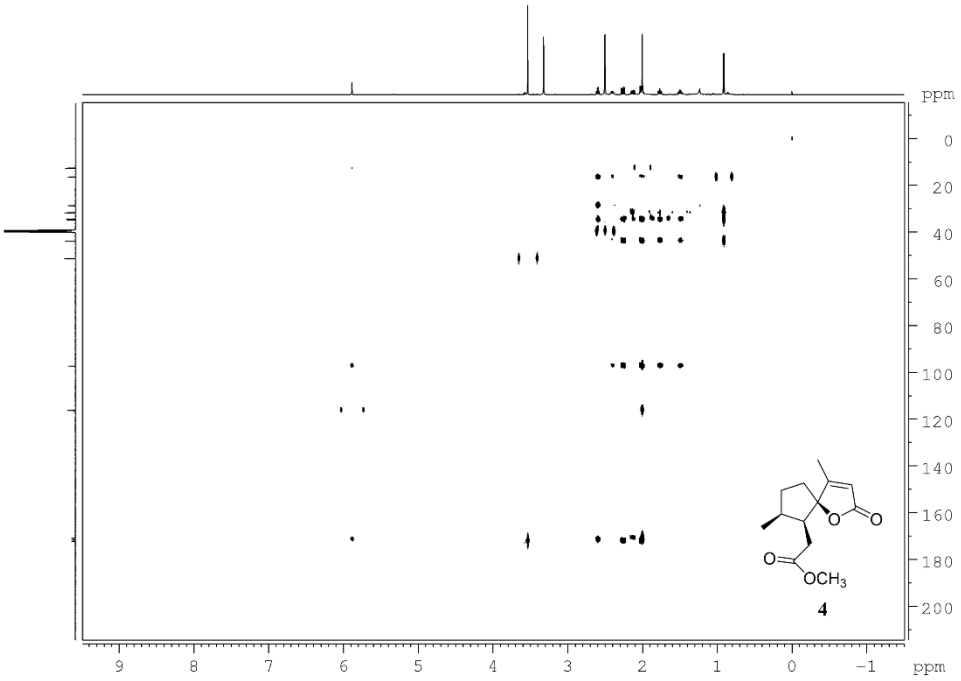


Fig. S45. HMBC (600 MHz, DMSO-d_6) spectrum of the new compound **4**

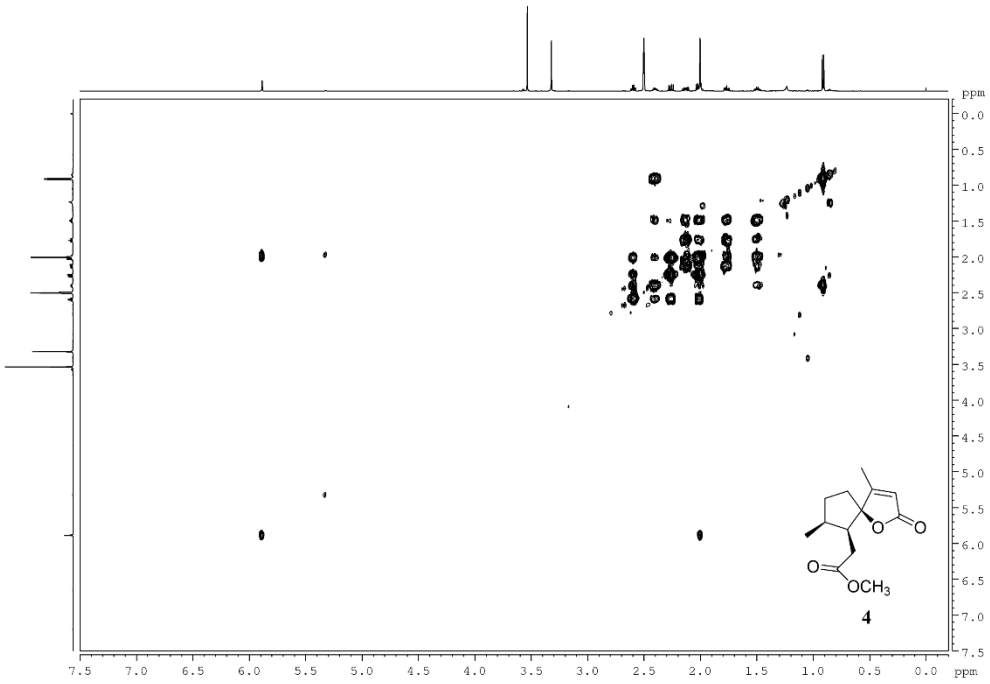


Fig. S46. ^{1}H-^{1}H COSY (600 MHz, DMSO-d_6) spectrum of the new compound **4**

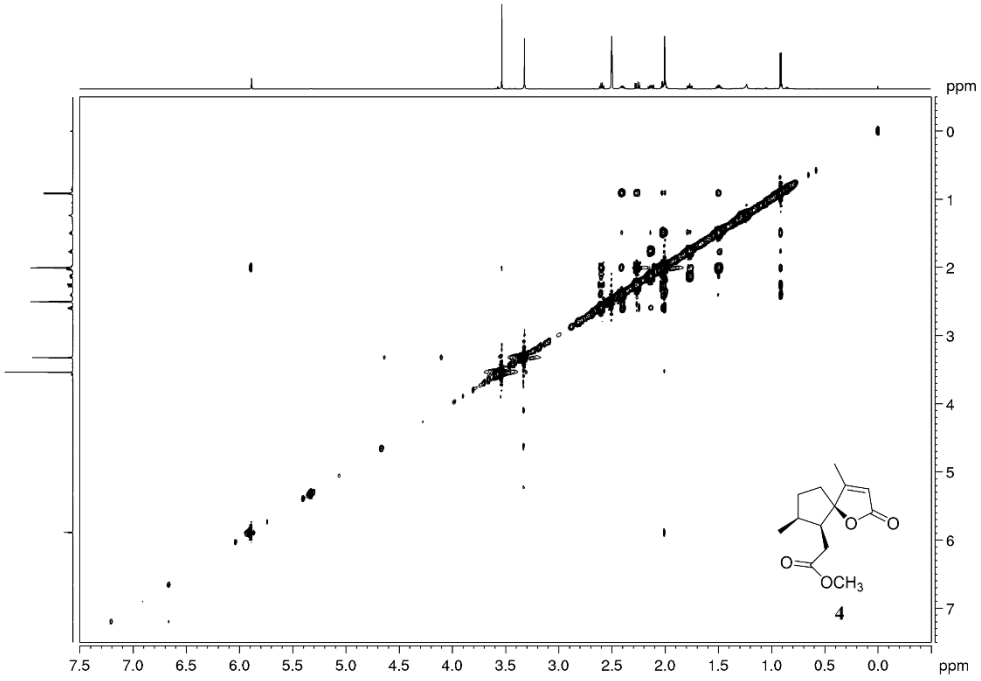


Fig. S47. NOESY (600 MHz, DMSO-d_6) spectrum of the new compound **4**

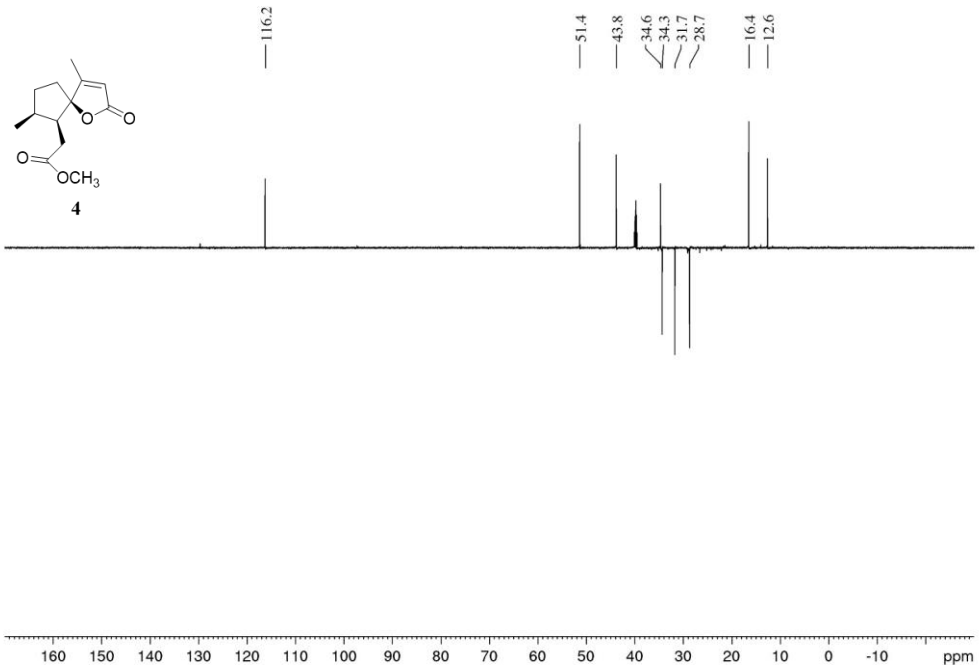


Fig. S48. DEPT (600 MHz, DMSO-d_6) spectrum of the new compound **4**

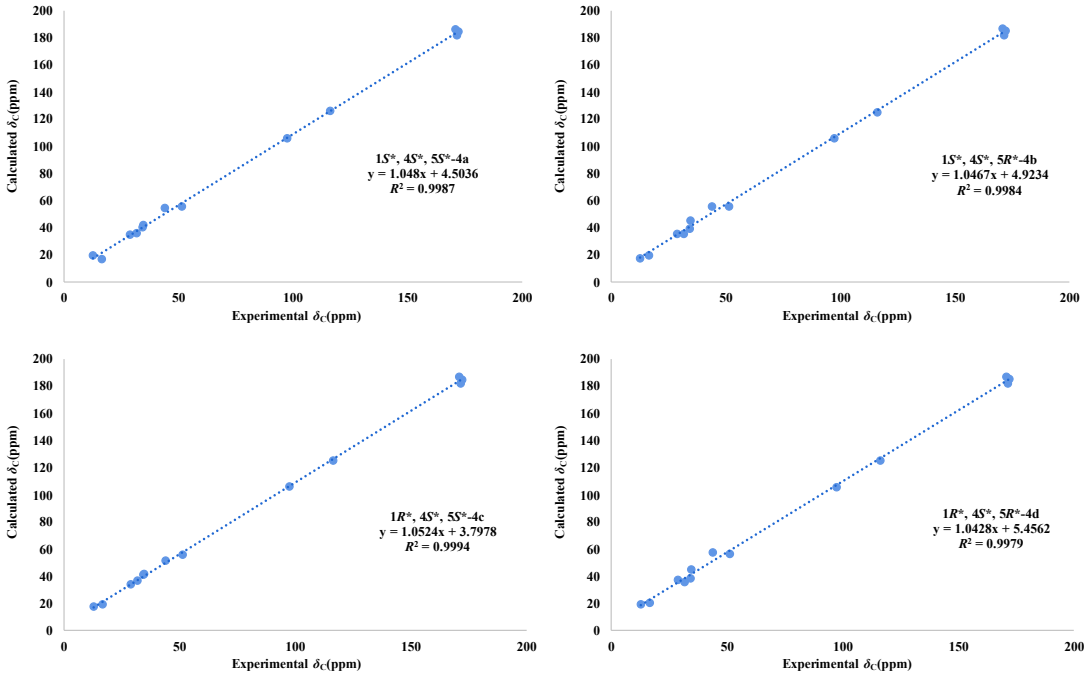


Fig. S49. Linear correlation between the experimental and calculated ^{13}C NMR chemical shifts of **4a**–**4d**

Isomer Nº			1	2	3	4
DP4+ (%)		H data	0.02%	0.07%	99.83%	0.08%
		C data	0.00%	0.00%	100.00%	0.00%
		All data	0.00%	0.00%	100.00%	0.00%
Type	sp2?	Exp	1	2	3	4
C		97.29	106.3575965	106.220472	105.817365	105.481556
C		34.33	40.43704288	39.51563315	41.1953833	38.3435639
C		31.71	36.25722919	35.80742761	36.8269793	35.6659091
C		34.64	42.1949898	45.79901629	41.5289271	44.8766517
C		43.79	54.93436219	55.68727525	51.5930497	57.6607419
C		28.66	34.97046866	35.6158676	33.7348484	37.1783054
C	X	172.19	184.56	185.13	184.84	185.1
C	X	171.44	181.78	181.88	181.99	182.12
C	X	116.24	126.15	125.44	125.07	125.06
C	X	170.79	186.21	186.74	186.72	186.93
C		12.57	19.88709052	17.58626017	17.5175845	19.2233849
C		16.44	17.30627447	19.82952542	19.4199852	20.5037284
C		51.35	56.10492778	56.03690003	56.0022769	56.1830863
H		1.77	2.069927848	1.963526312	2.02239028	2.1924044
H		2.13	2.350632009	2.423613989	2.3394245	2.23015201
H		1.49	1.719883478	1.60610951	1.77515605	1.77085257
H		2	2.307682284	2.215139082	2.29436625	2.06105189
H		2.4	2.647742618	2.284662678	2.60617599	2.04943988
H		2.6	3.227438865	2.408999929	2.90399579	2.7466339
H		2	2.357559088	2.372815547	2.23738809	2.1754811
H		2.26	2.543551004	2.251540243	2.49414585	2.35277937
H	X	5.88	6	5.97	5.99	5.96
H		2	2.319638019	2.321673035	2.27382083	2.29693511
H		2	2.319638019	2.321673035	2.27382083	2.29693511
H		2	2.319638019	2.321673035	2.27382083	2.29693511
H		0.91	1.022571311	1.130169409	1.11717157	1.09645596
H		0.91	1.022571311	1.130169409	1.11717157	1.09645596
H		0.91	1.022571311	1.130169409	1.11717157	1.09645596
H		3.53	3.785536273	3.739276417	3.76415494	3.77387481
H		3.53	3.785536273	3.739276417	3.76415494	3.77387481
H		3.53	3.785536273	3.739276417	3.76415494	3.77387481

Fig. S50. Results of custom DP4+ analysis of **4a**–**4d**

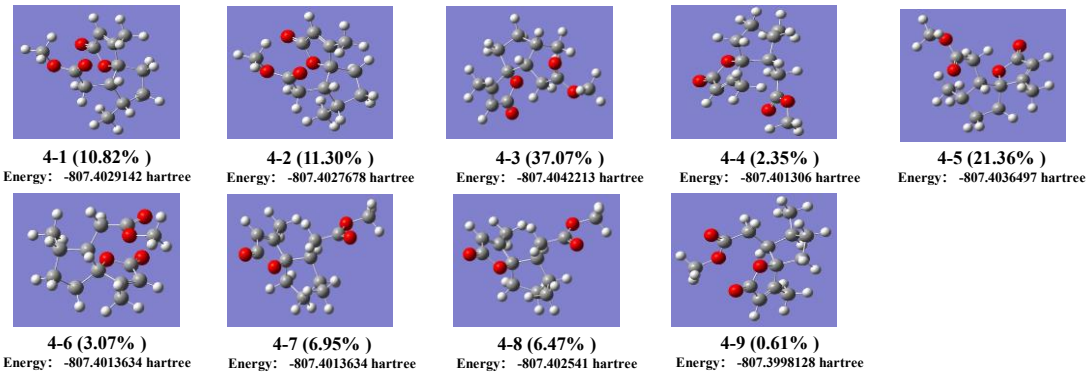


Fig. S51. Most stable conformers of the new compound **4** in solvated model calculations at the B3LYP/6-311++G (2d, p) level in ECD calculation

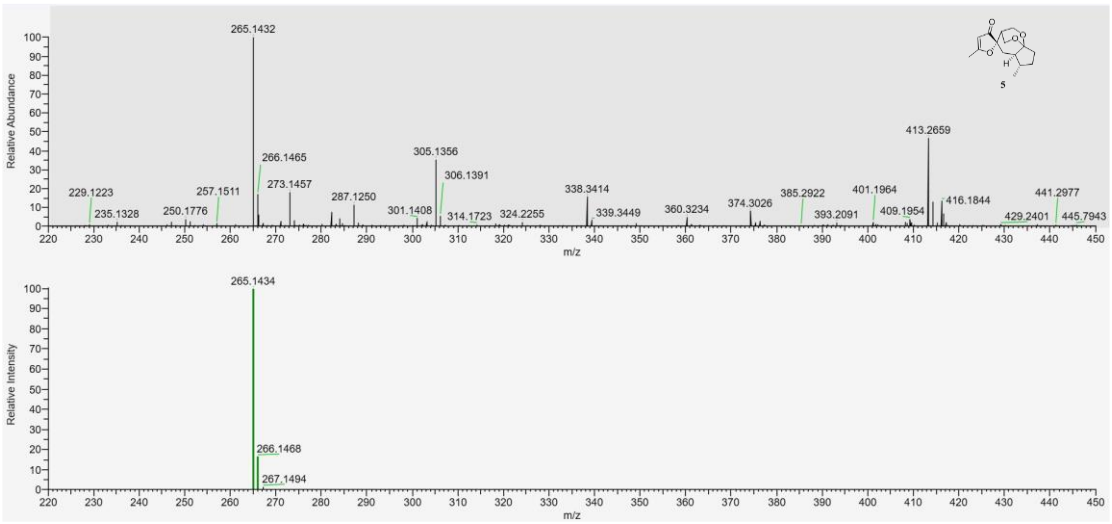


Fig. S52. The HR-ESIMS spectrum of the new compound **5**

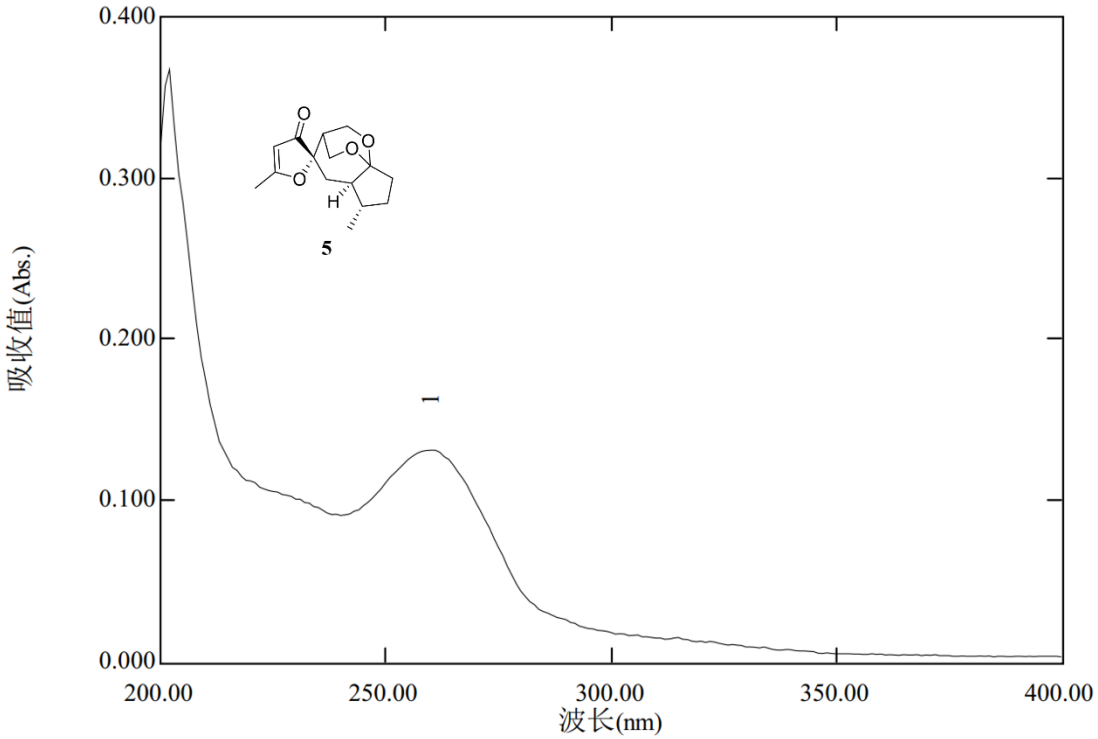


Fig. S53. The UV spectrum of the new compound **5**

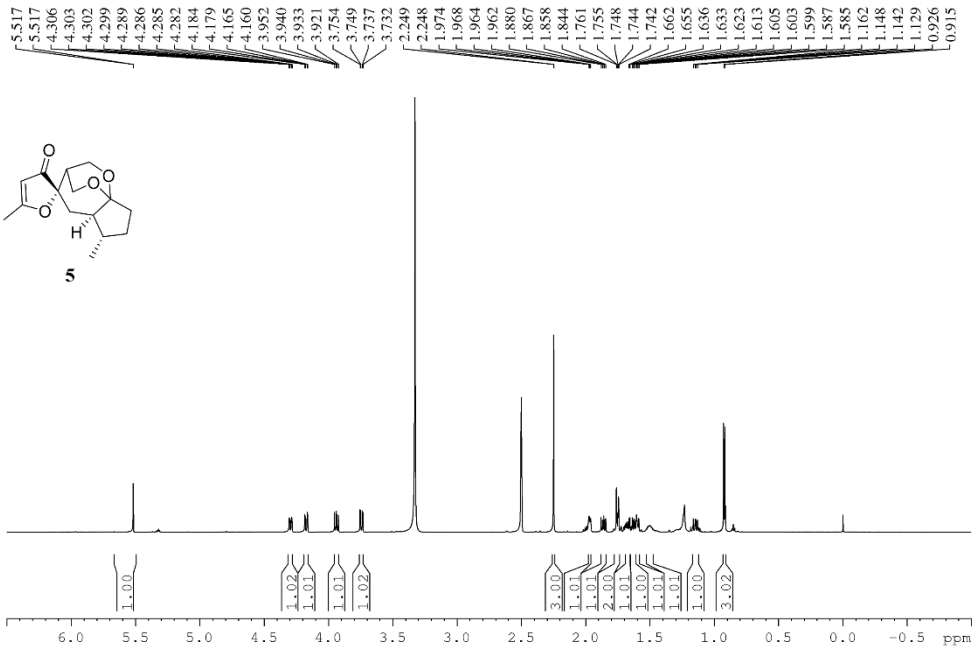


Fig. S54. ^{1}H NMR (600 MHz, DMSO-d_6) spectrum of the new compound **5**

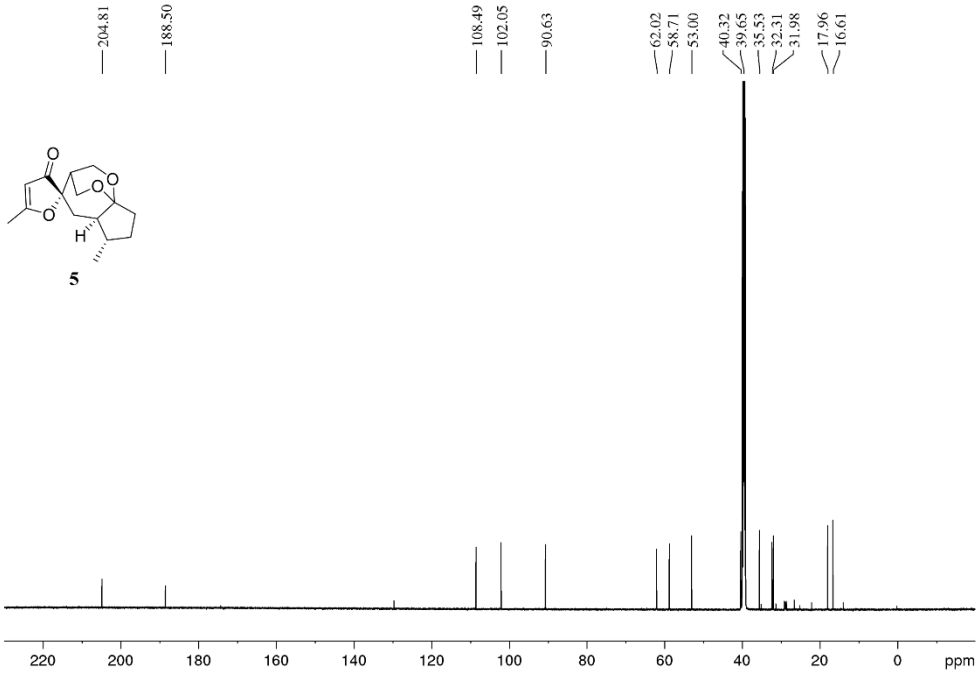


Fig. S55. ^{13}C NMR (150 MHz, DMSO-d_6) spectrum of the new compound **5**

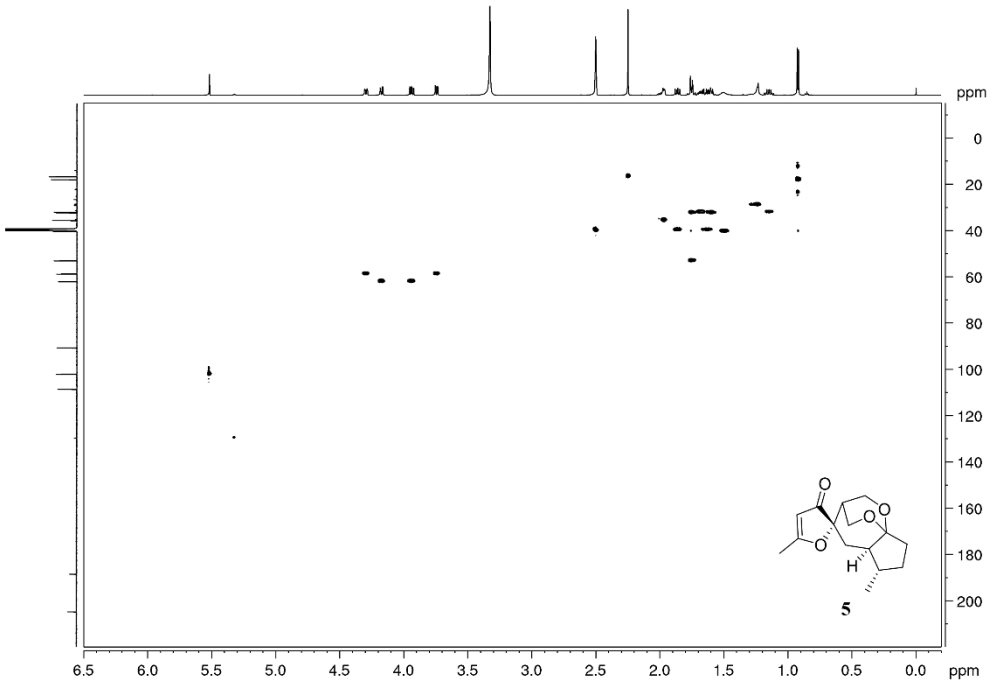


Fig. S56. HSQC (600 MHz, DMSO-d_6) spectrum of the new compound **5**

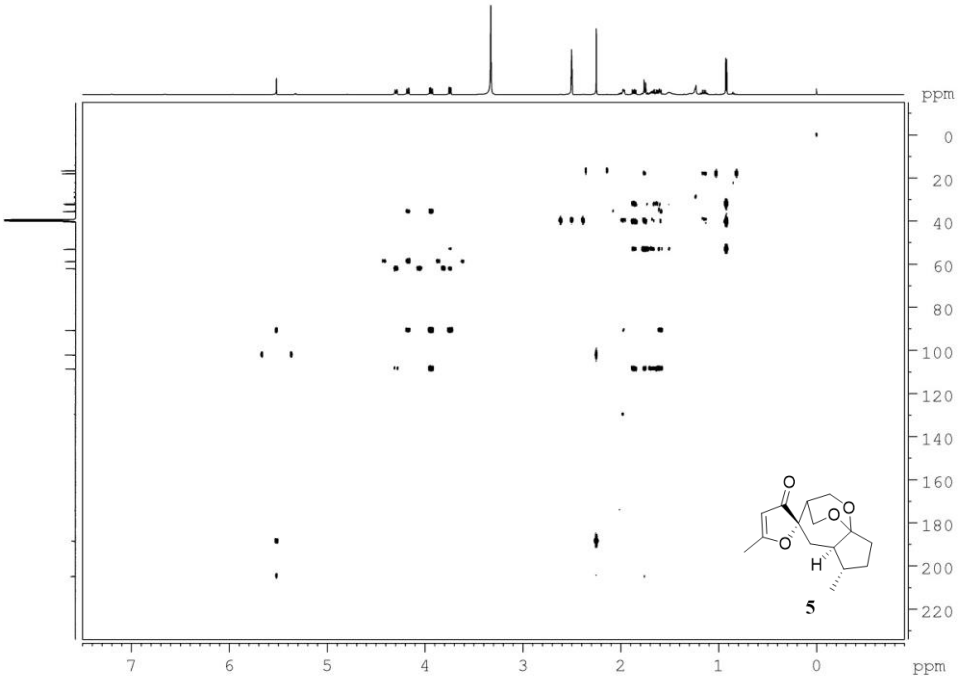


Fig. S57. HMBC (600 MHz, DMSO-d_6) spectrum of the new compound **5**

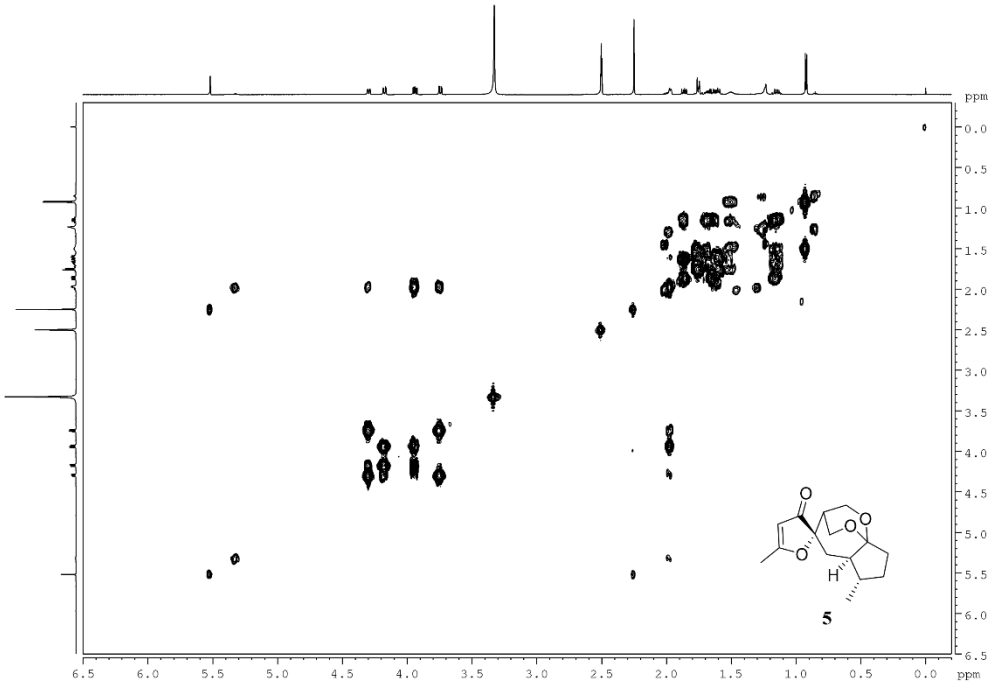


Fig. S58. ^{1}H-^{1}H COSY (600 MHz, DMSO-d_6) spectrum of the new compound **5**

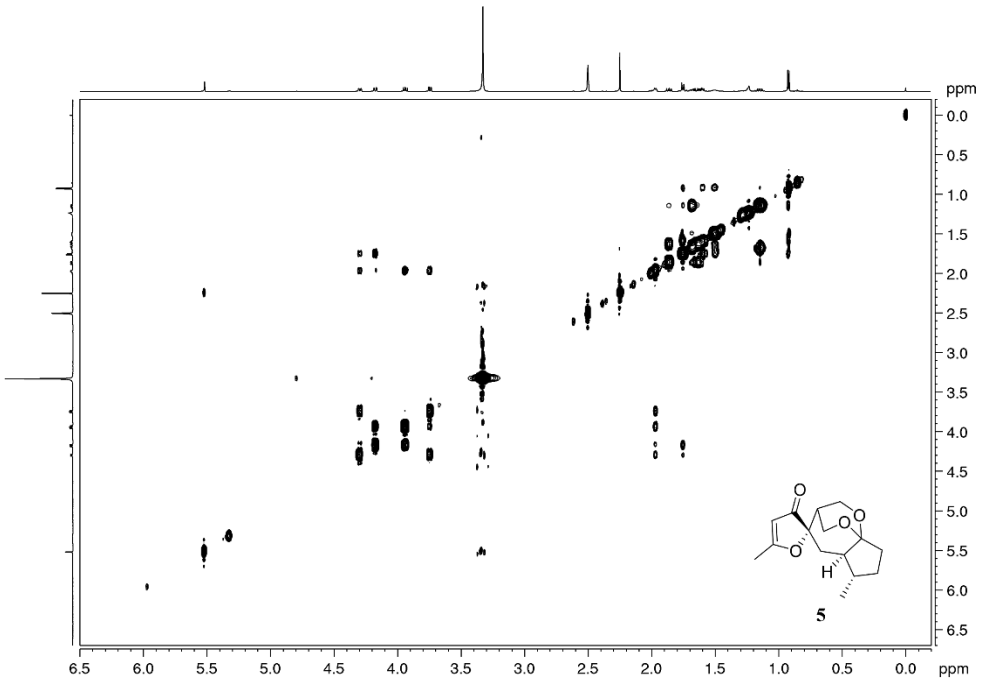


Fig. S59. NOESY (600 MHz, DMSO-d_6) spectrum of the new compound **5**

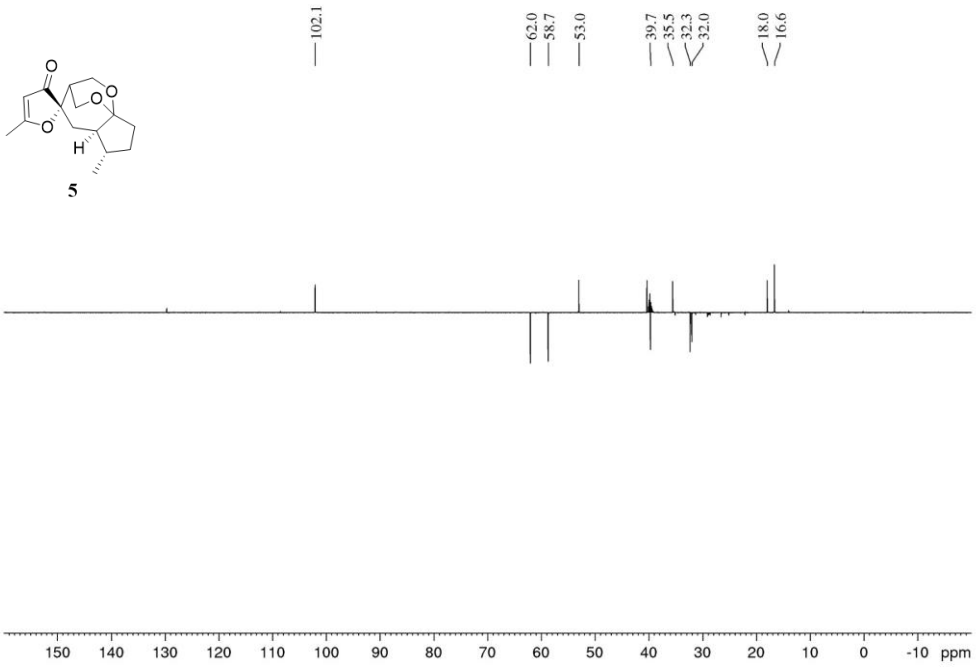


Fig. S60. DEPT (600 MHz, DMSO-d_6) spectrum of the new compound **5**

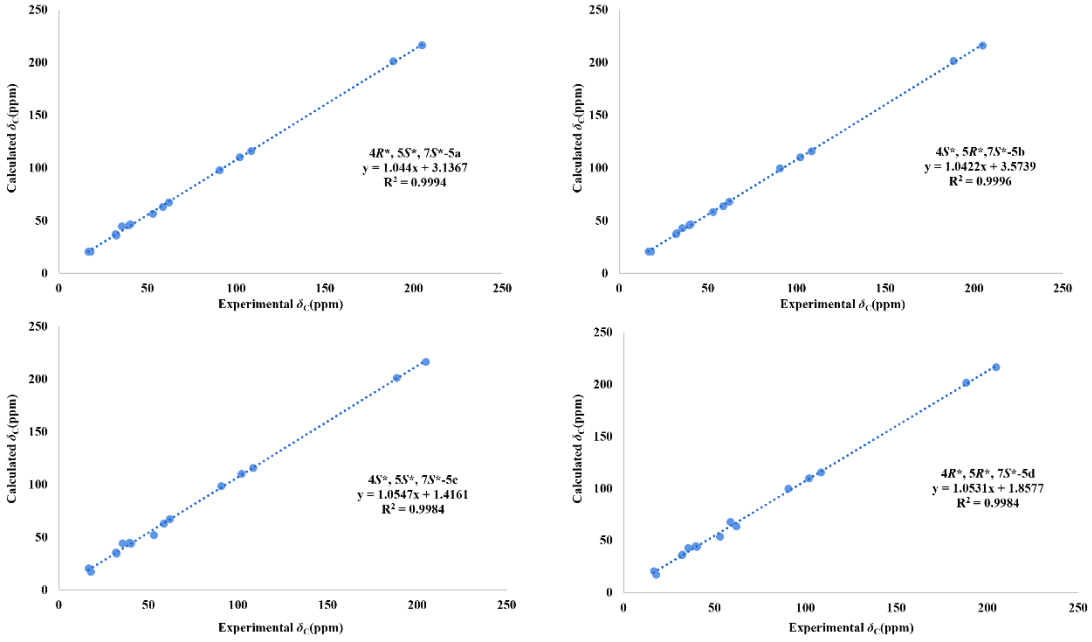
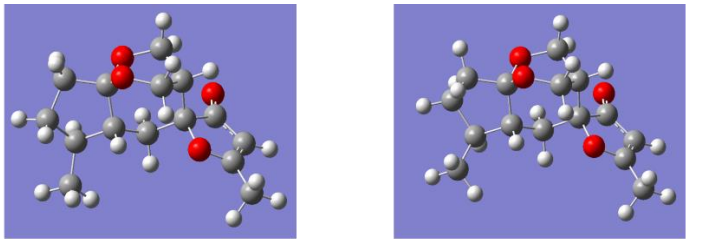


Fig. S61. Linear correlation between the experimental and calculated ^{13}C NMR chemical shifts of **5a**–**5d**

Isomer N°			1	2	3	4
DP4+ (%)		H data	3.89%	96.11%	0.00%	0.00%
		C data	35.12%	64.87%	0.00%	0.00%
		All data	2.15%	97.85%	0.00%	0.00%
Type	sp2?	Exp	1	2	3	4
C	x	204.84	216.2931327	215.872904	216.265667	216.214353
C	x	102.06	109.9925488	109.7932006	110.048507	109.606477
C	x	188.53	201.1197567	201.4197772	201.119649	201.513006
C		90.64	97.81763383	99.6471005	98.4318321	99.5804781
C		35.53	44.28533678	42.78876245	44.2042635	42.6762297
C		62.02	67.05470241	67.65267298	67.1822727	63.6128303
C		108.51	116.0325968	115.7113915	115.642197	115.445233
C		53.01	56.45842104	58.1161949	51.8226678	53.5597654
C		32.32	35.67253123	37.89366755	34.1895571	36.424083
C		58.72	62.77497821	63.40517849	62.8176218	67.714366
C		39.66	45.59537637	45.50288227	44.6836861	44.5129432
C		31.98	36.94492278	37.04421621	35.6123536	35.8091618
C		40.33	46.59837939	46.42499234	43.7531386	43.8212939
C		17.96	20.36732188	20.32339979	16.9879195	17.1354666
C		16.61	20.39749046	20.47463742	20.3925378	20.4691274
H	x	5.52	5.6163133	5.65843514	5.62293027	5.64700386
H		1.97	1.773456126	1.84141608	1.77999993	1.8421244
H		4.17	4.435940154	4.588368918	4.46922898	4.609847
H		3.94	4.23454298	4.145804061	4.24507653	4.16362998
H		1.75	2.146410892	2.071786448	2.77520816	2.71987499
H		1.75	2.057084975	1.948941856	2.21677973	2.15266602
H		1.75	1.892556761	1.755990385	1.69816946	1.57738911
H		4.3	5.035224128	4.713089764	5.05593898	4.7265111
H		3.74	3.857857682	4.040342188	3.88332707	4.04708684
H		1.86	2.067171516	2.078234646	2.02444694	2.02157682
H		1.63	1.885033268	1.882880771	1.98083612	1.98819186
H		1.68	1.825452744	1.860155159	1.93541109	1.95998054
H		1.15	1.443434162	1.454677787	1.53660517	1.57130944
H		1.5	1.733326605	1.799685288	2.30984469	2.34777486
H		0.92	1.077291128	1.096560865	0.98050853	1.00050489
H		0.92	1.077291128	1.096560865	0.98050853	1.00050489
H		0.92	1.077291128	1.096560865	0.98050853	1.00050489
H		2.53	2.420576602	2.443853198	2.41860794	2.43630689
H		2.53	2.420576602	2.443853198	2.41860794	2.43630689
H		2.53	2.420576602	2.443853198	2.41860794	2.43630689

Fig. S62. Results of custom DP4+ analysis of **5a**–**5d**



5-1 (96.78%)
Energy: -884.7955324 hartree

5-2 (3.22%)
Energy: -884.7923194 hartree

Fig. S63. Most stable conformers of the new compound **5** in solvated model calculations at the B3LYP/6-311++G (2d, p) level in ECD calculation

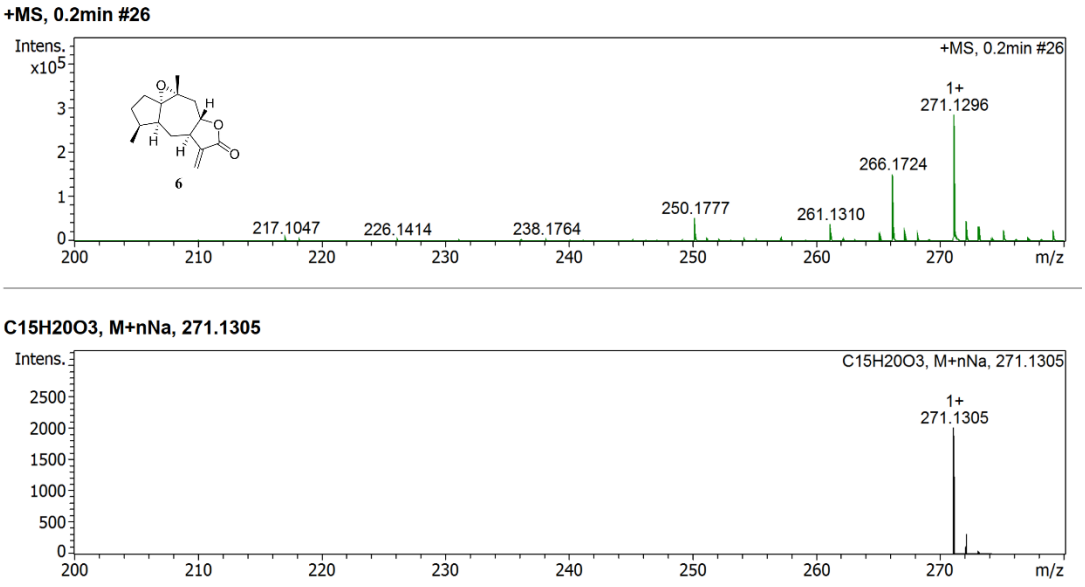


Fig. S64. The HR-ESIMS spectrum of the new compound **6**

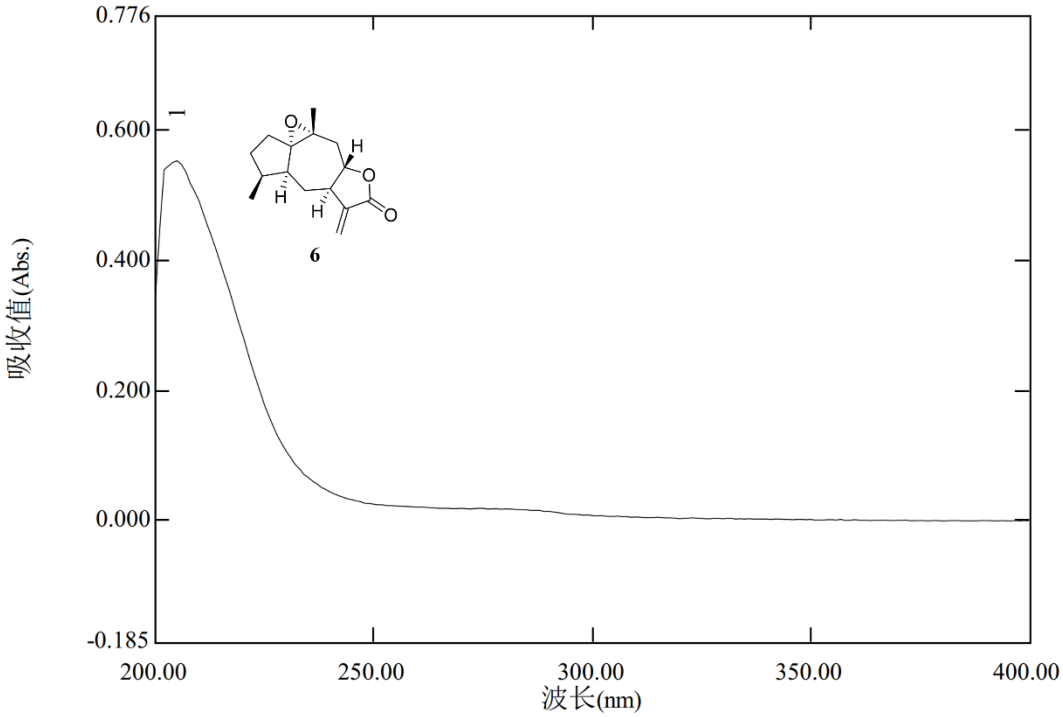
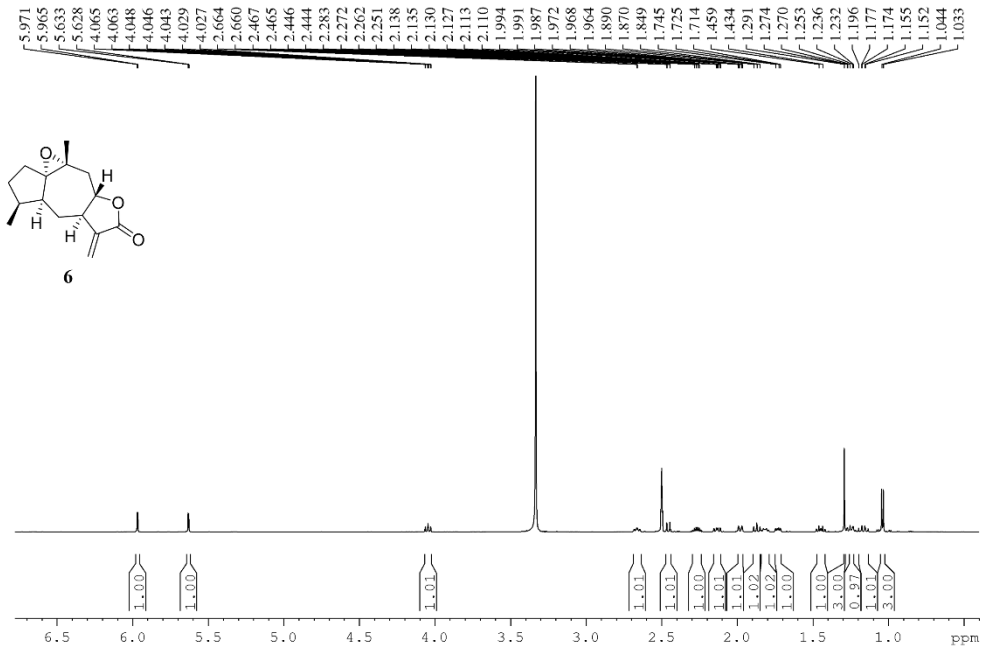
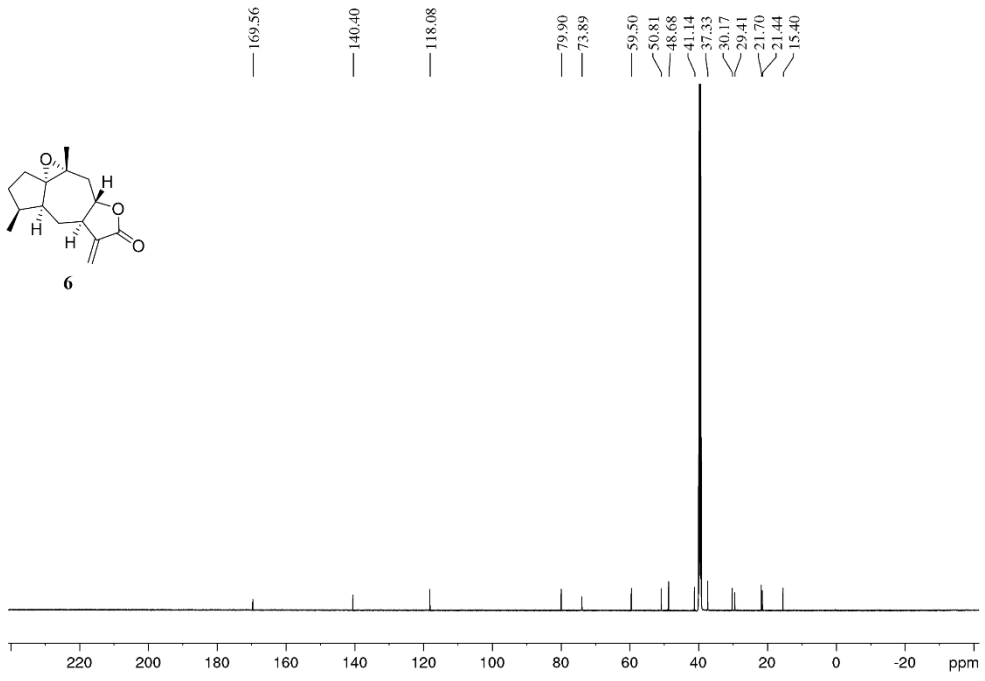


Fig. S65. The UV spectrum of the new compound **6**



6

Fig. S66. ^{1}H NMR (600 MHz, DMSO-d_6) spectrum of the new compound **6**



6

Fig. S67. ^{13}C NMR (600 MHz, DMSO-d_6) spectrum of the new compound **6**

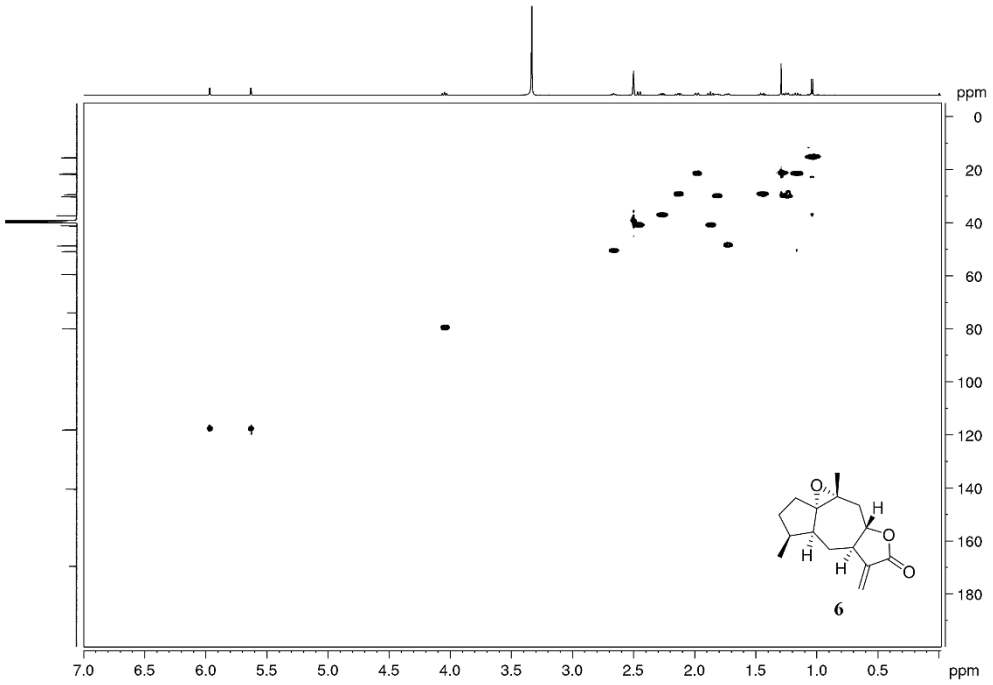


Fig. S68. HSQC (600 MHz, DMSO-d_6) spectrum of the new compound **6**

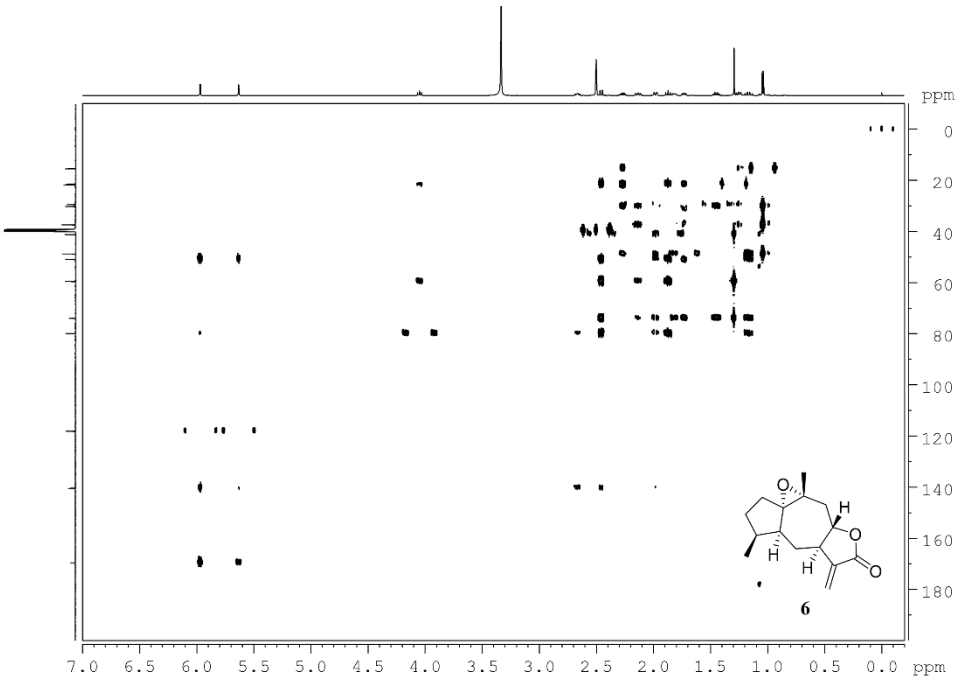


Fig. S69. HMBC (600 MHz, DMSO-d_6) spectrum of the new compound **6**

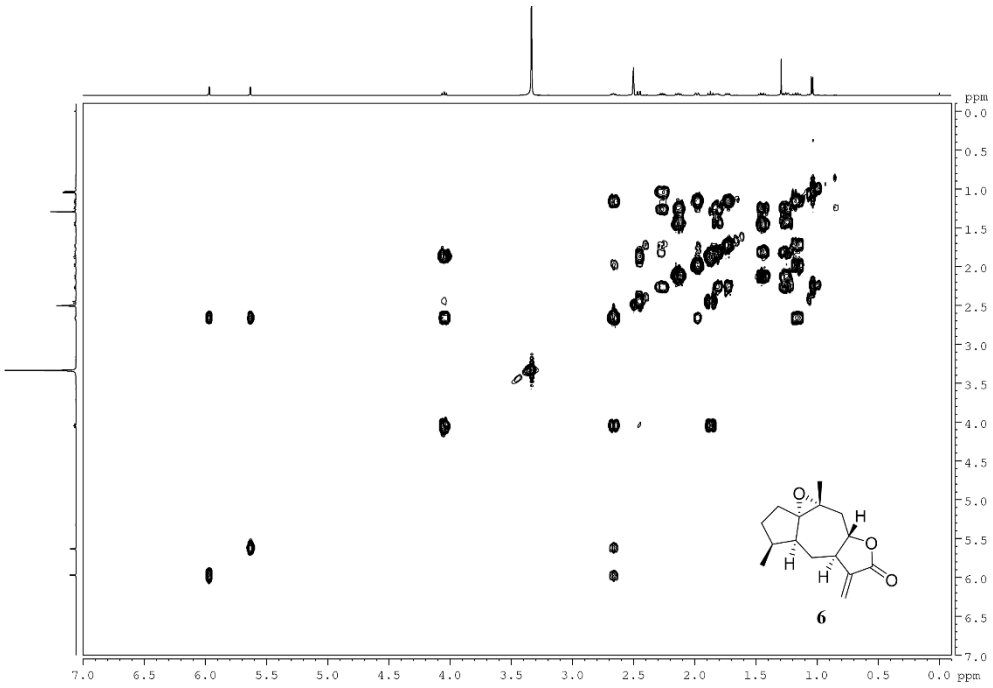


Fig. S70. ^{1}H-^{1}H COSY (600 MHz, DMSO-d_6) spectrum of the new compound **6**

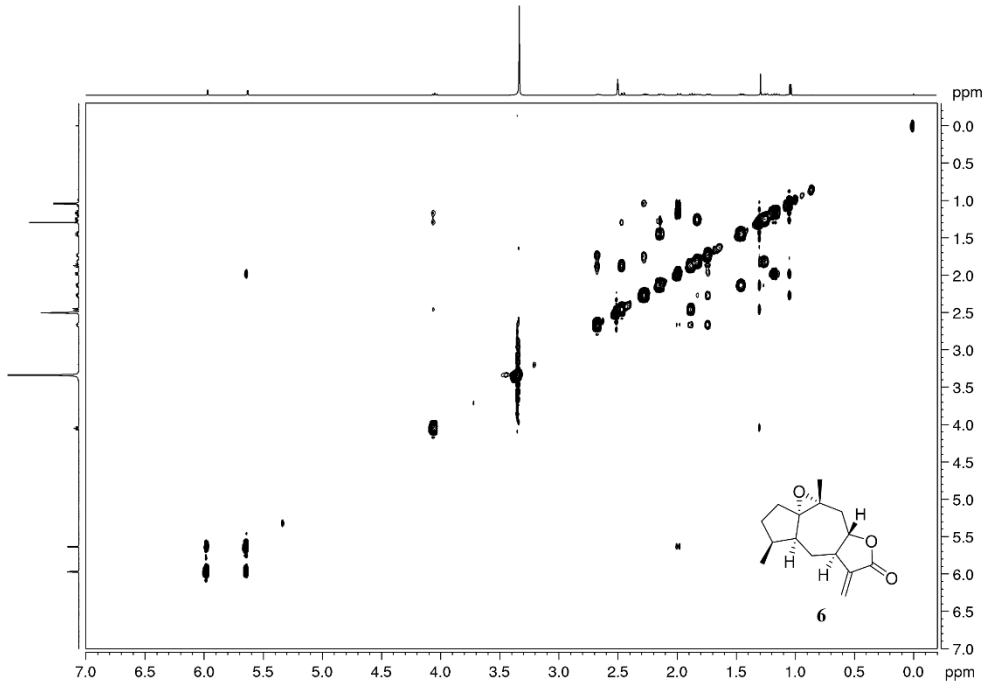


Fig. S71. NOESY (600 MHz, DMSO-d_6) spectrum of the new compound **6**

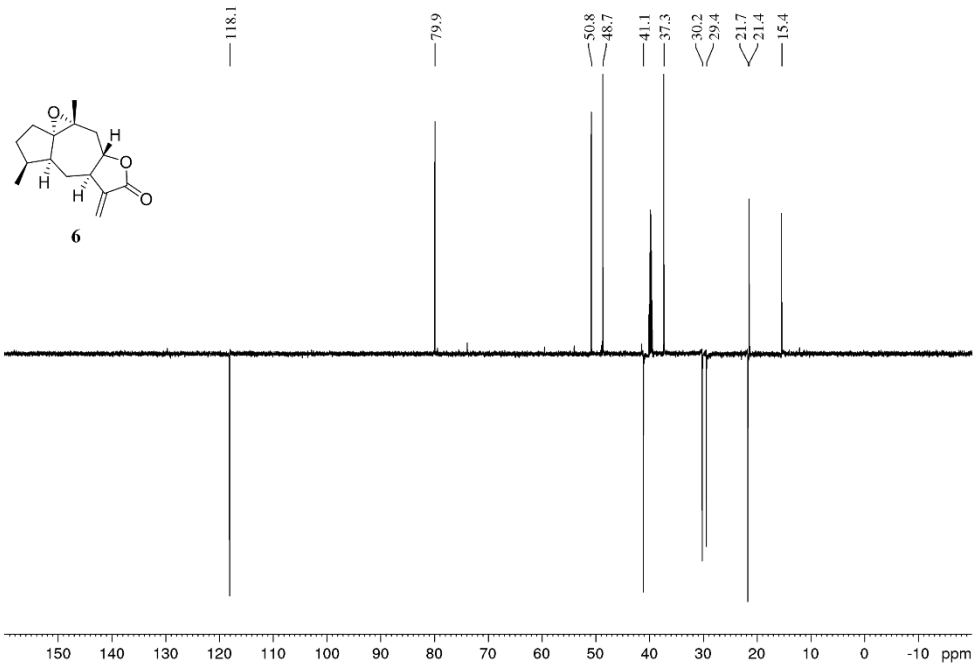
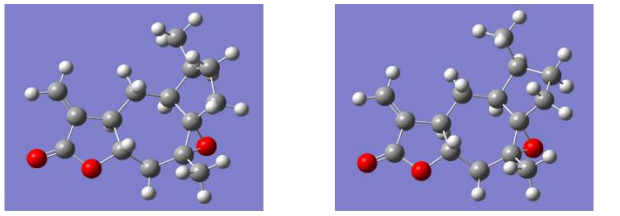


Fig. S72. DEPT (600 MHz, DMSO-d_6) spectrum of the new compound **6**



6-1 (98.98%)
Energy：-809.5318111 hartree

6-2 (1.02%)
Energy：-809.5274891 hartree

Fig. S73. Most stable conformers of the new compound **6** in solvated model calculations at the B3LYP/6-311++G (2d, p) level in ECD calculation

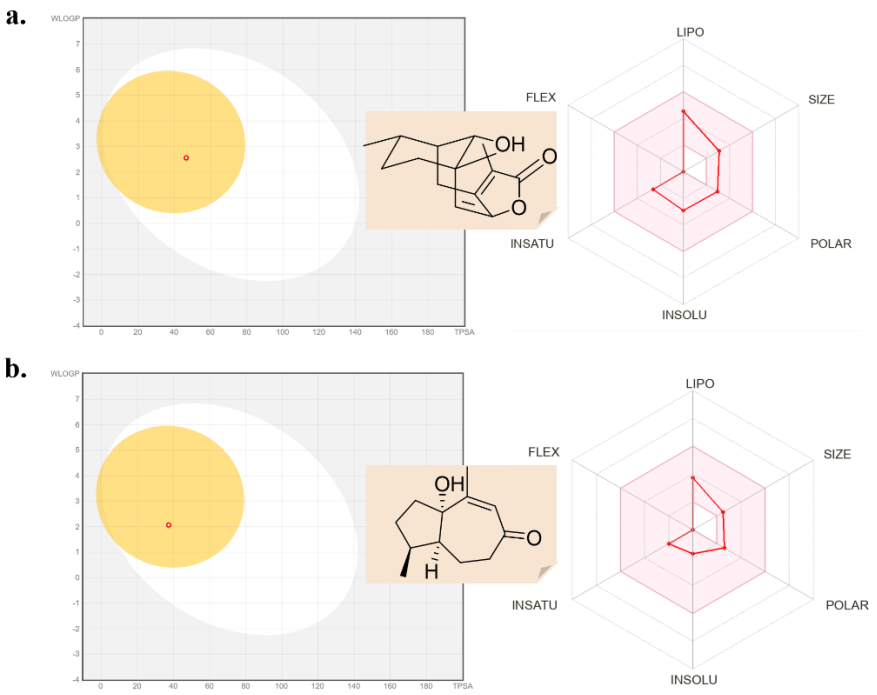


Fig. S74. The BOILED-Egg plot and the Bioavailability Radar plot of **2** (**a**) and **3** (**b**). The BOILED-Egg allows for intuitive evaluation of passive gastrointestinal absorption and brain penetration in function of the position of the molecules in the WLOGP-versus-TPSA referential. The white region is for high probability of passive absorption by the gastrointestinal tract, and the yellow region (yolk) is for high probability of brain penetration. Yolk and white areas are not mutually exclusive. In addition the points are colored in blue if predicted as actively effluxed by P-gp (PGP+) and in red if predicted as non-substrate of P-gp (PGP−). The Bioavailability Radar enables a first glance at the drug-likeness of a molecule and the pink area represents the optimal range for each properties.