

Supporting Information

Jatrophane diterpenoids from *Euphorbia peplus* Linn. as activators of autophagy and inhibit Tau pathology

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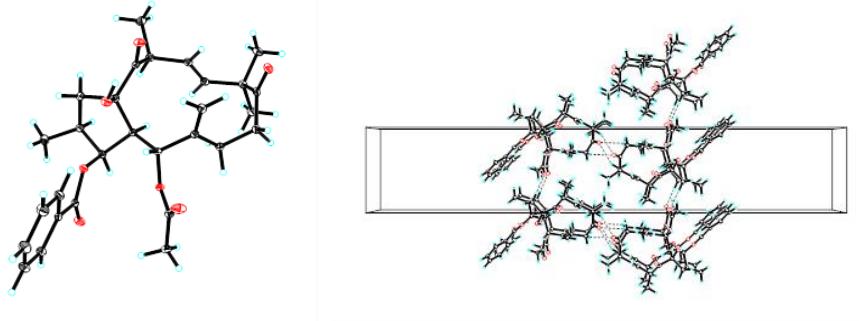
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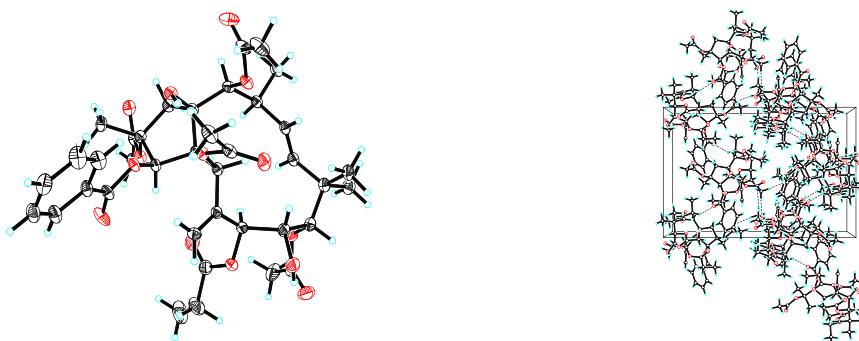
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S1. X-ray Crystallographic Analysis of Compound **1**.



The crystal structure and absolute configuration of **1** were determined by single crystal X-ray diffraction analysis. Crystal data for compound **1**: $C_{29}H_{36}O_7$, $M = 496.58$, $a = 6.36920(10)$ Å, $b = 8.7069(2)$ Å, $c = 48.6471(11)$ Å, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 90^\circ$, $V = 2697.77(10)$ Å³, $T = 100$. (2) K, space group P212121, $Z = 4$, $\mu(\text{Cu K}\alpha) = 0.706$ mm⁻¹, 43259 reflections measured, 5322 independent reflections ($R_{\text{int}} = 0.0351$). The final R_1 values were 0.0258 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.0662 ($I > 2\sigma(I)$). The final R_1 values were 0.0262 (all data). The final $wR(F^2)$ values were 0.0666 (all data). The goodness of fit on F^2 was 1.029. Flack parameter = 0.05(3). CCDC-2224640 (**1**), contain the supplementary crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre (<http://www.ccdc.cam.ac.uk/>).

S2. X-ray Crystallographic Analysis of Compound **3**.



The crystal structure and absolute configuration of **3** were determined by single crystal X-ray diffraction analysis. Crystal data for compound **3**: $C_{38}H_{50}O_{14}$, $M = 730.78$, $a = 11.7516(5)$ Å, $b = 15.0592(7)$ Å, $c = 22.2397(10)$ Å, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 90^\circ$, $V = 3935.8(3)$ Å³, $T = 100$. (2) K, space group P212121, $Z = 4$, $\mu(\text{Cu K}\alpha) = 0.783$ mm⁻¹, 38614 reflections measured, 7782 independent

reflections ($R_{\text{int}} = 0.1520$). The final R_1 values were 0.0621 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.1548 ($I > 2\sigma(I)$). The final R_1 values were 0.0891 (all data). The final $wR(F^2)$ values were 0.1790 (all data). The goodness of fit on F^2 was 1.046. Flack parameter = -0.10(18). CCDC-2224638 (**3**), contain the supplementary crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre (<http://www.ccdc.cam.ac.uk/>).

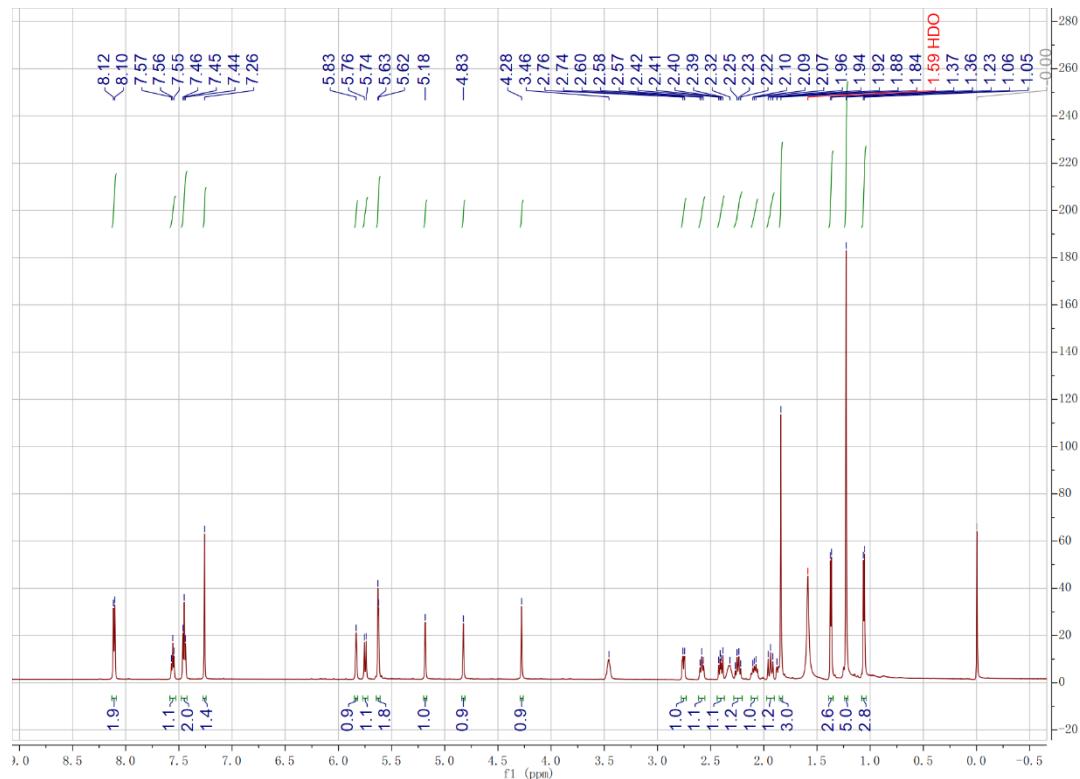


Figure S1. ^1H NMR spectrum of euphjatrophane A (**1**)

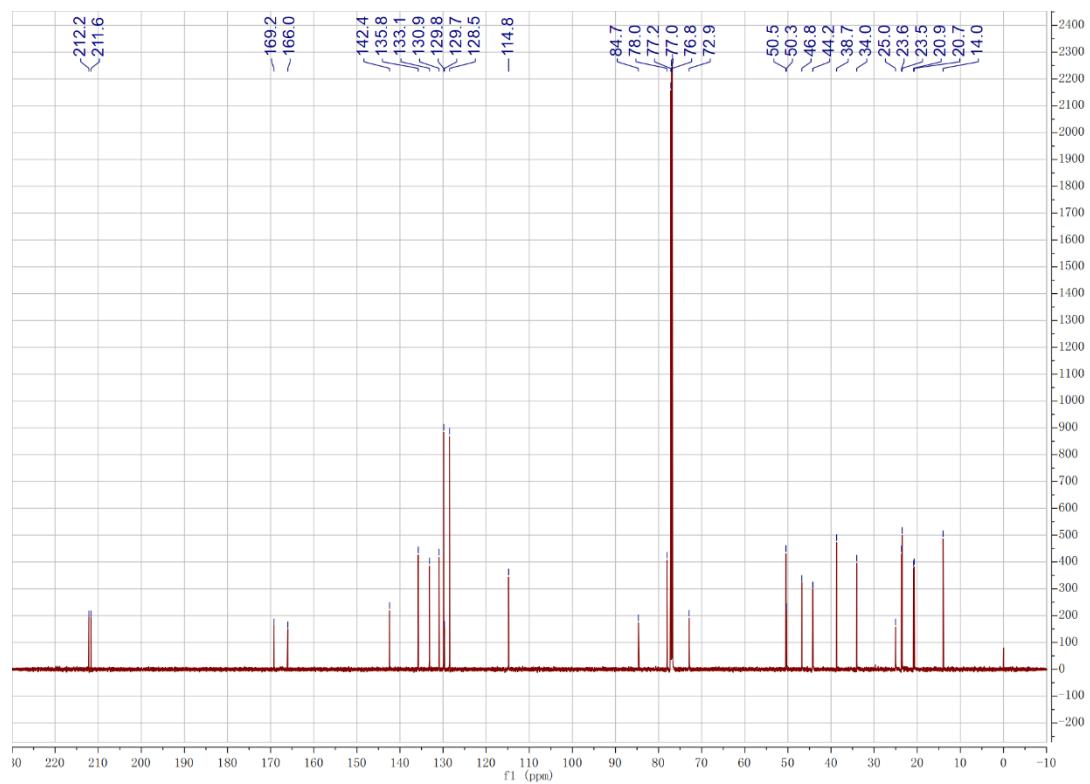


Figure S2. ^{13}C NMR spectrum of euphjatrophane A (**1**)

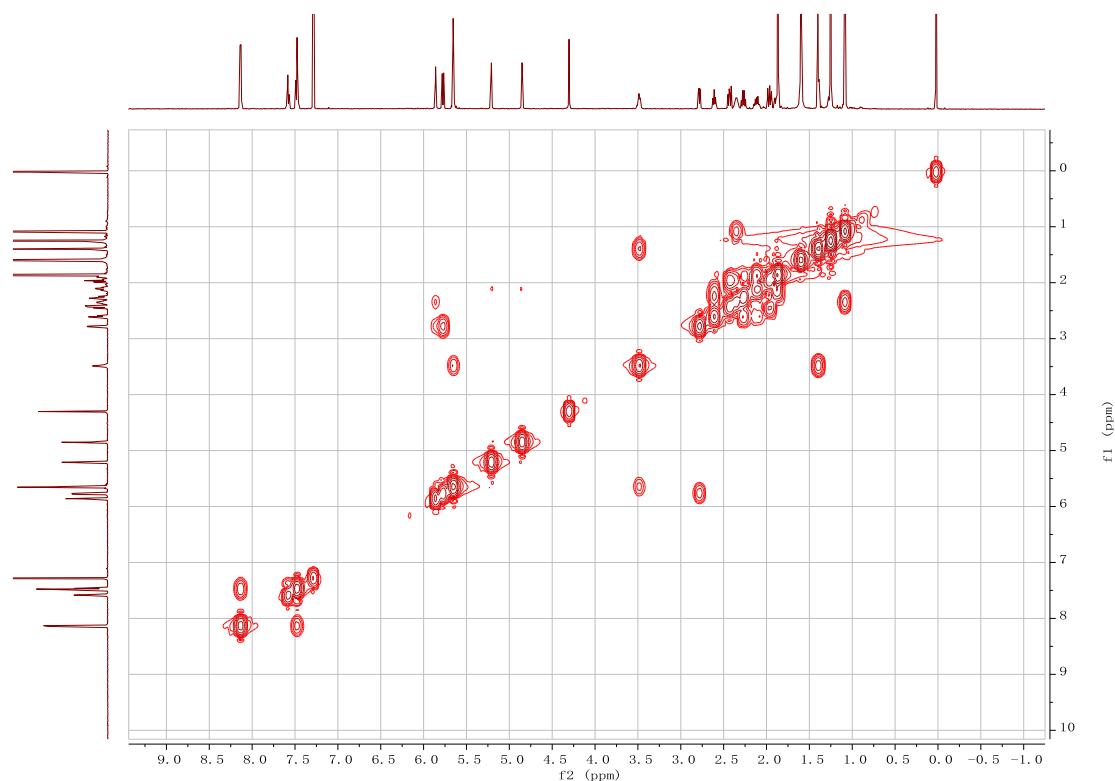


Figure S3. ^1H - ^1H COSY spectrum of euphjatrophane A (**1**)

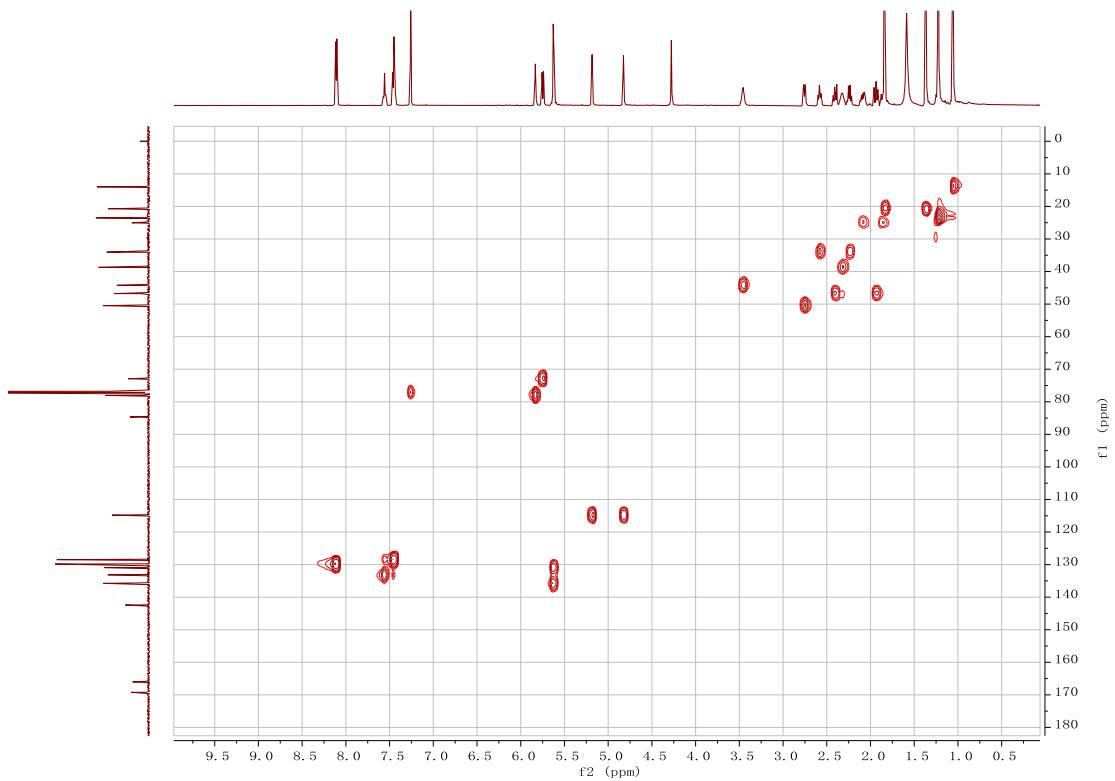


Figure S4. HSQC spectrum of euphjatrophane A (**1**)

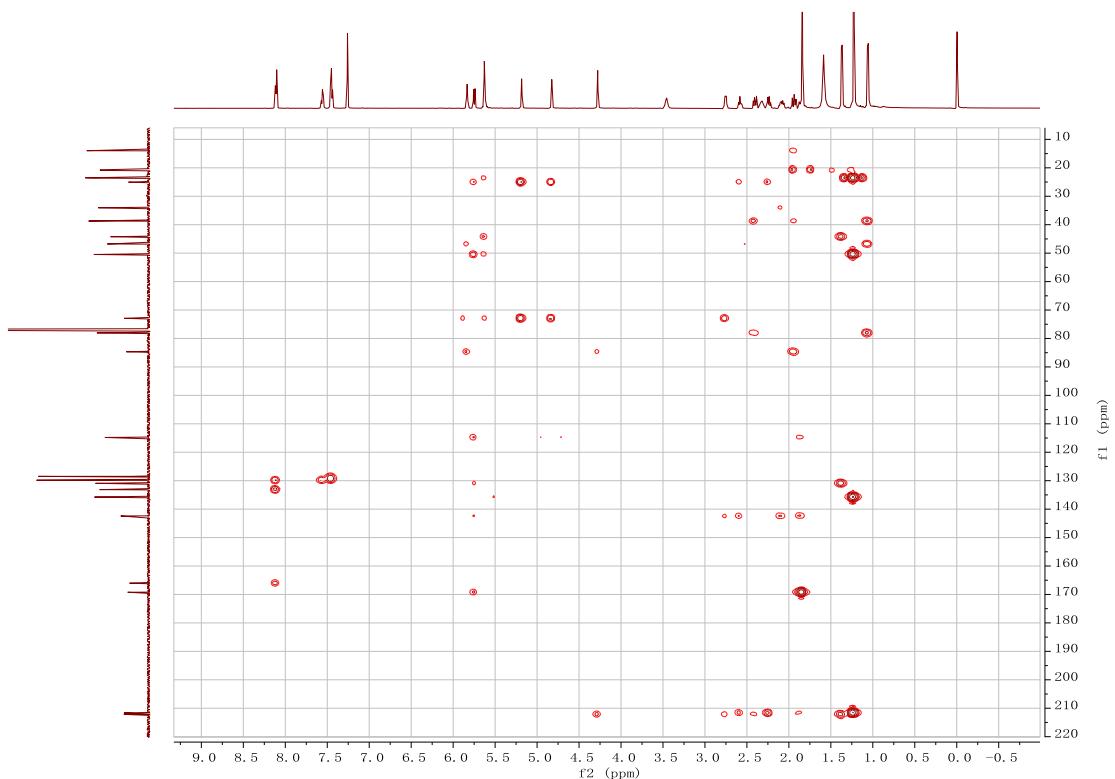


Figure S5. HMBC spectrum of euphjatrophane A (**1**)

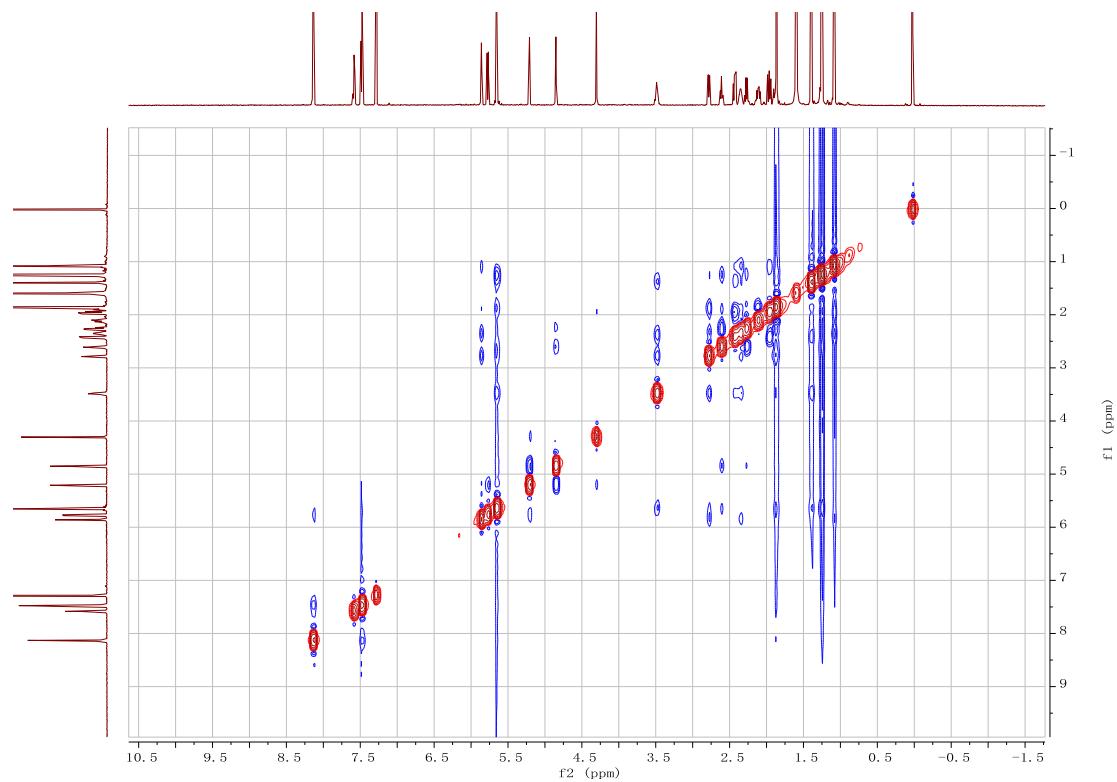


Figure S6. ROESY spectrum of euphatropane A (**1**)

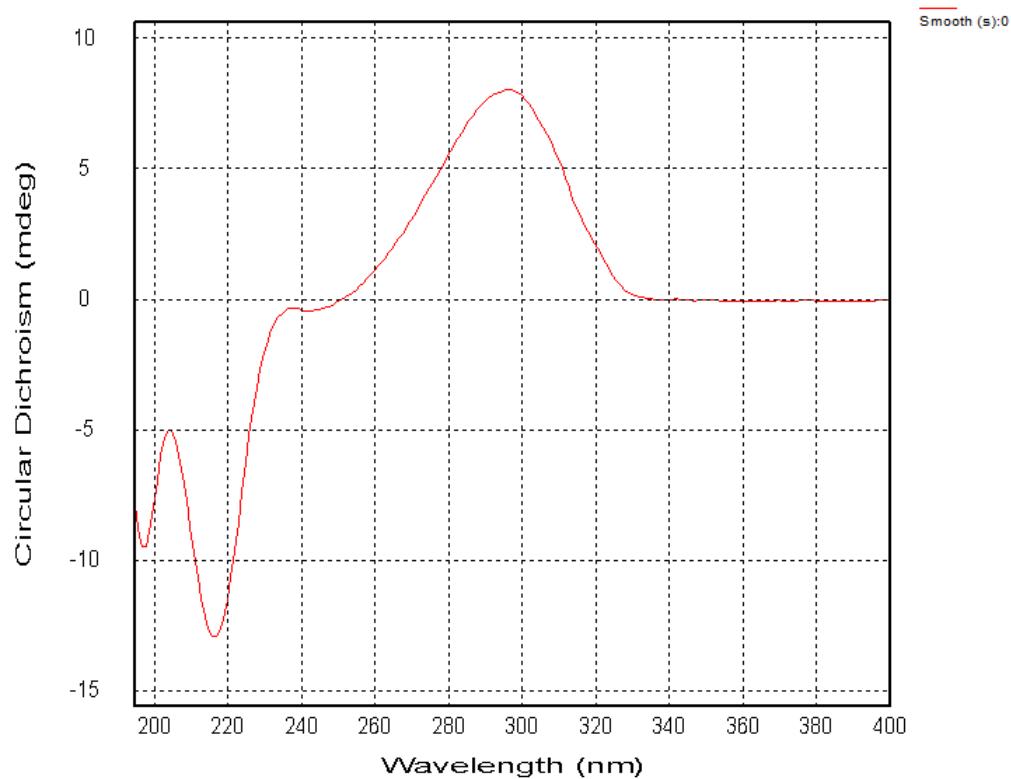


Figure S7. CD spectrum of euphatropane A (**1**)

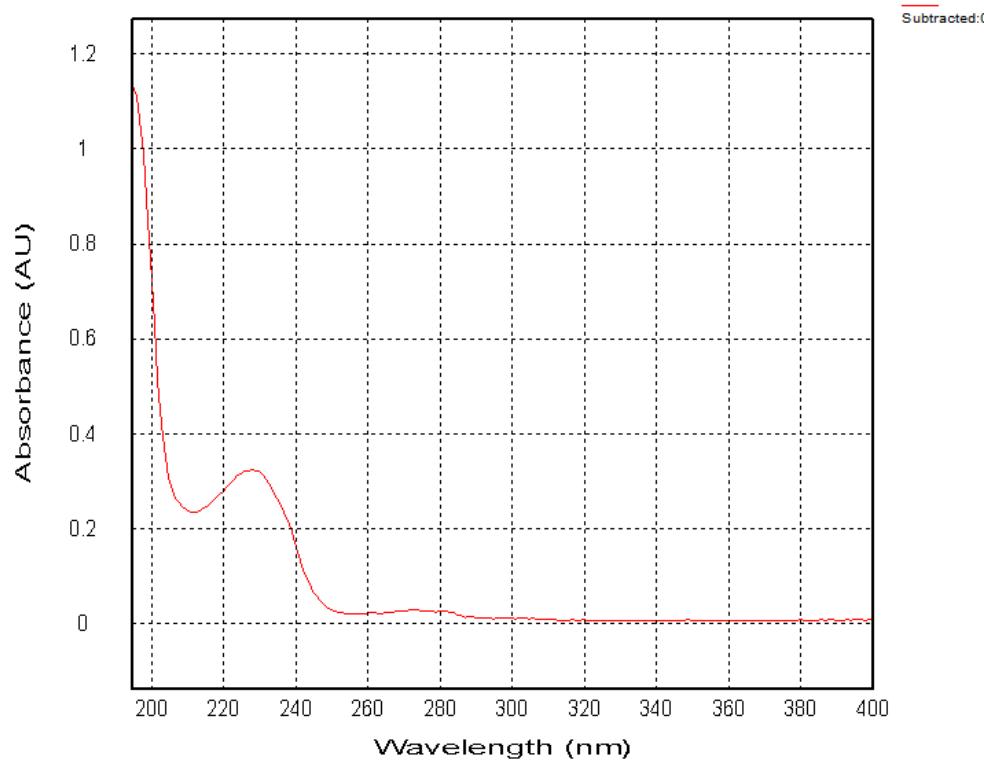


Figure S8. UV spectrum of euphjatrophane A (**1**)

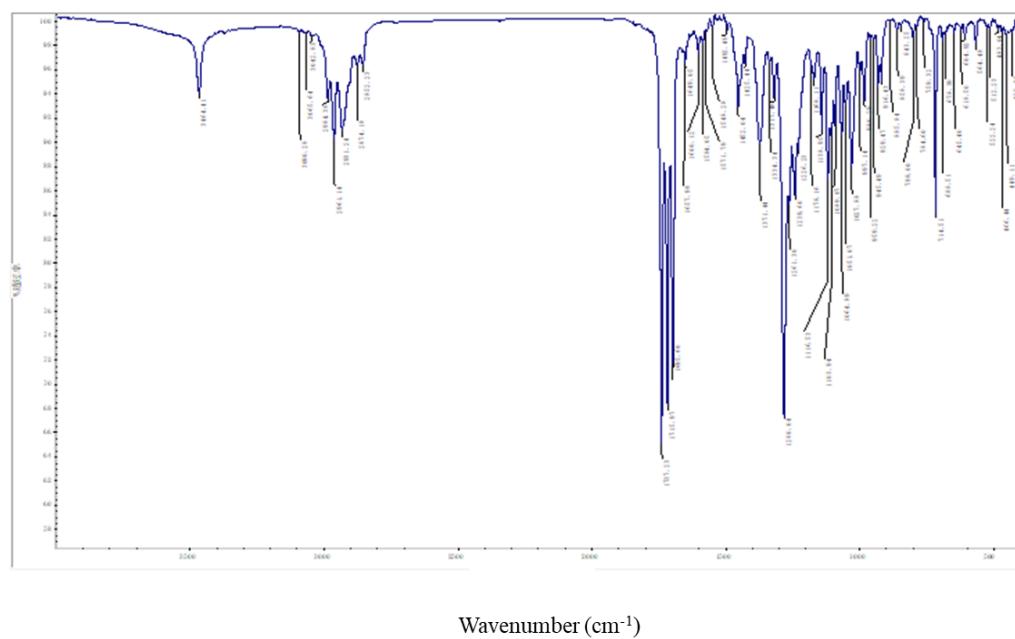
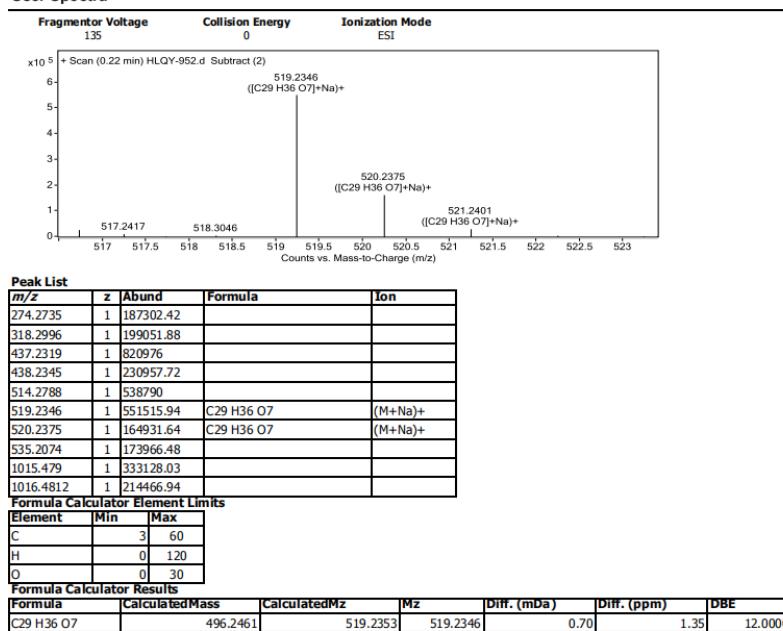


Figure S9. IR spectrum of euphjatrophane A (**1**)

Qualitative Analysis Report

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Sample Type	Sample	Position	P1-A3
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IRM Calibration Status	Success	DA Method	Default.m
Comment			
Sample Group		Info.	
Acquisition SW	6200 series TOF/6500 series		
Version	Q-TOF B.05.01 (B5125.2)		

User Spectra



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Figure S10. (+)-HRESIMS spectrum of euphjatrophane A (**1**)

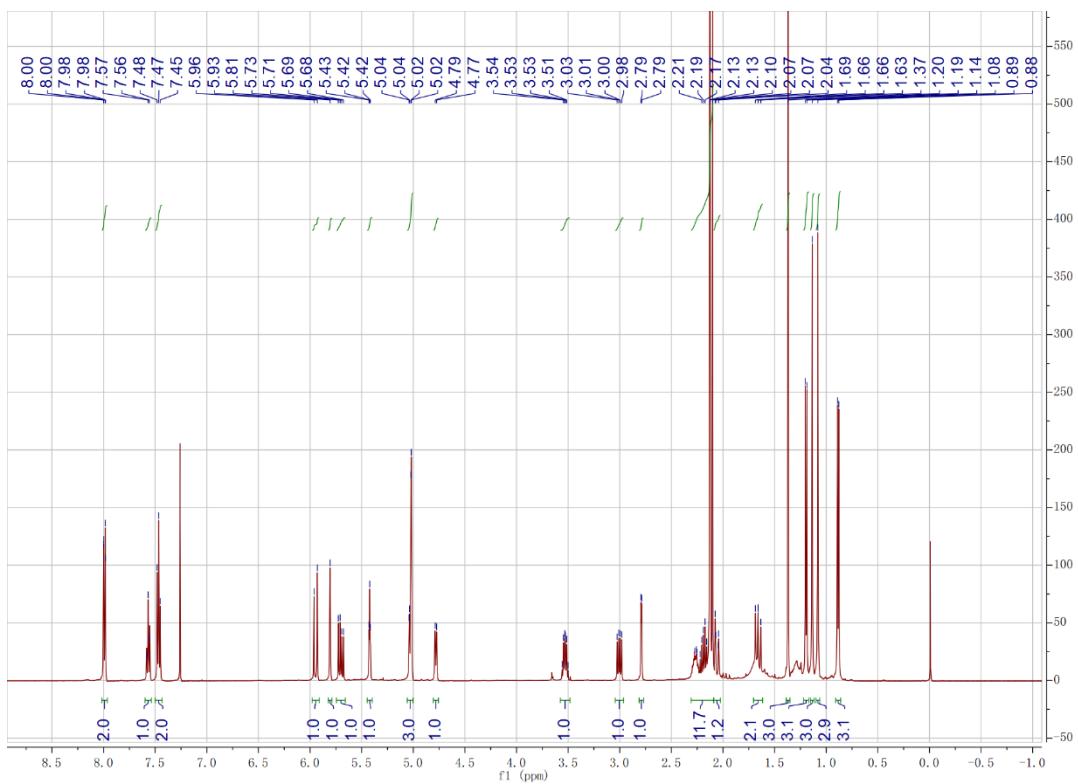


Figure S11. ¹H NMR spectrum of euphjatrophane B (2)

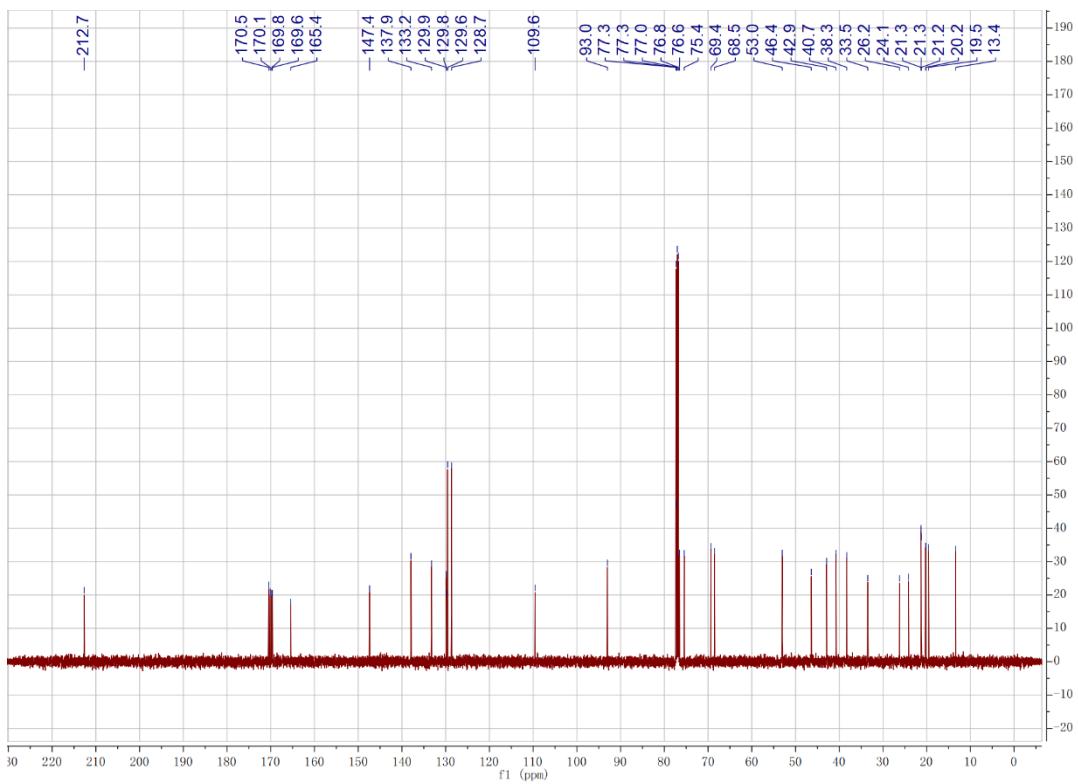


Figure S12. ¹³C NMR spectrum of euphjatrophane B (2)

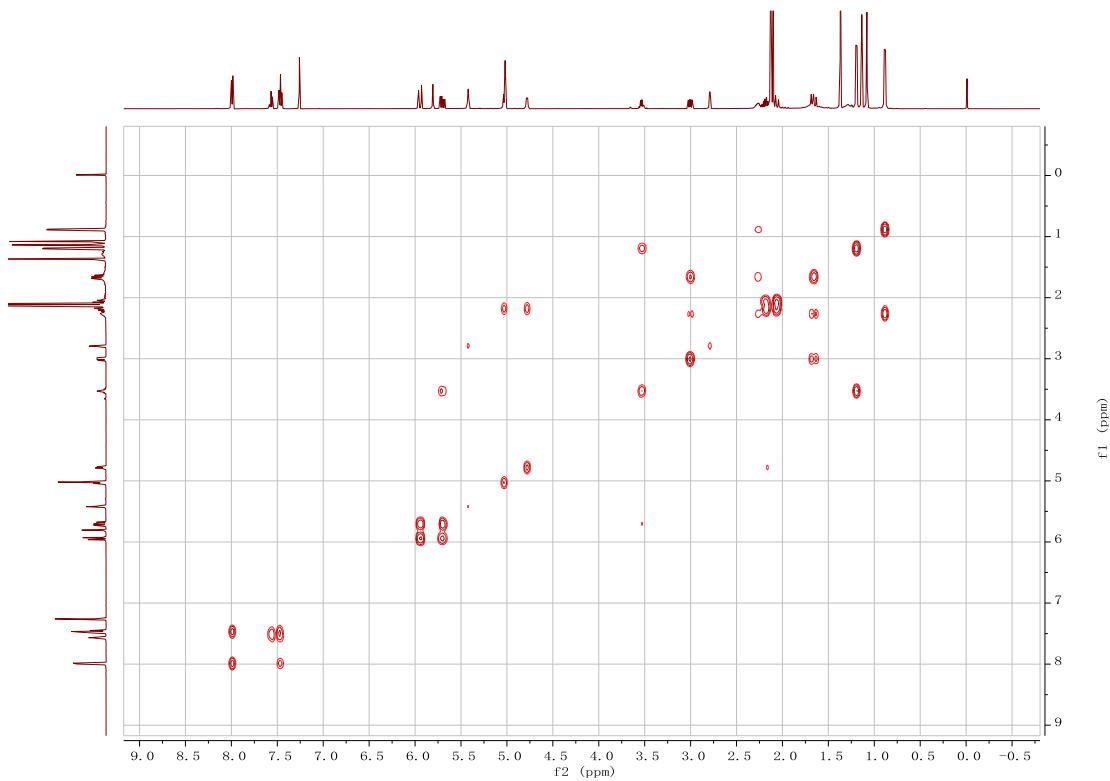


Figure S13. ¹H-¹H COSY spectrum of euphjatrophane B (2)

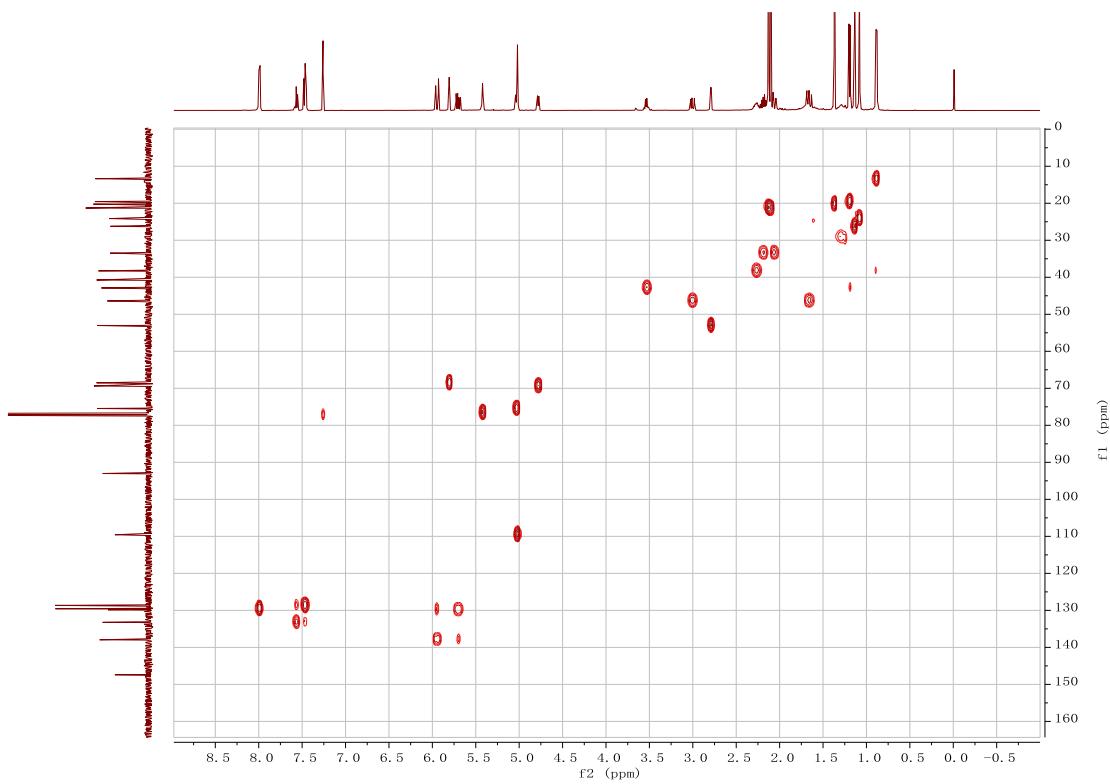


Figure S14. HSQC spectrum of euphjatrophane B (2)

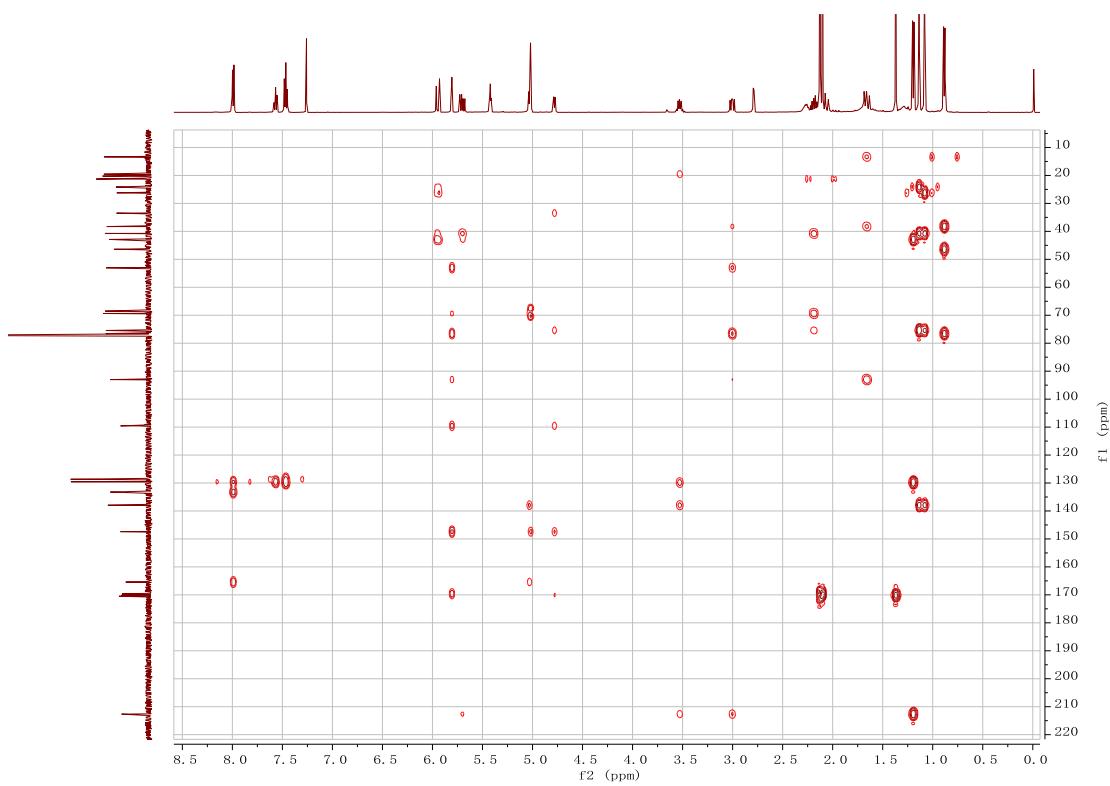


Figure S15. HMBC spectrum of euphatropane B (2)

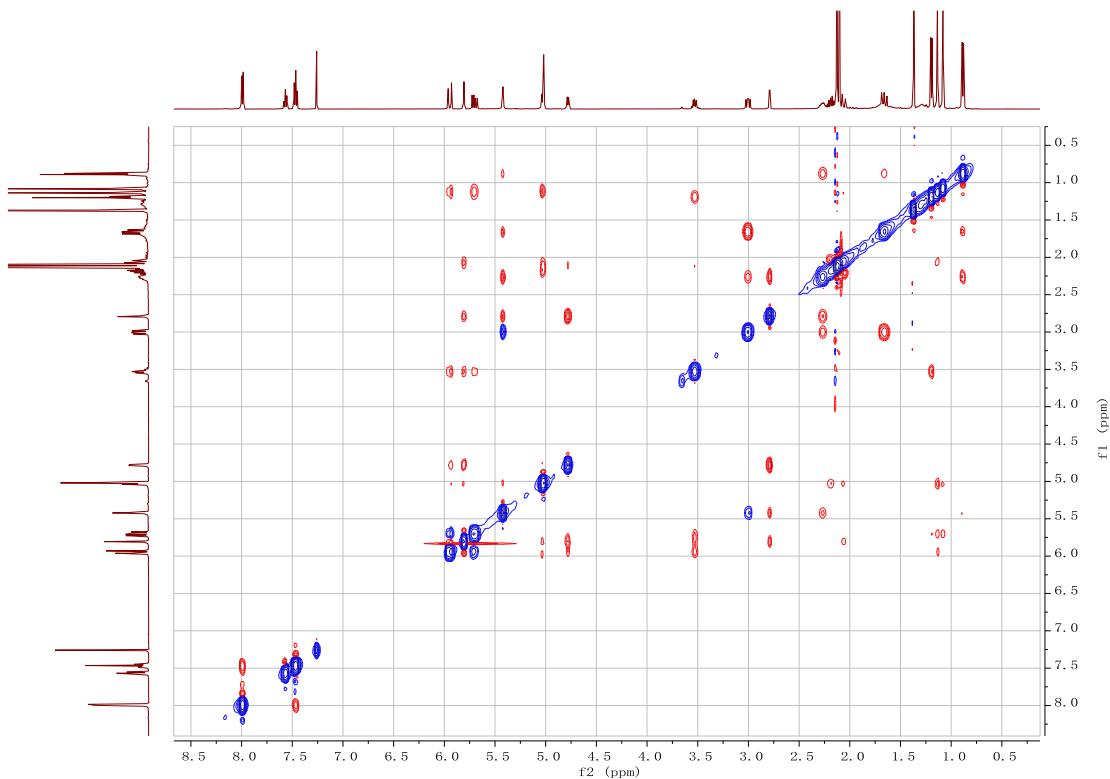


Figure S16. ROESY spectrum of euphatropane B (2)

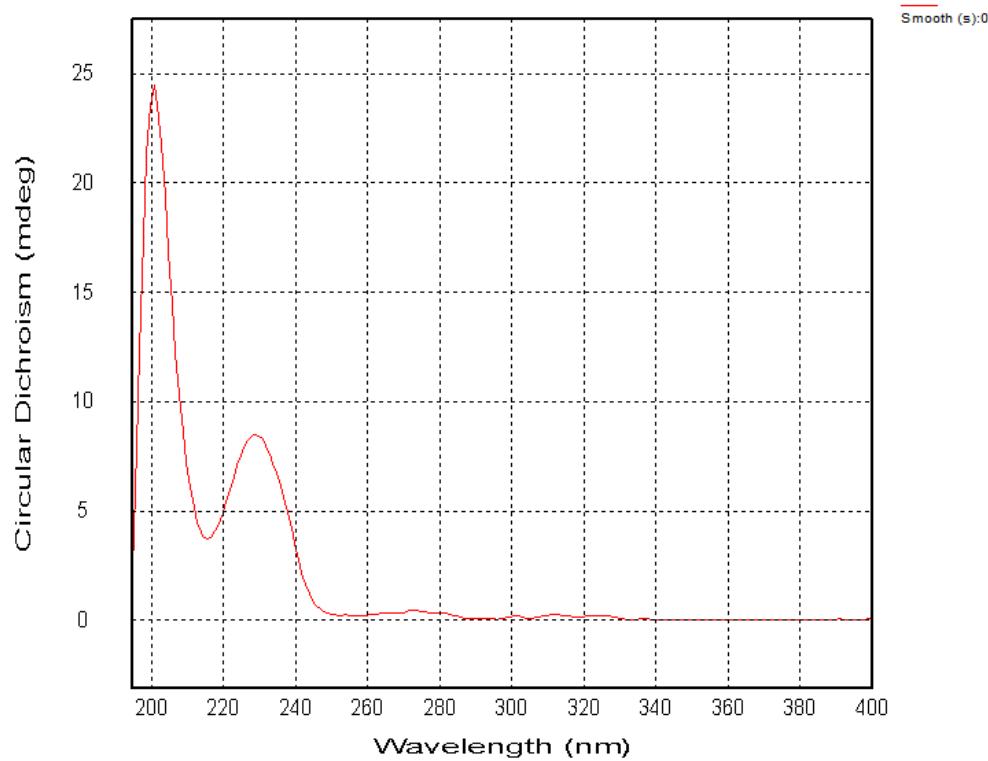


Figure S17. CD spectrum of euphatropane B (**2**)

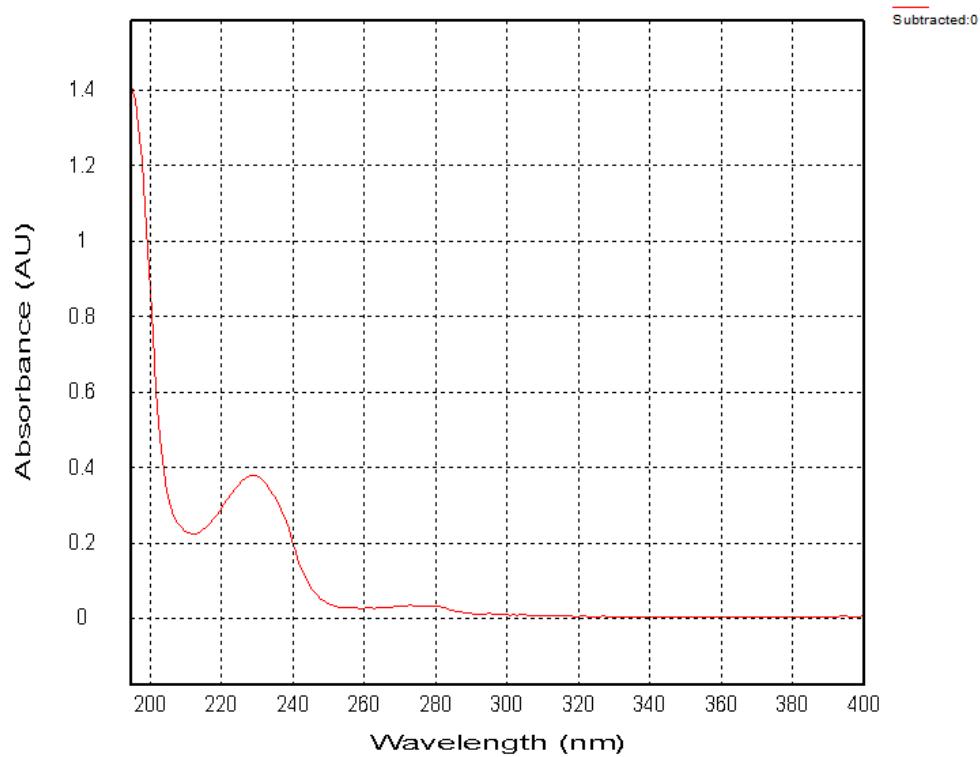


Figure S18. UV spectrum of euphatropane B (**2**)

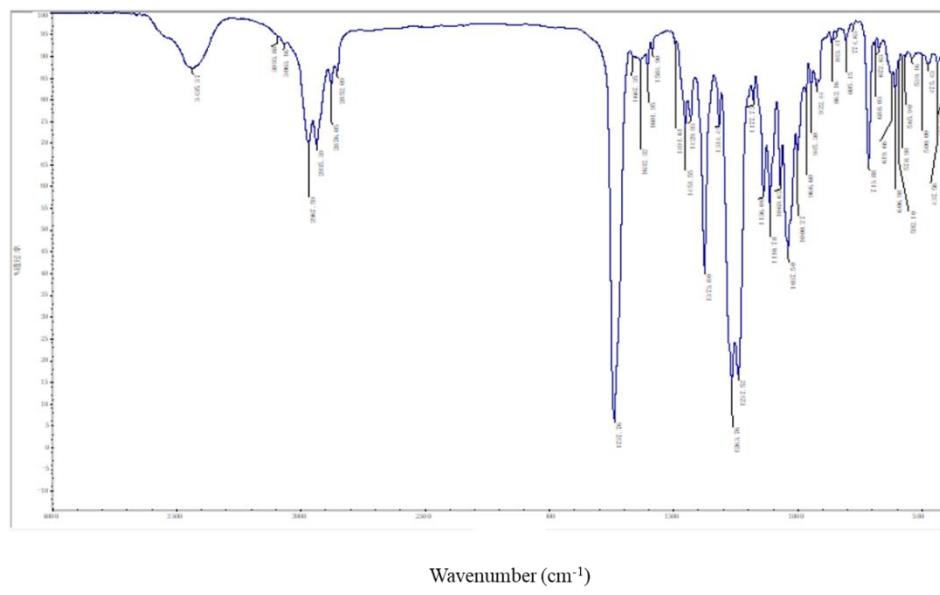
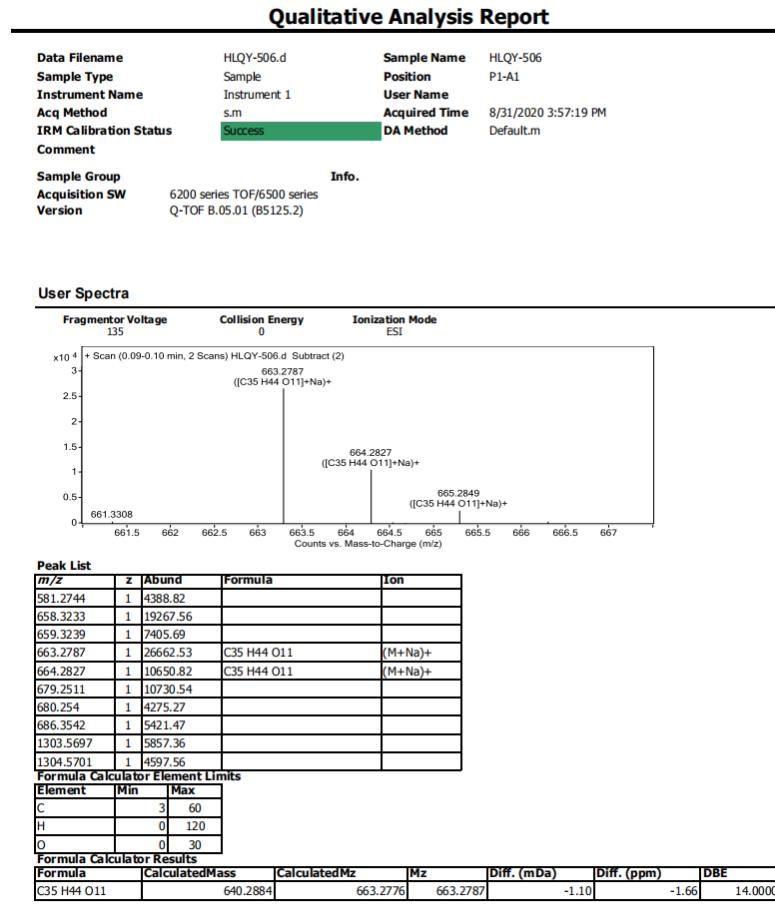


Figure S19. IR spectrum of euphjatrophane B (2)



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Figure S20. (+)-HRESIMS spectrum of euphjatrophane B (2)

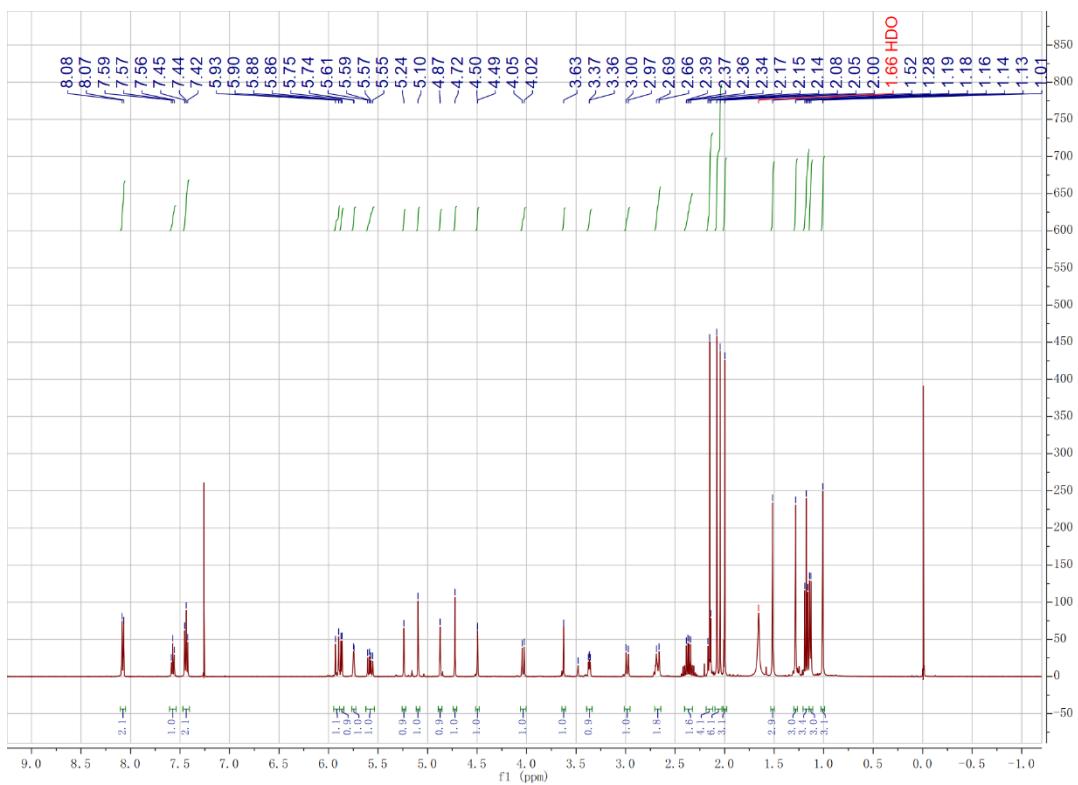


Figure S21. ¹H NMR spectrum of euphepepluone G (3)

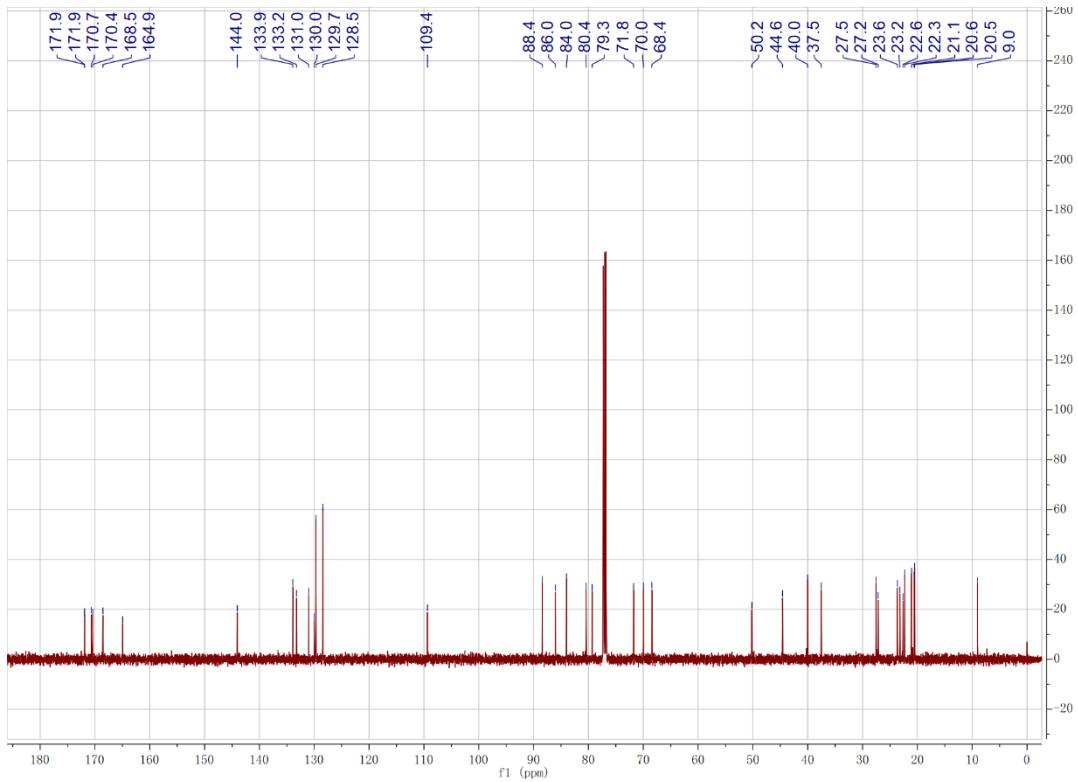


Figure S22. ¹³C NMR spectrum of euphepepluone G (3)

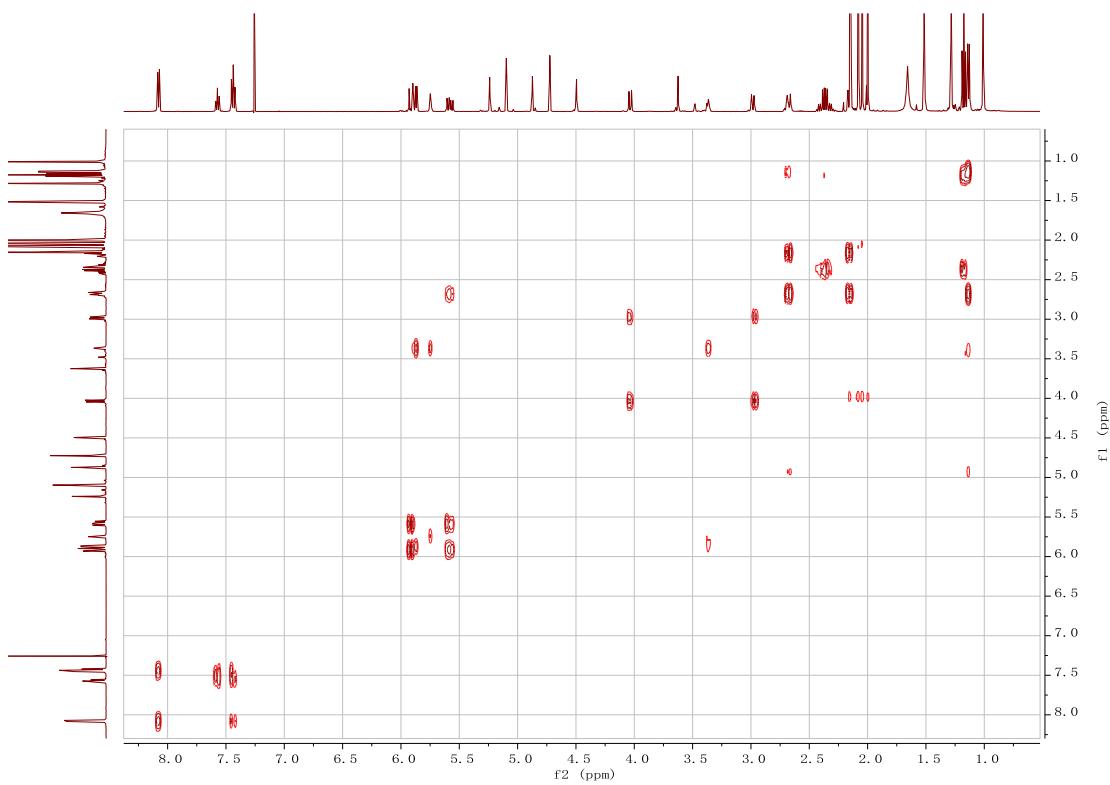


Figure S23. ¹H-¹H COSY spectrum of euphepepluone G (3)

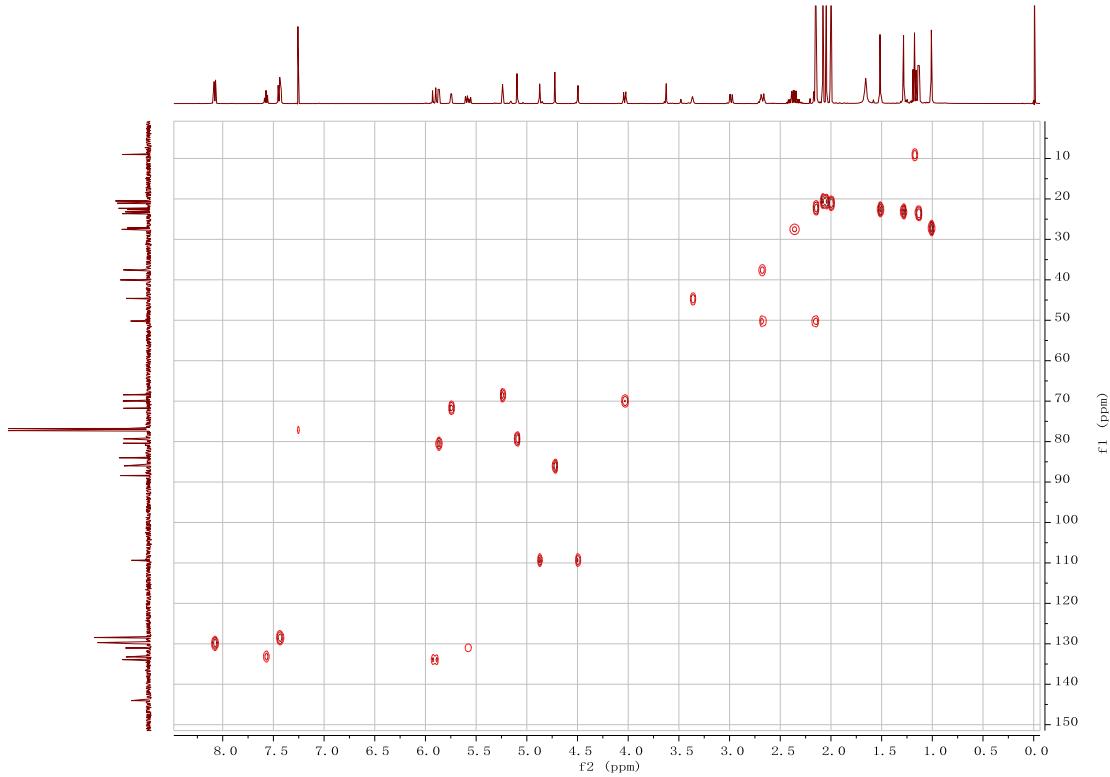


Figure S24. HSQC spectrum of euphepepluone G (3)

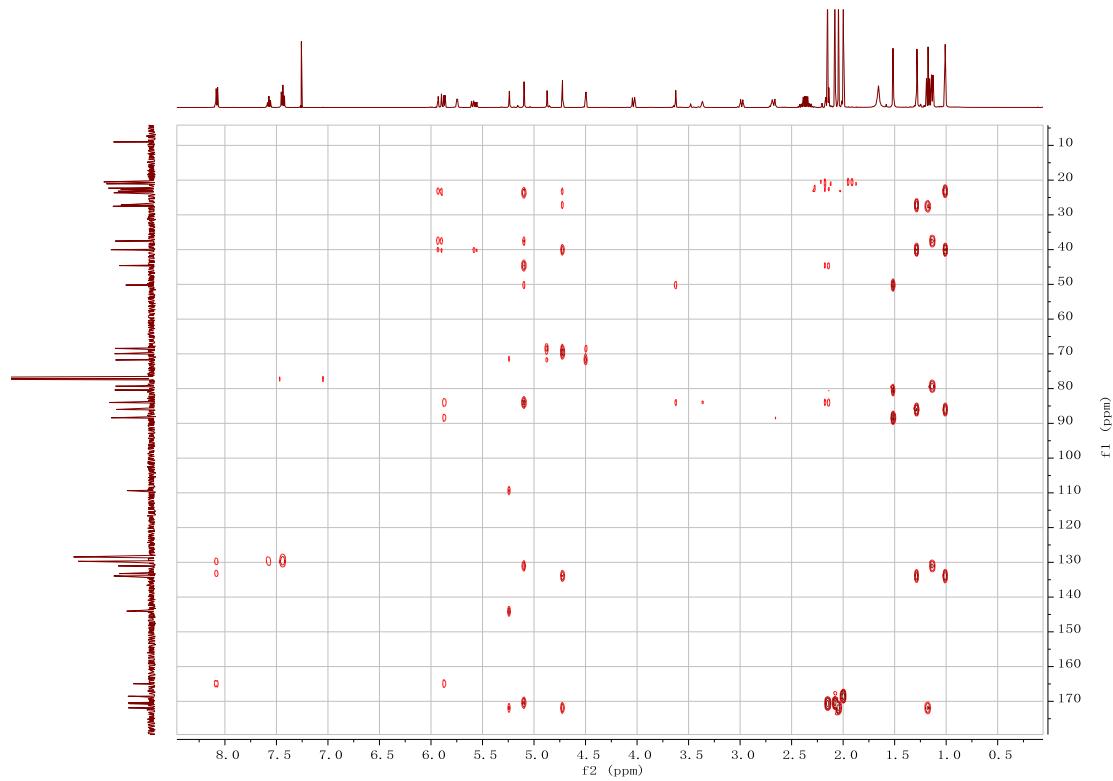


Figure S25. HMBC spectrum of euphepluone G (**3**)

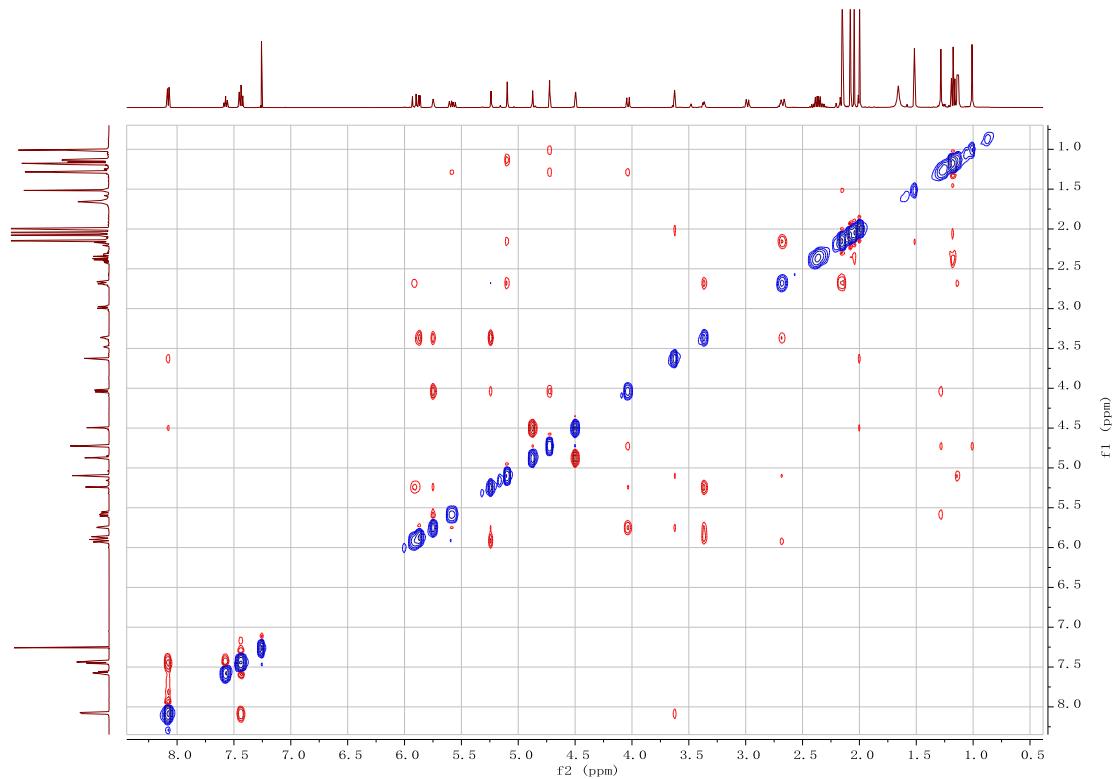


Figure S26. ROESY spectrum of euphepepluone G (**3**)

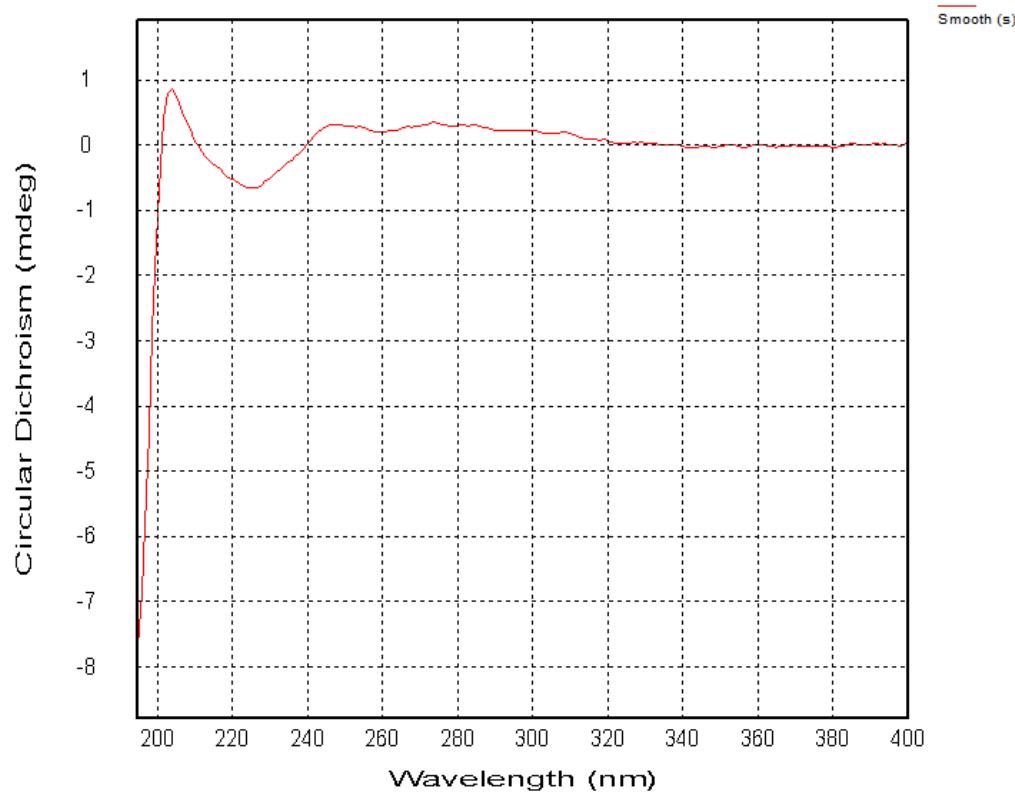


Figure S27. CD spectrum of euphepepluone G (3)

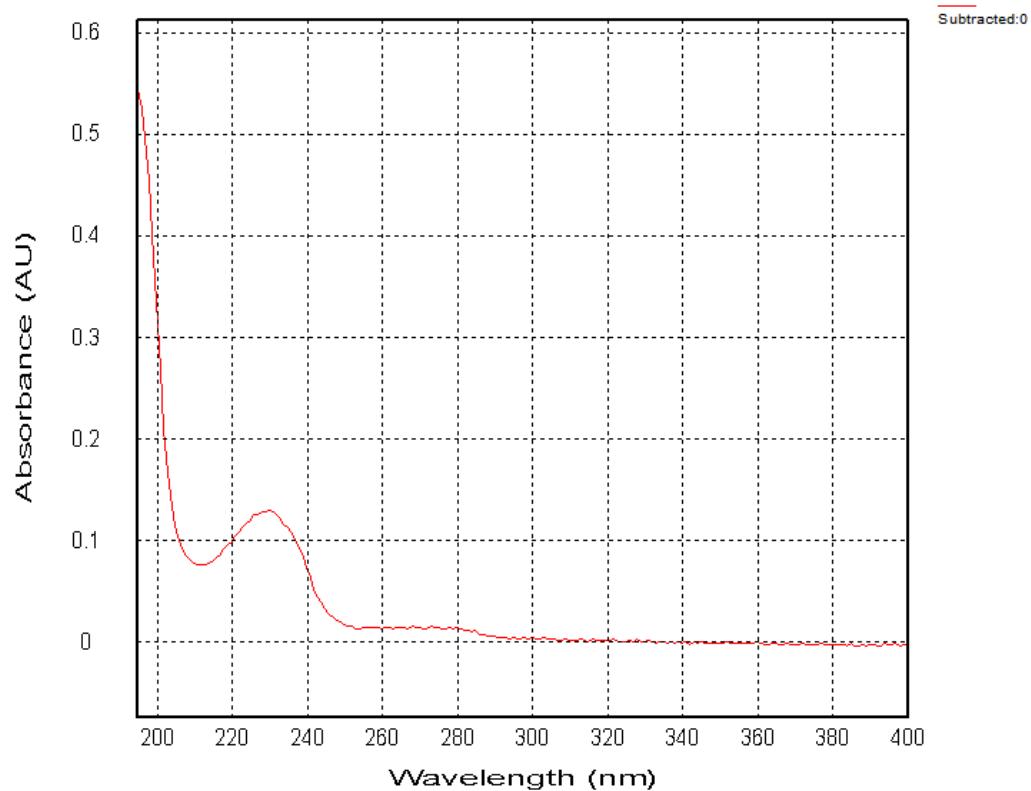


Figure S28. UV spectrum of euphepepluone G (3)

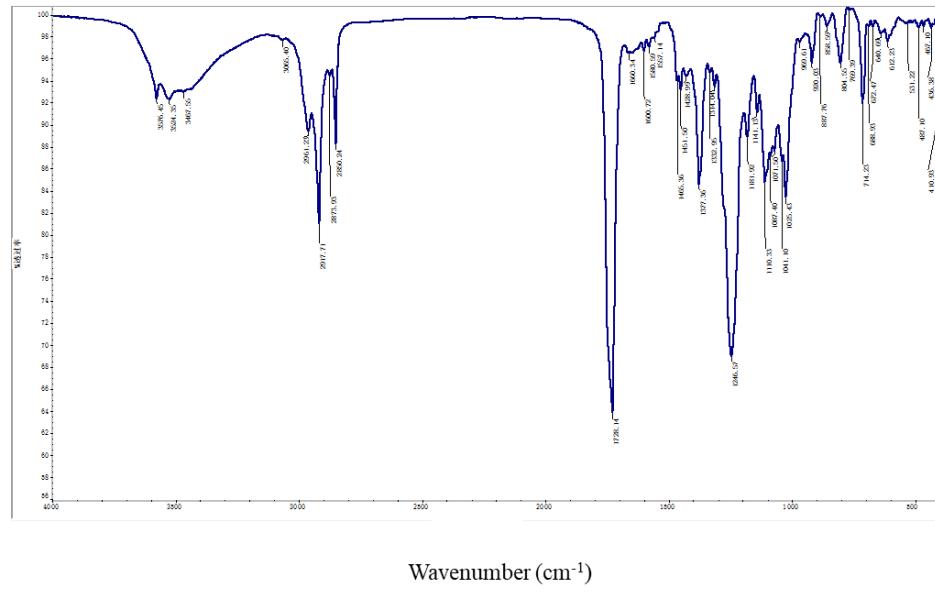


Figure S29. IR spectrum of euphepepluone G (3)

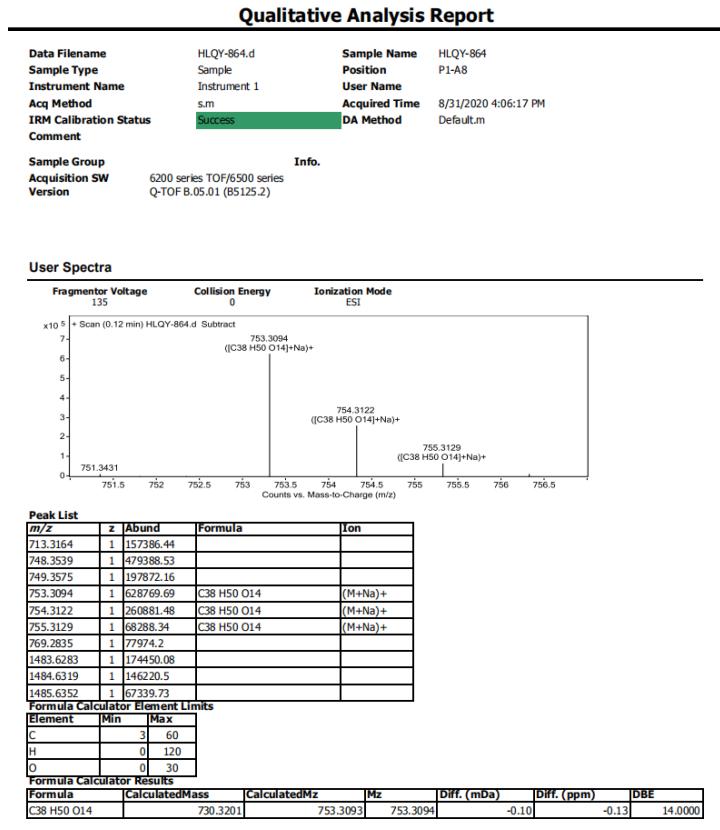


Figure S30. (+)-HRESIMS spectrum of euphepepluone G (3)



Figure S31. ¹H NMR spectrum of euphjatrophane C (4)

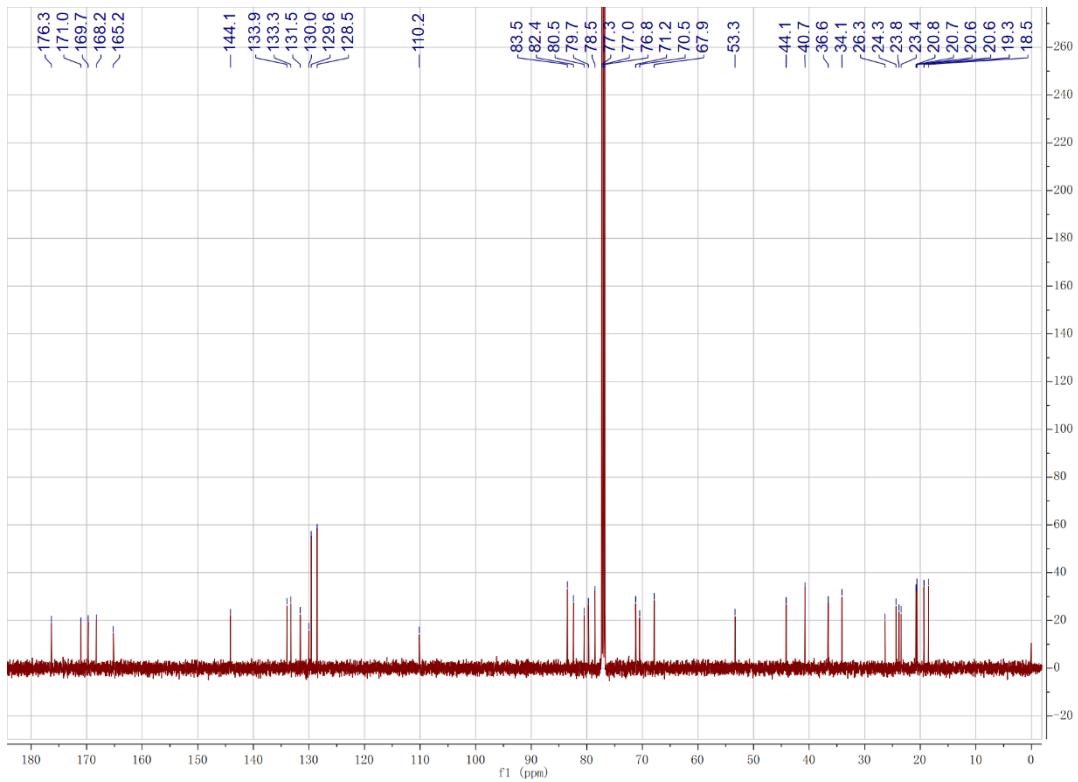


Figure S32. ¹³C NMR spectrum of euphjatrophane C (4)

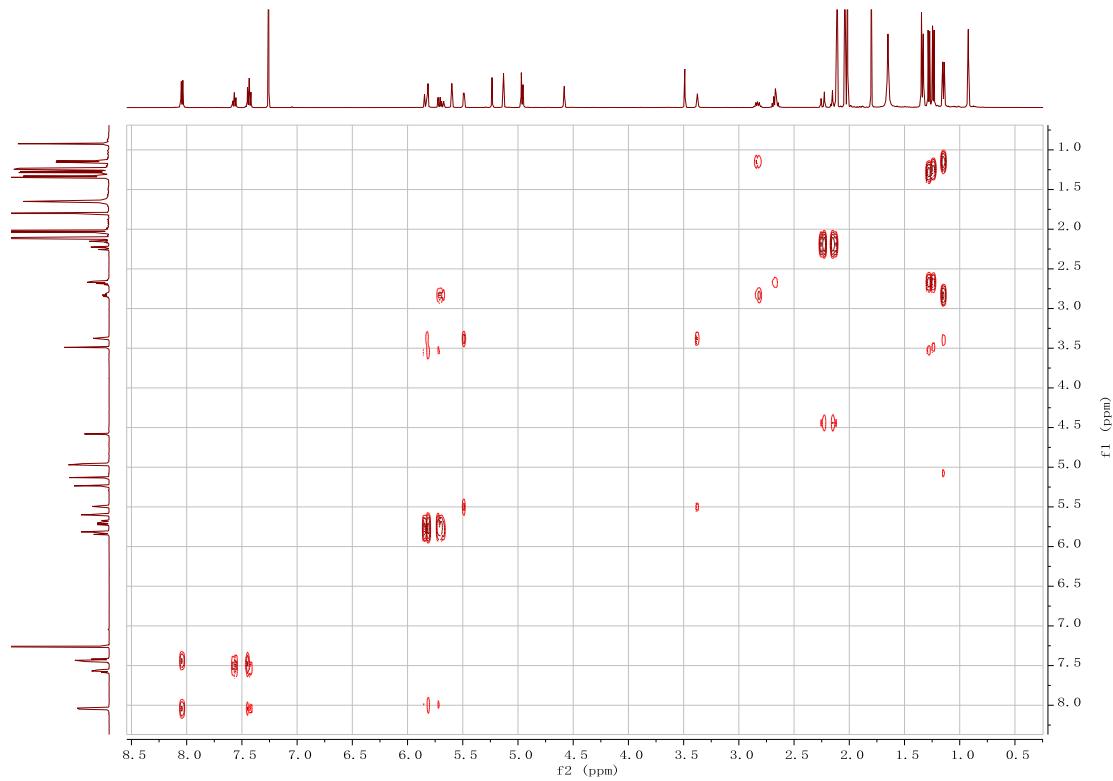


Figure S33. ^1H - ^1H COSY spectrum of euphjatrophane C (**4**)

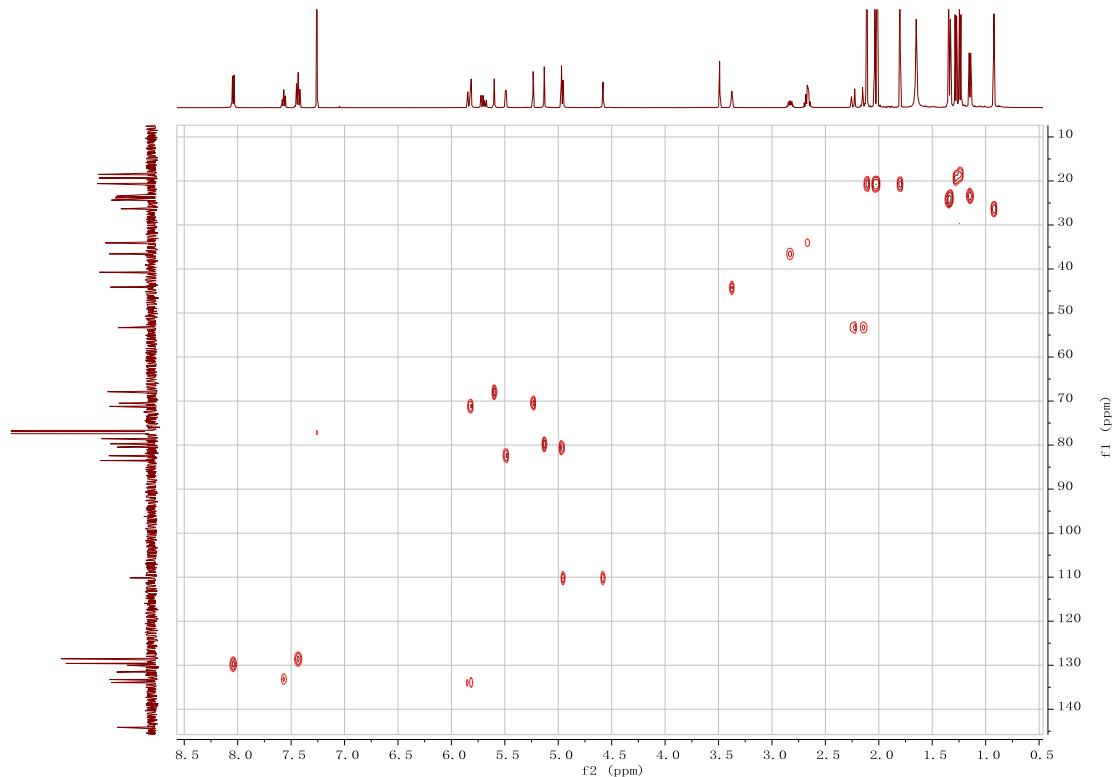


Figure S34. HSQC spectrum of euphjatrophane C (**4**)

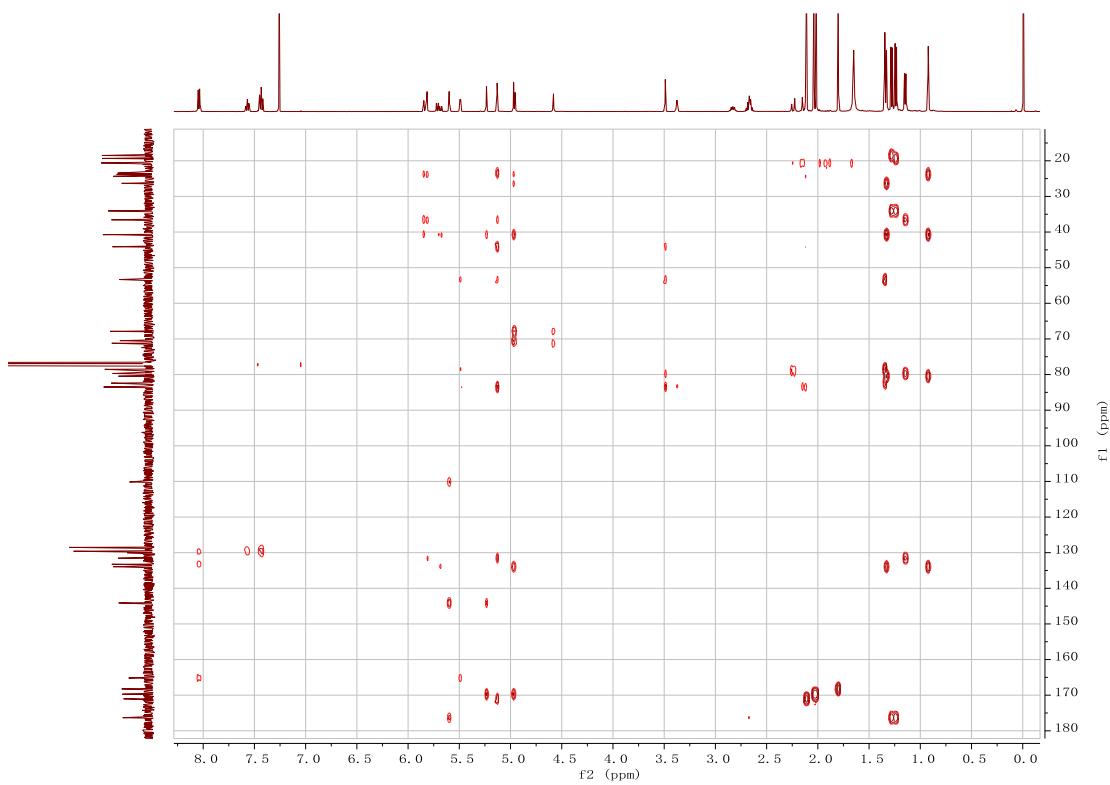


Figure S35. HMBC spectrum of euphatropane C (4)

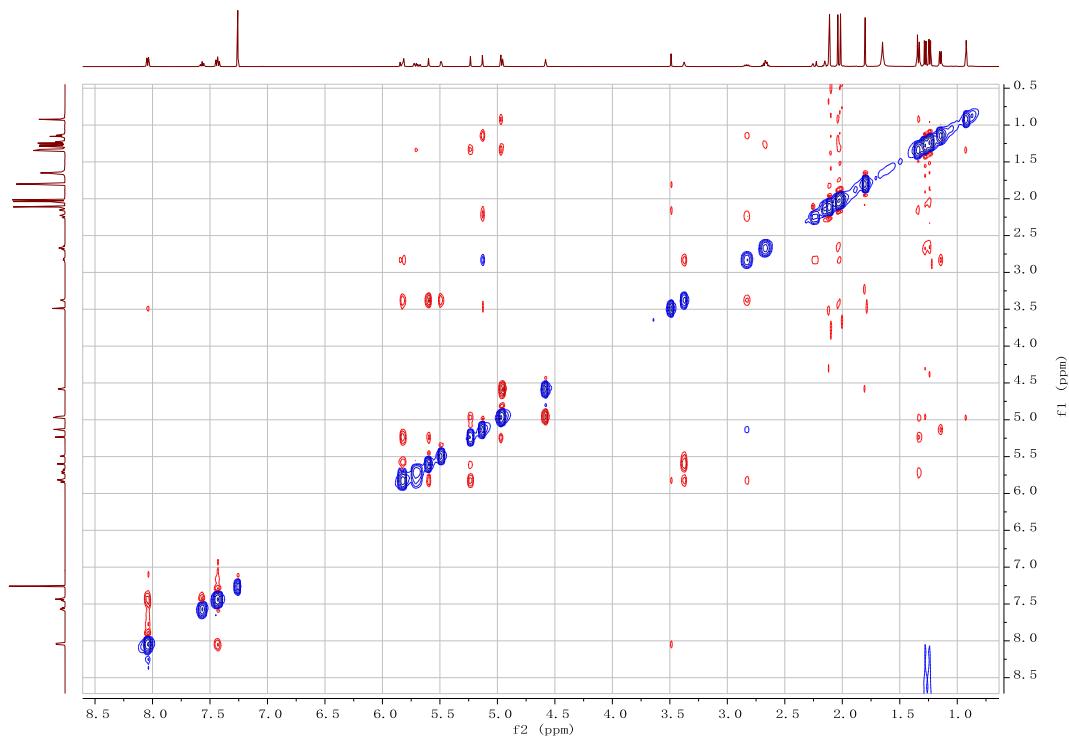


Figure S36. ROESY spectrum of euphatropane C (4)

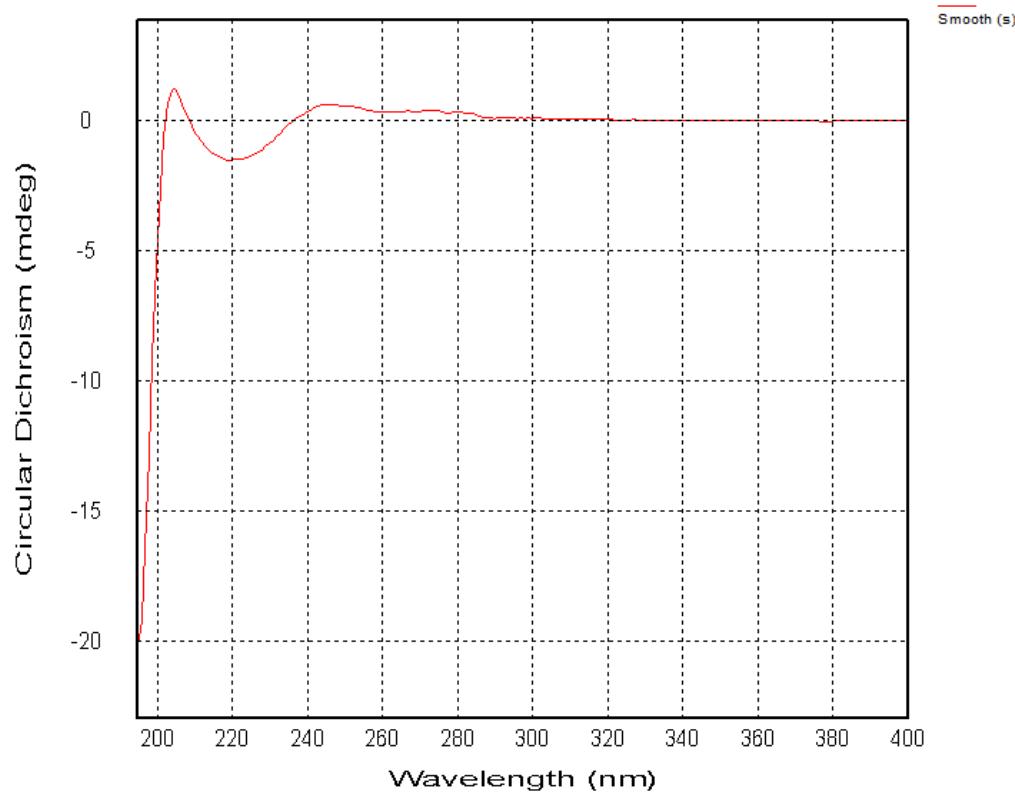


Figure S37. CD spectrum of euphatropane C (4)

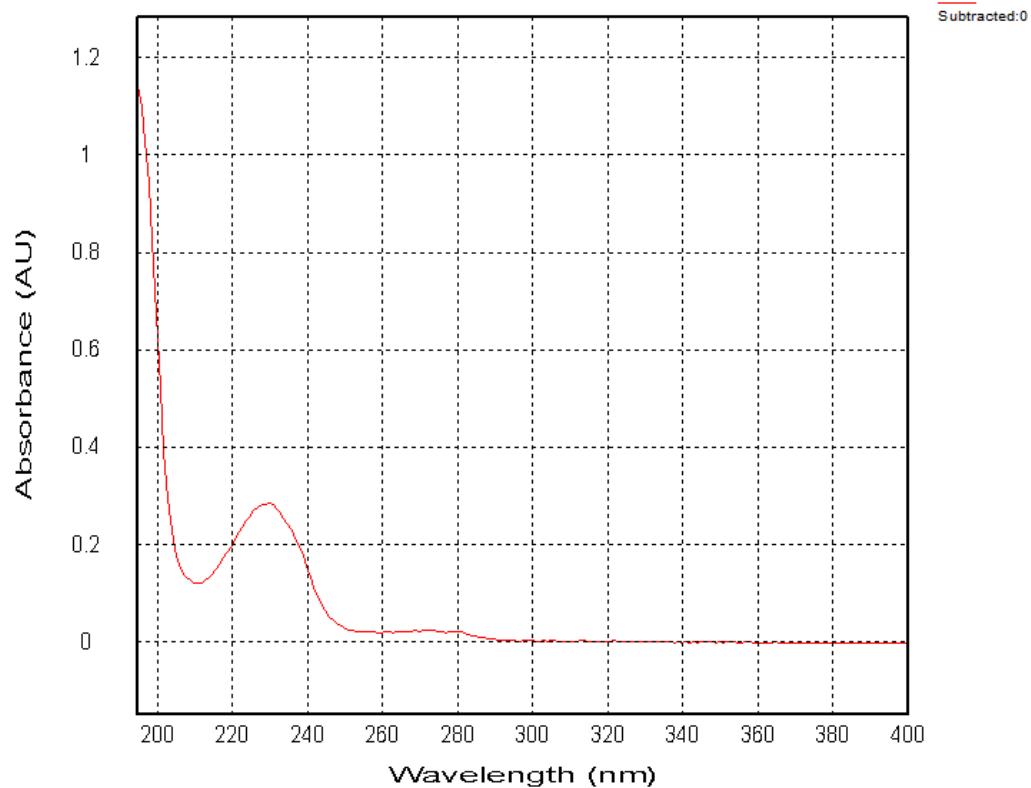


Figure S38. UV spectrum of euphatropane C (4)

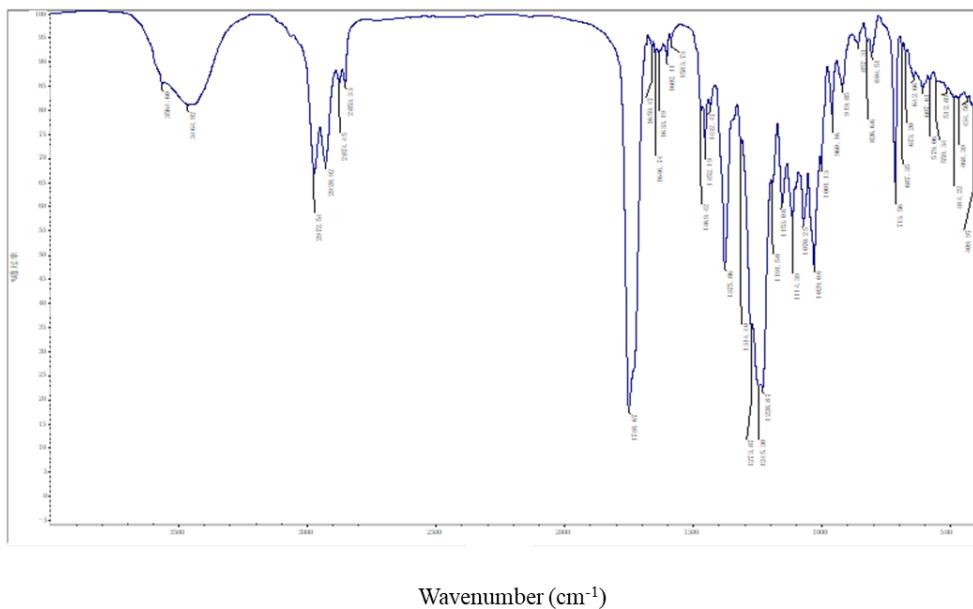
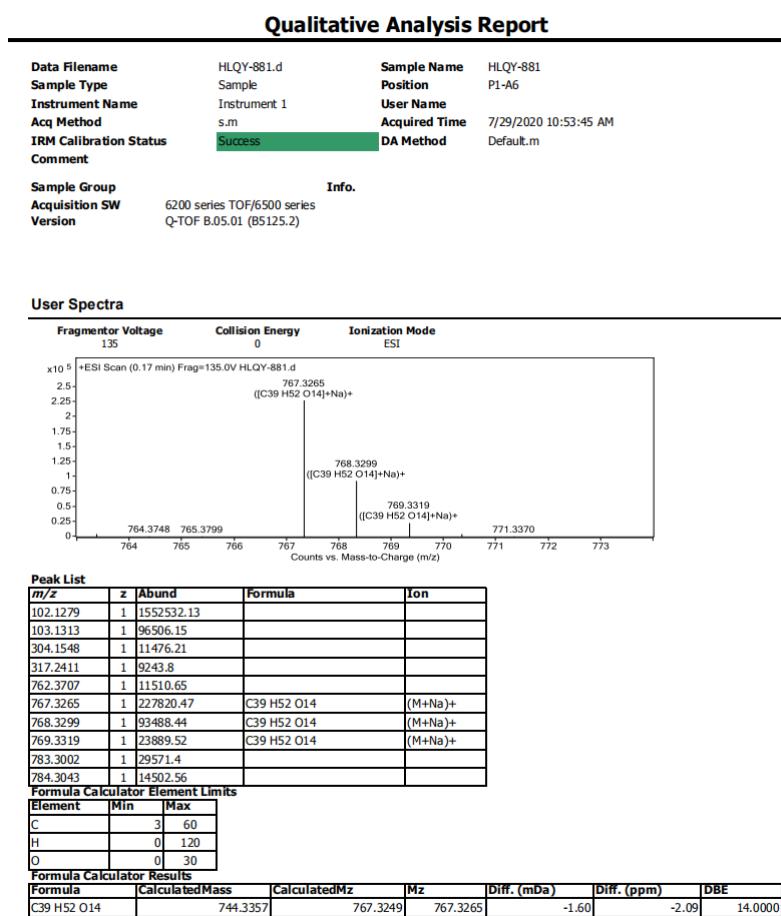


Figure S39. IR spectrum of euphjatrophane C (4)



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Figure S40. (+)-HRESIMS spectrum of euphjatrophane C (4)

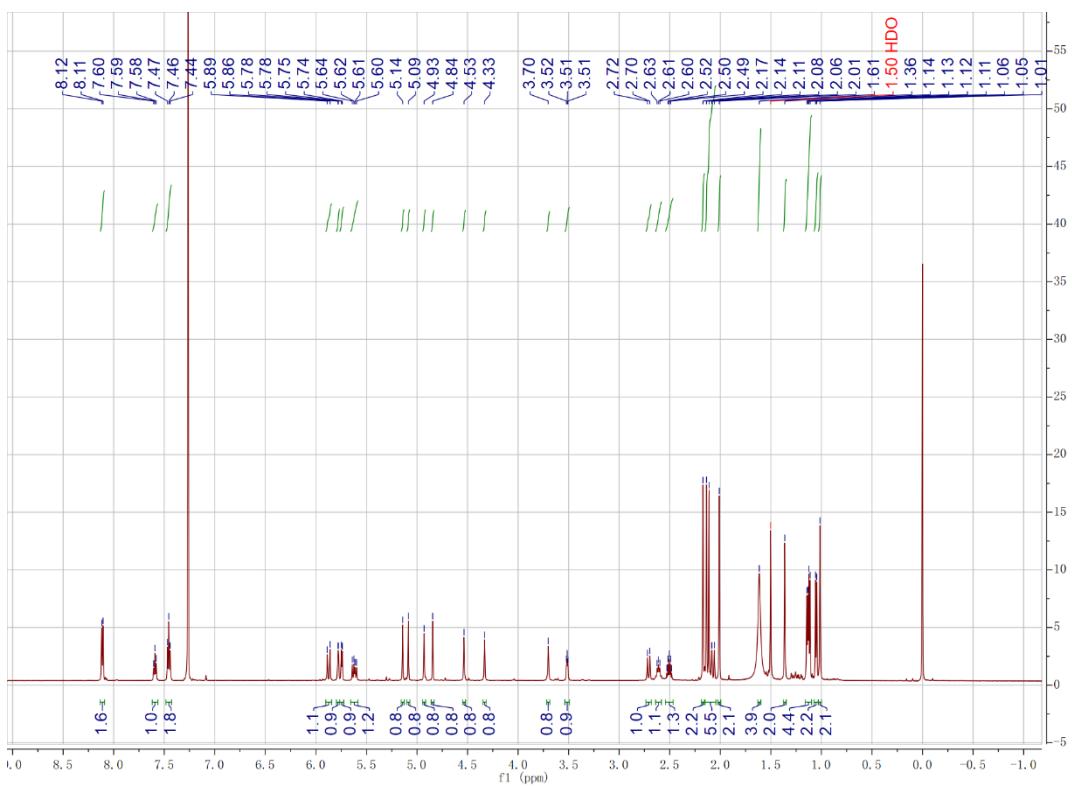


Figure S41. ¹H NMR spectrum of euphjatrophane D (**5**)

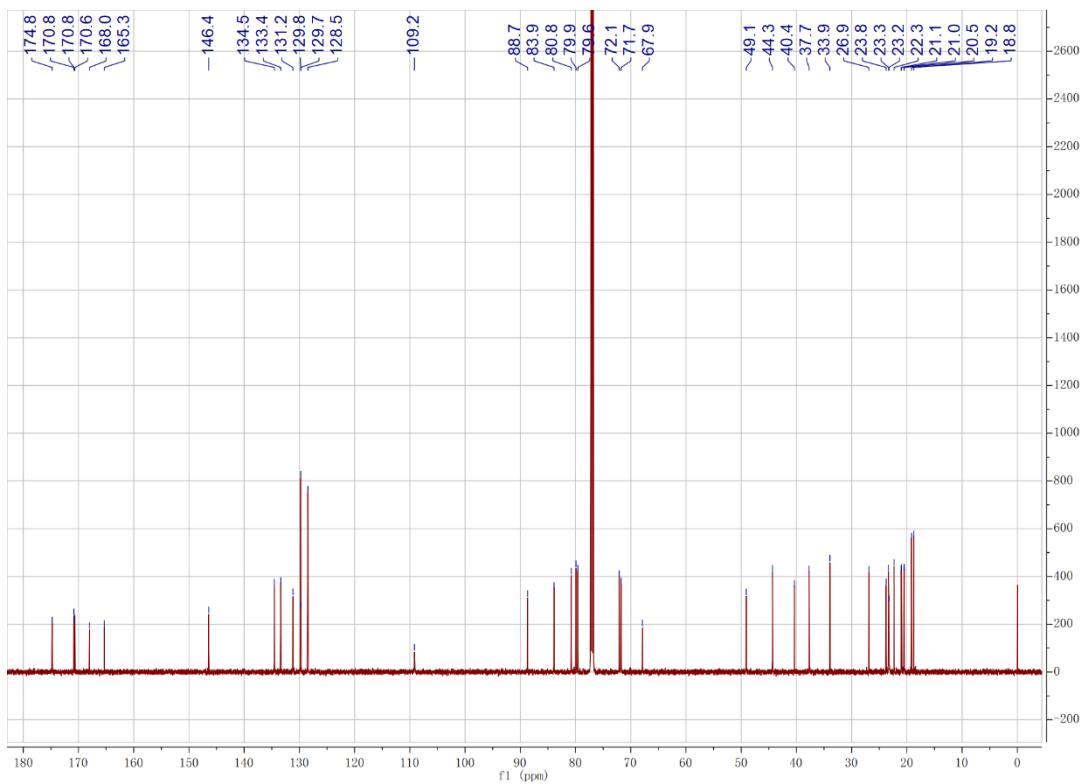


Figure S42. ¹³C NMR spectrum of euphjatrophane D (**5**)

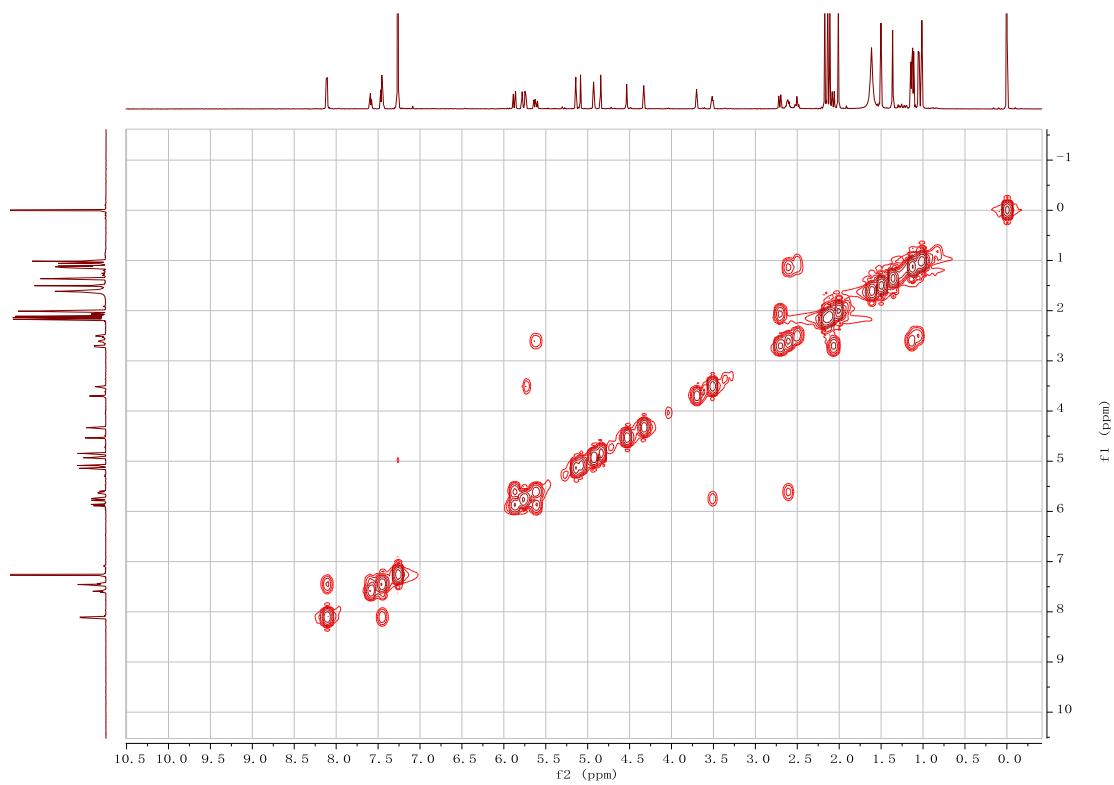


Figure S43. ^1H - ^1H COSY spectrum of euphjatrophane D (**5**)

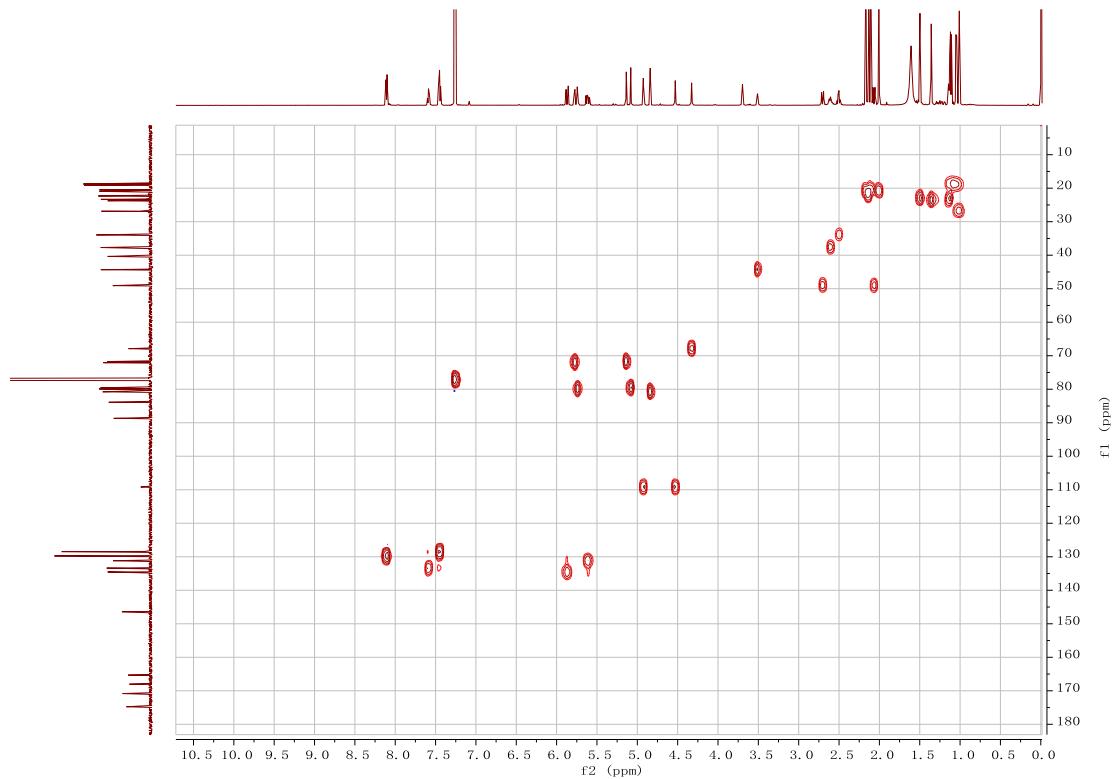


Figure S44. HSQC spectrum of euphjatrophane D (**5**)

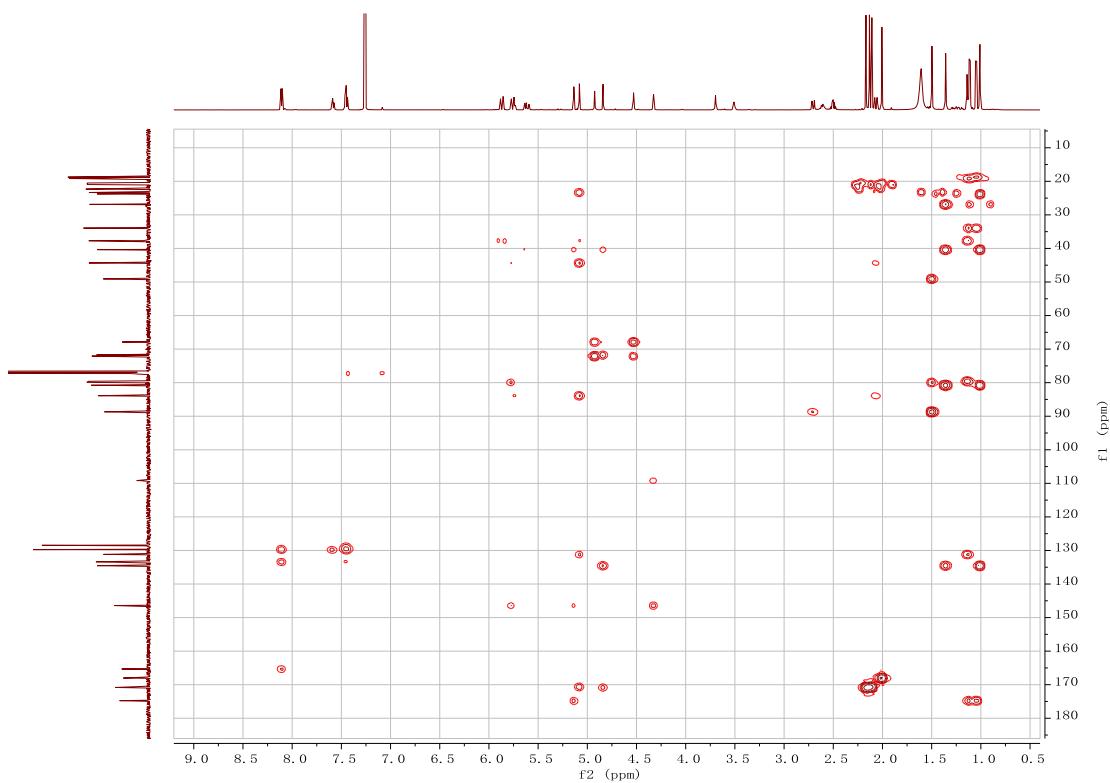


Figure S45. HMBC spectrum of eupjatrophane D (5)

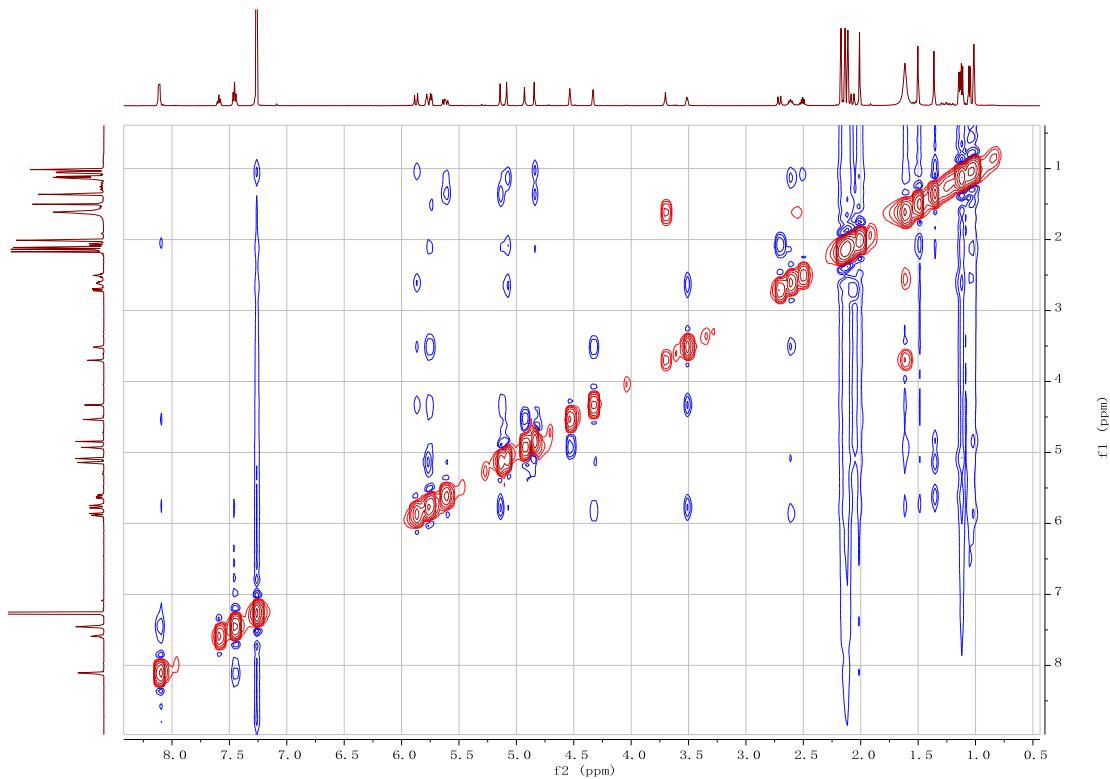


Figure S46. ROESY spectrum of eupjatrophane D (5)

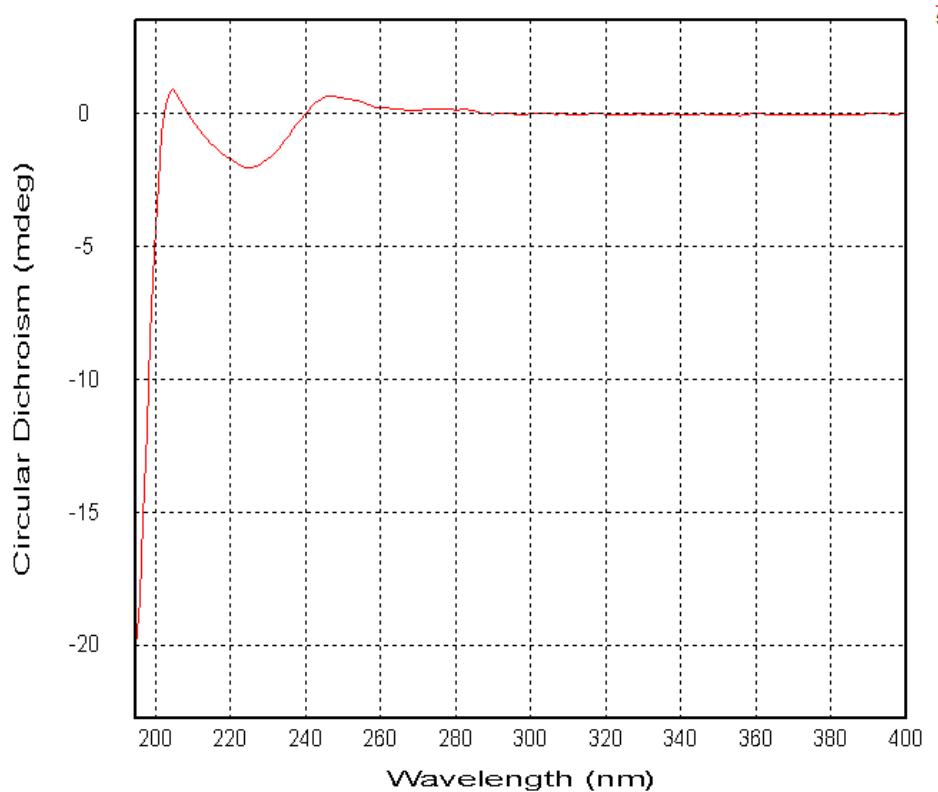


Figure S47. CD spectrum of euphatropane D (**5**)

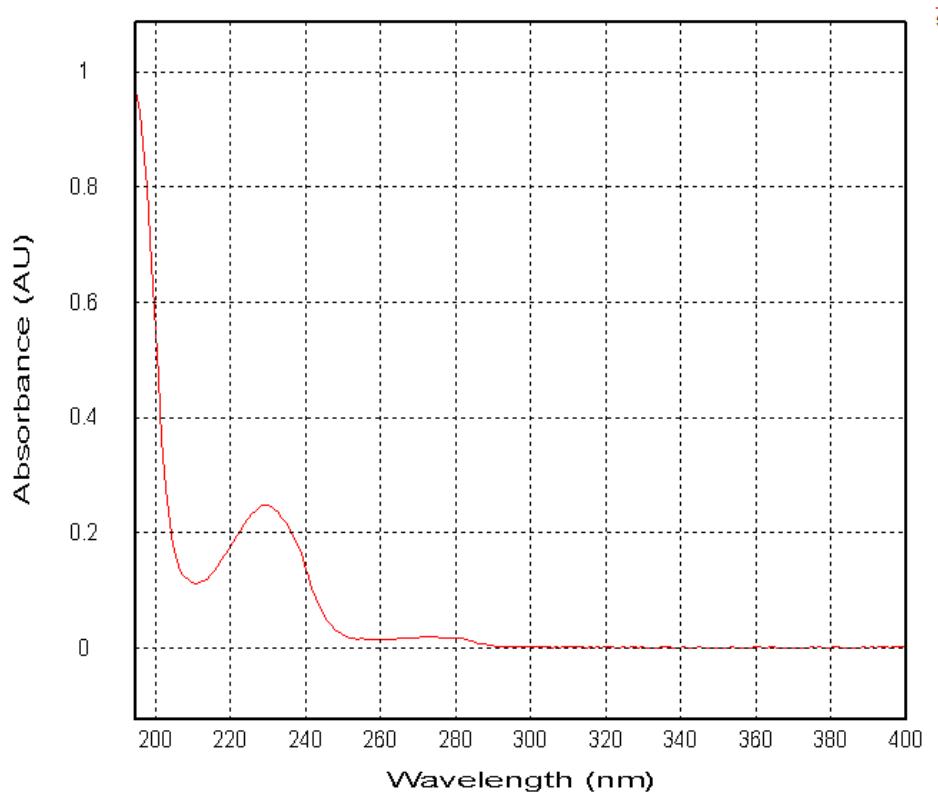


Figure S48. UV spectrum of euphatropane D (**5**)

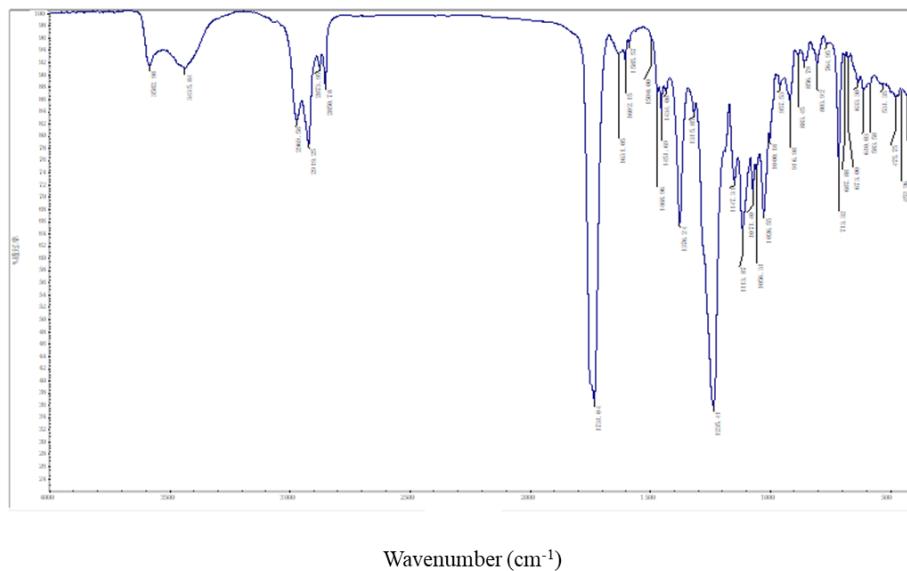
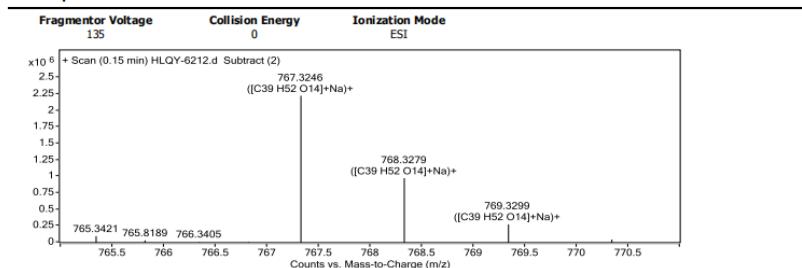


Figure S49. IR spectrum of euphjatrophane D (**5**)

Qualitative Analysis Report

Data File Name	HLQY-6212.d	Sample Name	HLQY-6212
Sample Type	Sample	Position	P1-A6
Instrument Name	Instrument 1	User Name	
Acq Method	s.m	Acquired Time	8/31/2020 4:03:42 PM
IRM Calibration Status	Success	DA Method	Default.m
Comment			
Sample Group	Info.		
Acquisition SW	6200 series TOF/6500 series		
Version	Q-TOF B.05.01 (B5125.2)		

User Spectra



Peak List

m/z	z	Abund	Formula	Ion
727.3323	1	3352046.5		
728.3354	1	1477377.5		
729.338	1	415997.06		
762.3691	1	2333769.5		
763.3727	1	1032560.44		
764.3563	1	383109		
767.3246	1	2223751	C39 H52 O14	(M+Na)+
768.3279	1	974630.06	C39 H52 O14	(M+Na)+
769.3299	1	277421.38	C39 H52 O14	(M+Na)+
783.298	1	359401.5		

Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	0	30

Formula Calculator Results

Formula	Calculated Mass	Calculated Mz	Mz	Dif. (mDa)	Dif. (ppm)	DBE
C39 H52 O14	744.3357	767.3249	767.3246	0.30	0.39	14.0000

-- End Of Report --

Figure S50. (+)-HRESIMS spectrum of euphjatrophane D (**5**)

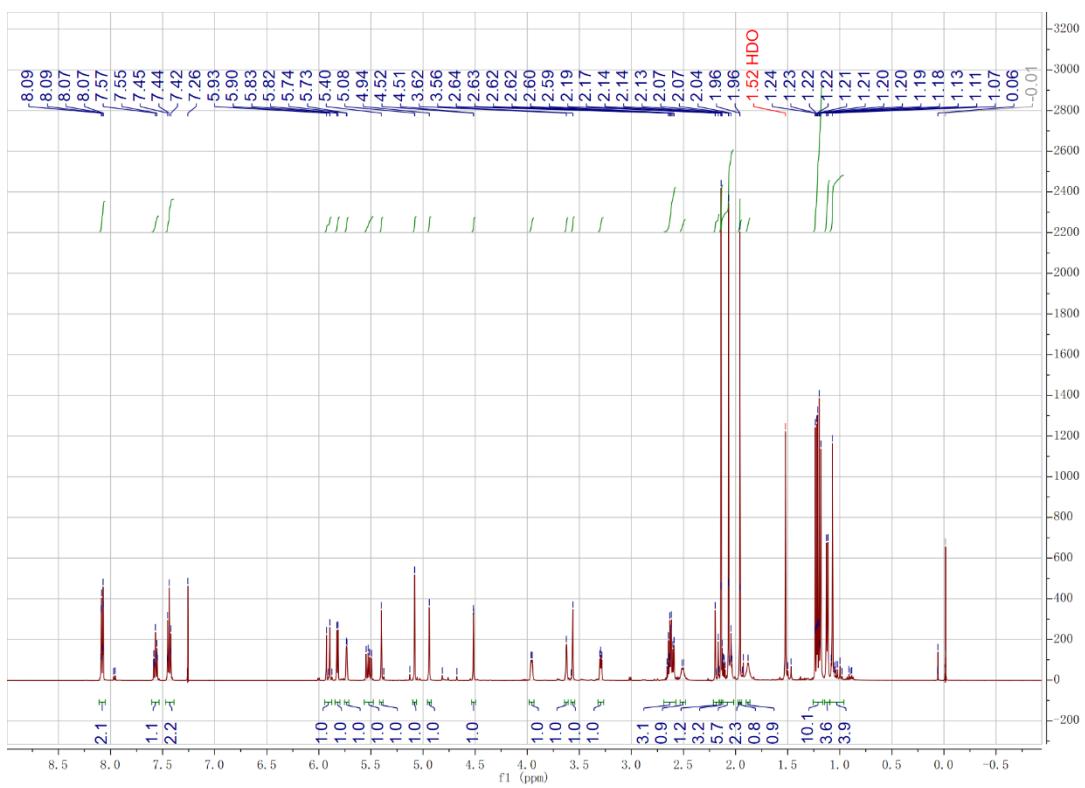


Figure S51. ^1H NMR spectrum of euphjatrophane E (**6**)

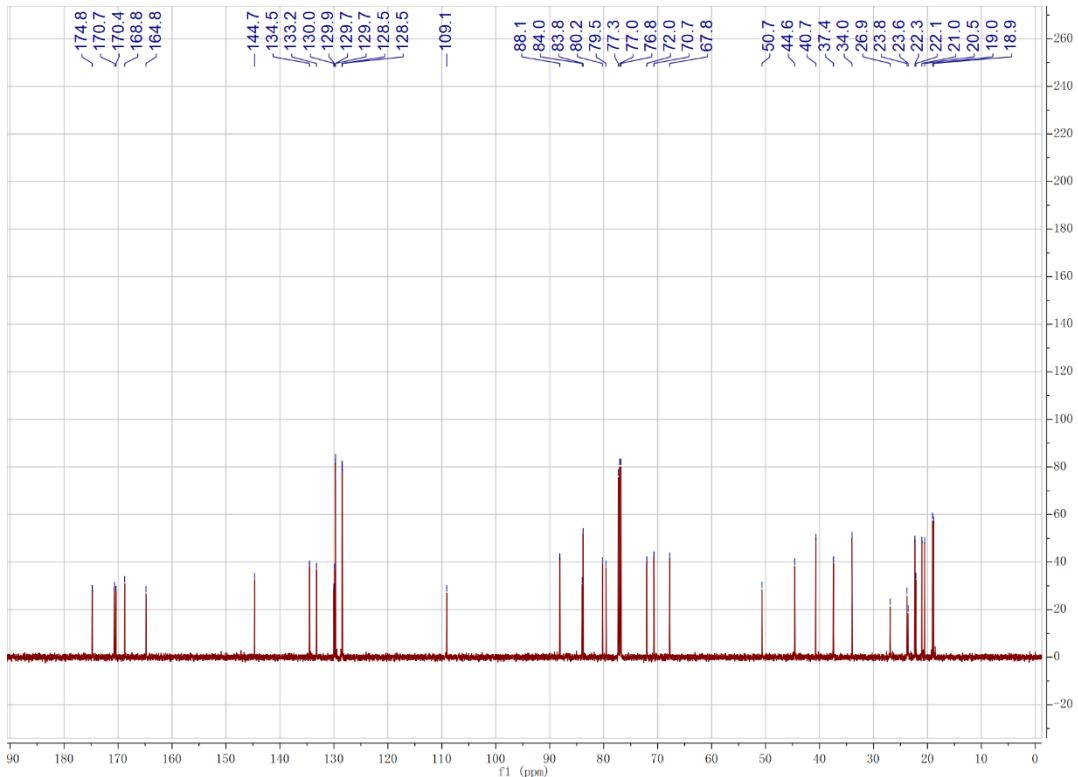


Figure S52. ^{13}C NMR spectrum of euphjatrophane E (**6**)

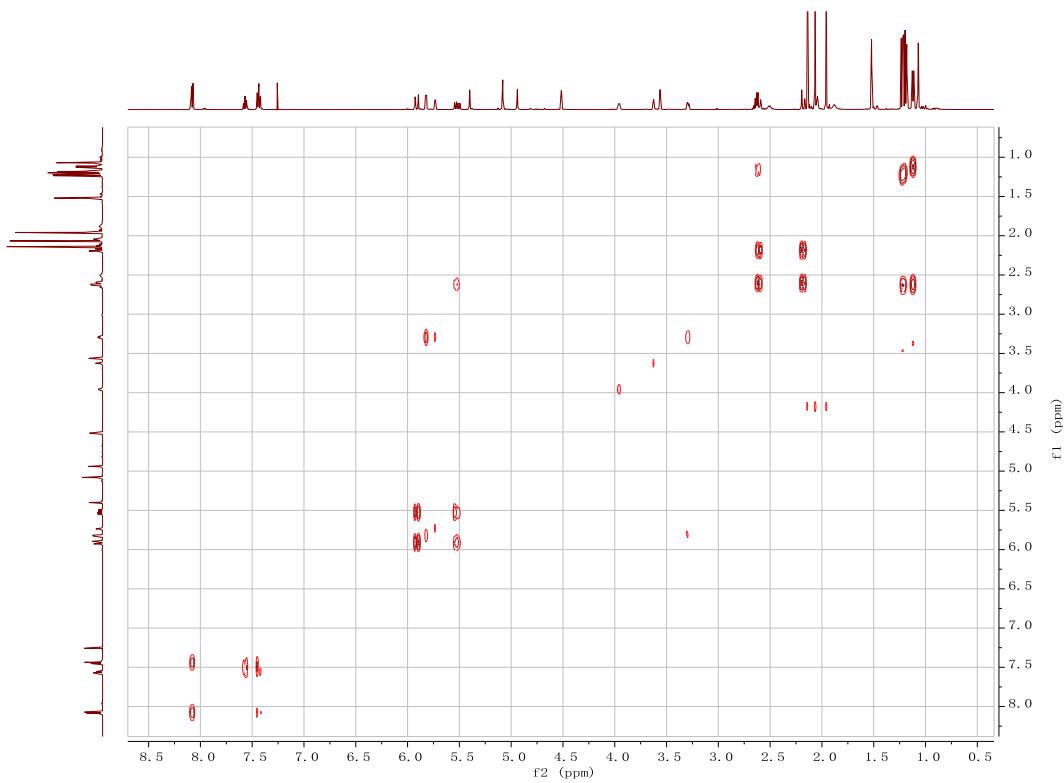


Figure S53. ¹H-¹H COSY spectrum of euphjatrophane E (6)

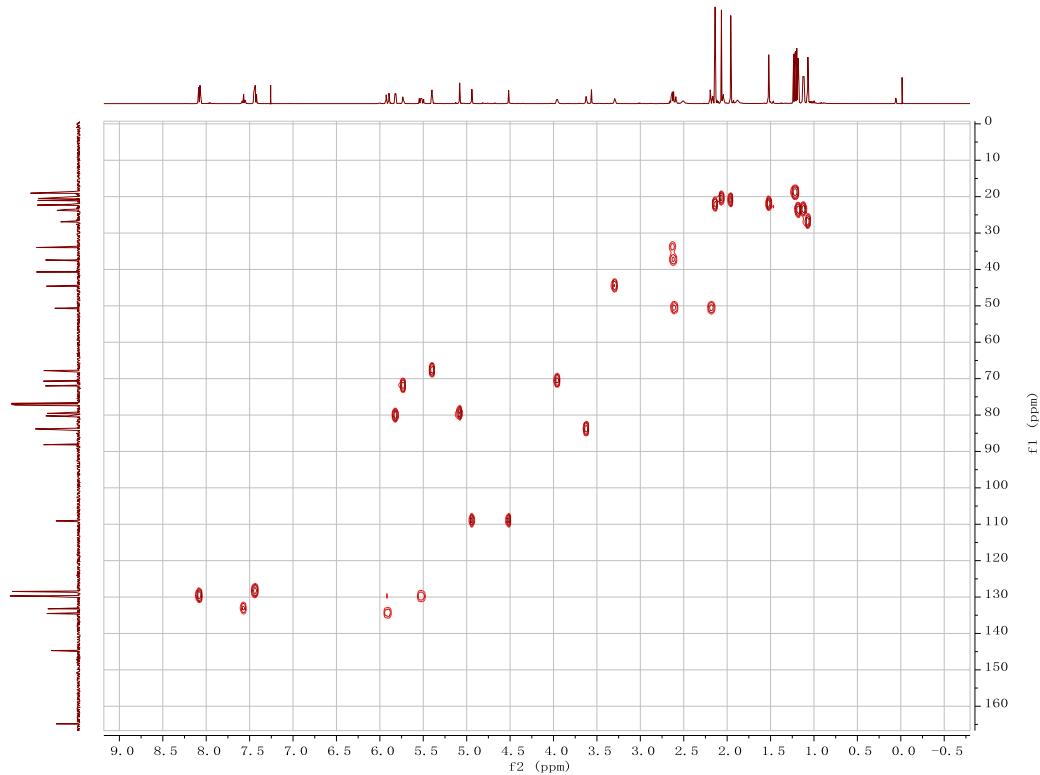


Figure S54. HSQC spectrum of euphjatrophane E (6)

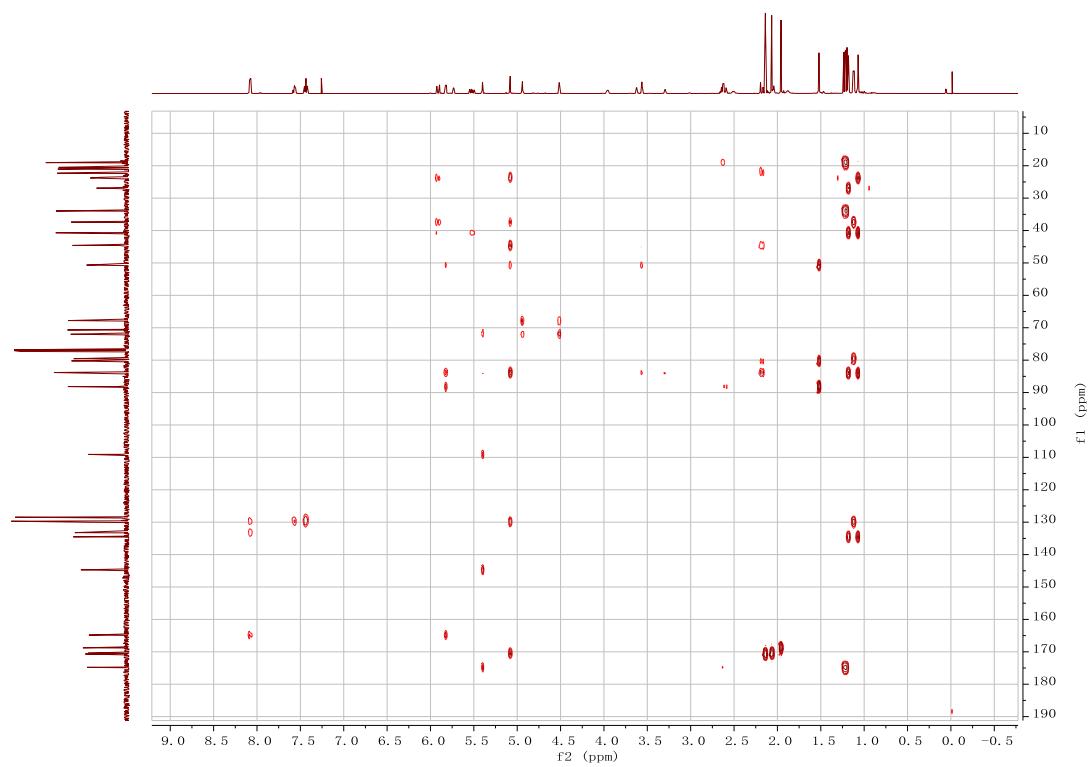


Figure S55. HMBC spectrum of euphatropane E (6)

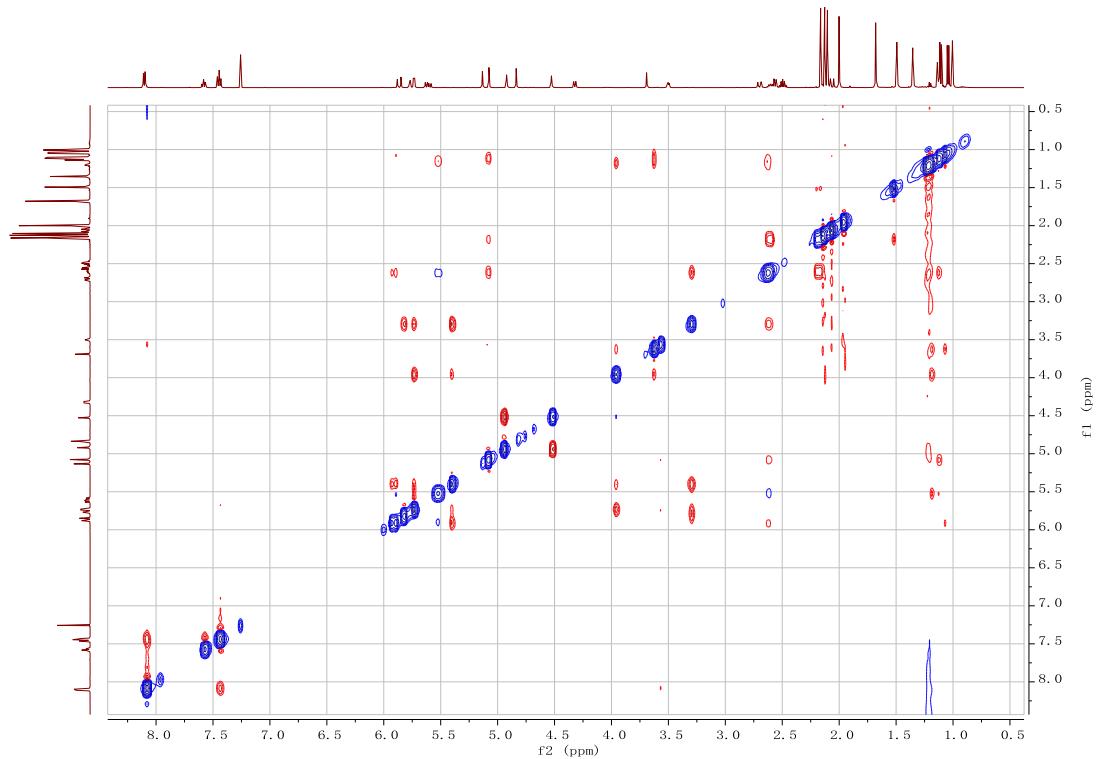


Figure S56. ROESY spectrum of euphatropane E (6)

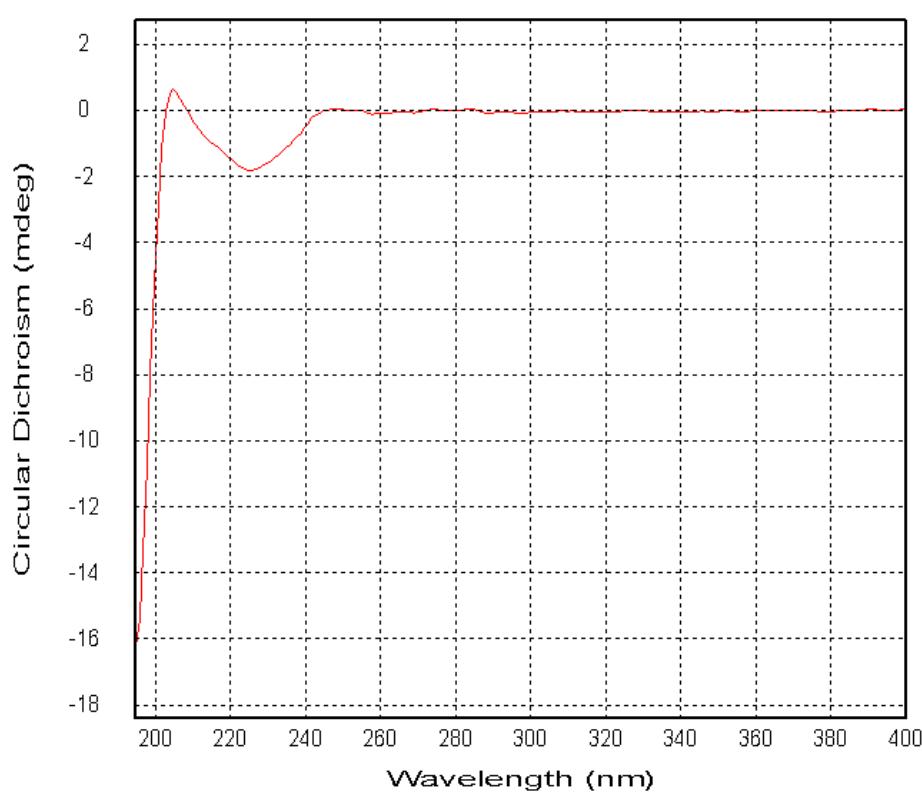


Figure S57. CD spectrum of euphatropane E (6)

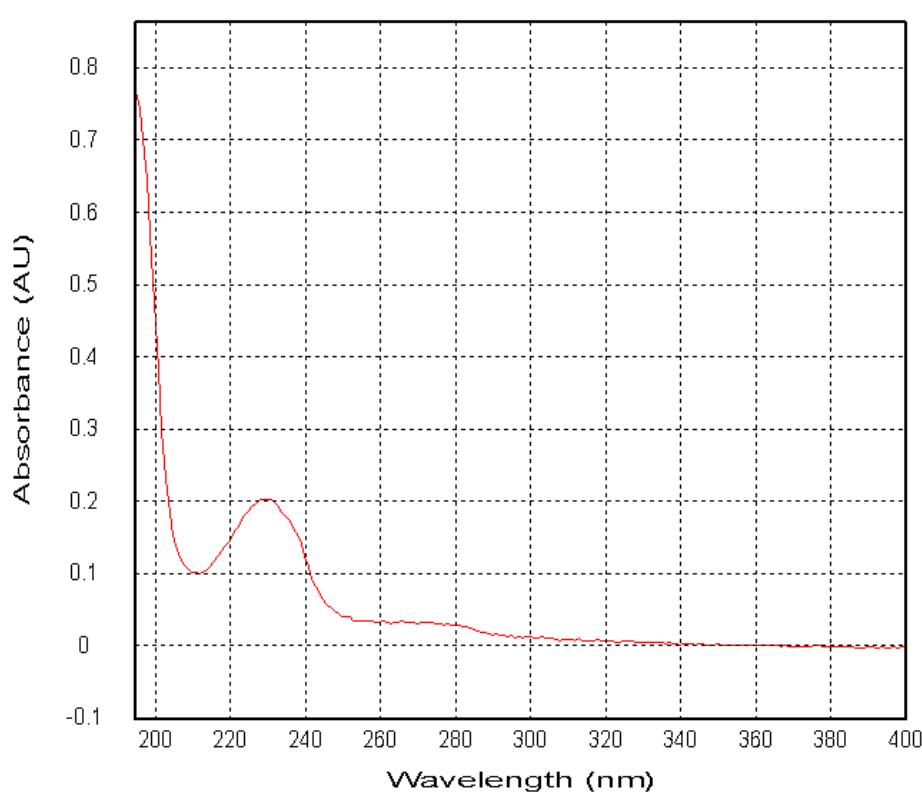


Figure S58. UV spectrum of euphatropane E (6)

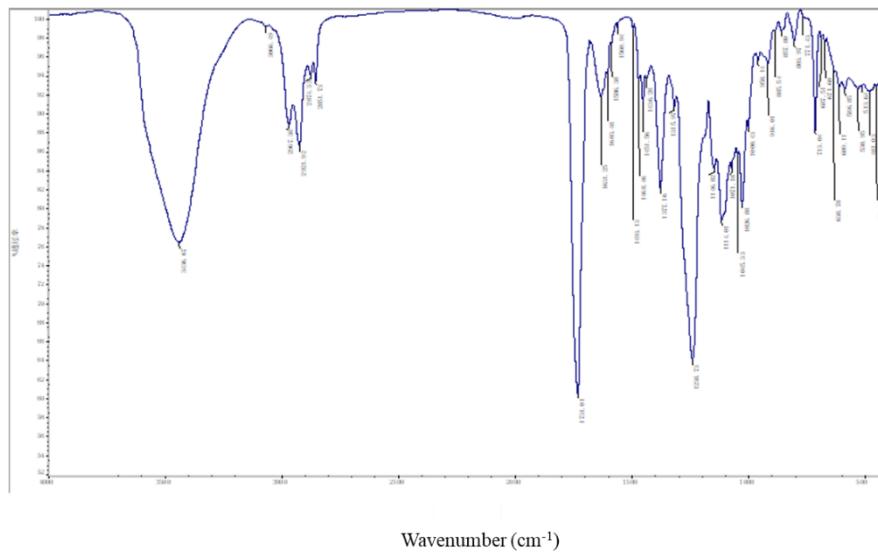
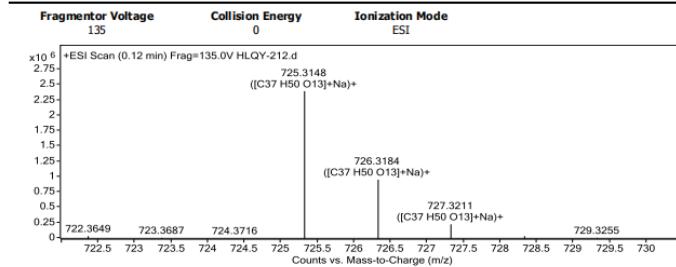


Figure S59. IR spectrum of euphjatrophane E (6)

Qualitative Analysis Report

Data Filename	HLQY-212.d	Sample Name	HLQY-212
Sample Type	Sample	Position	P1-C2
Instrument Name	Instrument 1	User Name	
Acq Method	s.m	Acquired Time	7/13/2020 3:08:00 PM
IRM Calibration Status	Success	DA Method	Default.m
Comment			
Sample Group	Info.		
Acquisition SW	6200 series TOF/6500 series		
Version	Q-TOF B.05.01 (B5125.2)		

User Spectra



Peak List			
m/z	z	Abund	Formula
720.3595	1	397637.34	
721.3624	1	163782.09	
725.3148	1	2393288.75	C37 H50 O13 (M+Na)+
726.3184	1	955570.06	C37 H50 O13 (M+Na)+
727.3211	1	228703.84	C37 H50 O13 (M+Na)+
741.2887	1	140841.22	
748.3908	1	260615.67	
1427.6409	1	373467.72	
1428.6441	1	299112.44	
1429.6466	1	131236.53	

Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	0	30

Formula Calculator Results

Formula	CalculatedMass	CalculatedMz	Mz	Diff. (mDa)	Diff. (ppm)	DBE
C37 H50 O13	702.3251	725.3144	725.3148	-0.40	-0.55	13.0000

--- End Of Report ---

Figure S60. (+)-HRESIMS spectrum of euphjatrophane E (6)

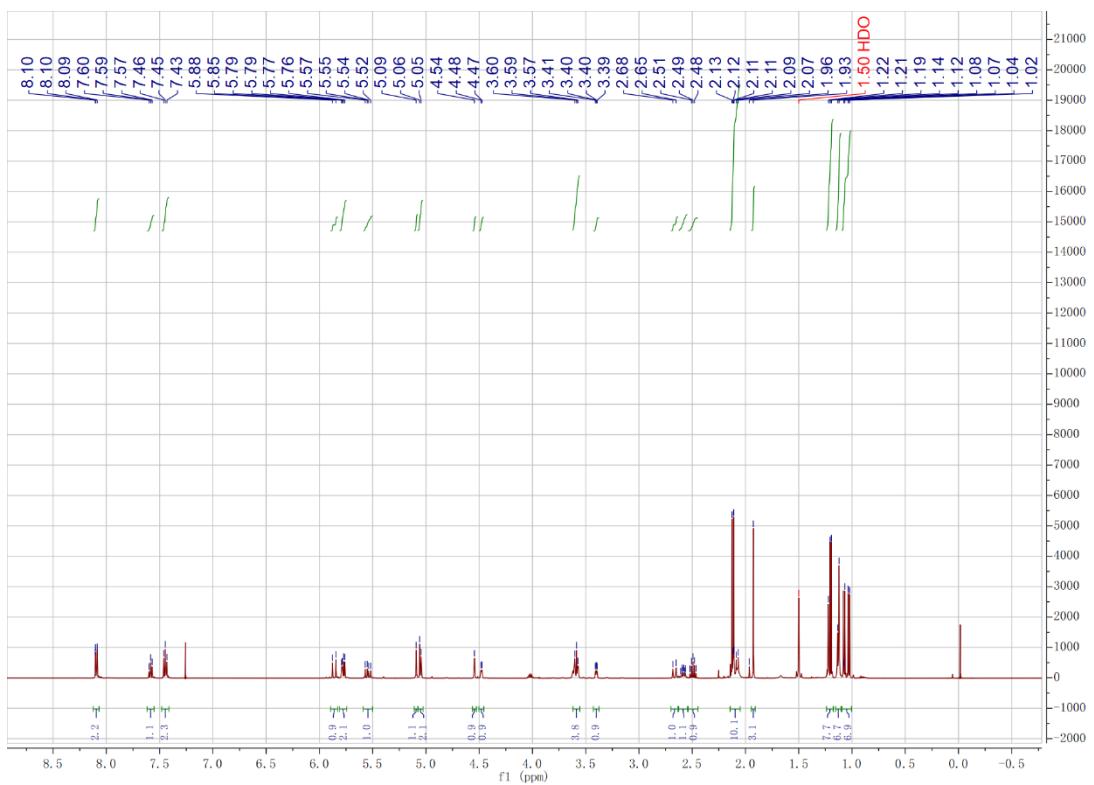


Figure S61. ^1H NMR spectrum of euphjatrophane F (**7**)

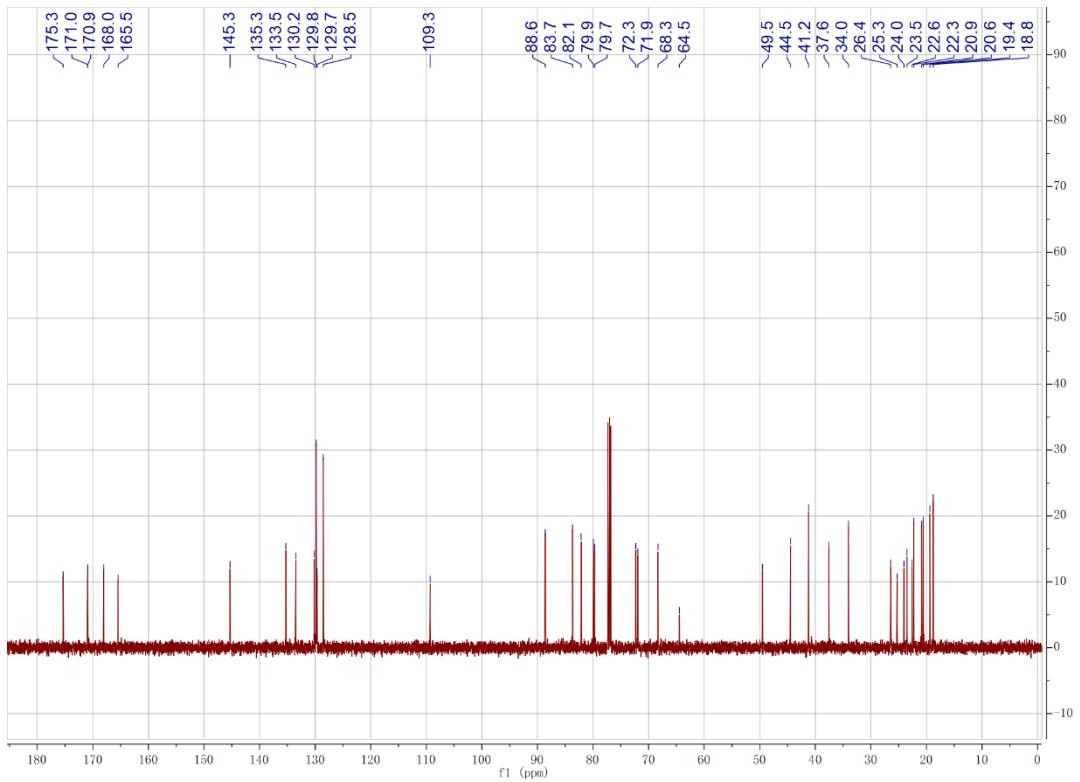


Figure S62. ^{13}C NMR spectrum of euphjatrophane F (**7**)

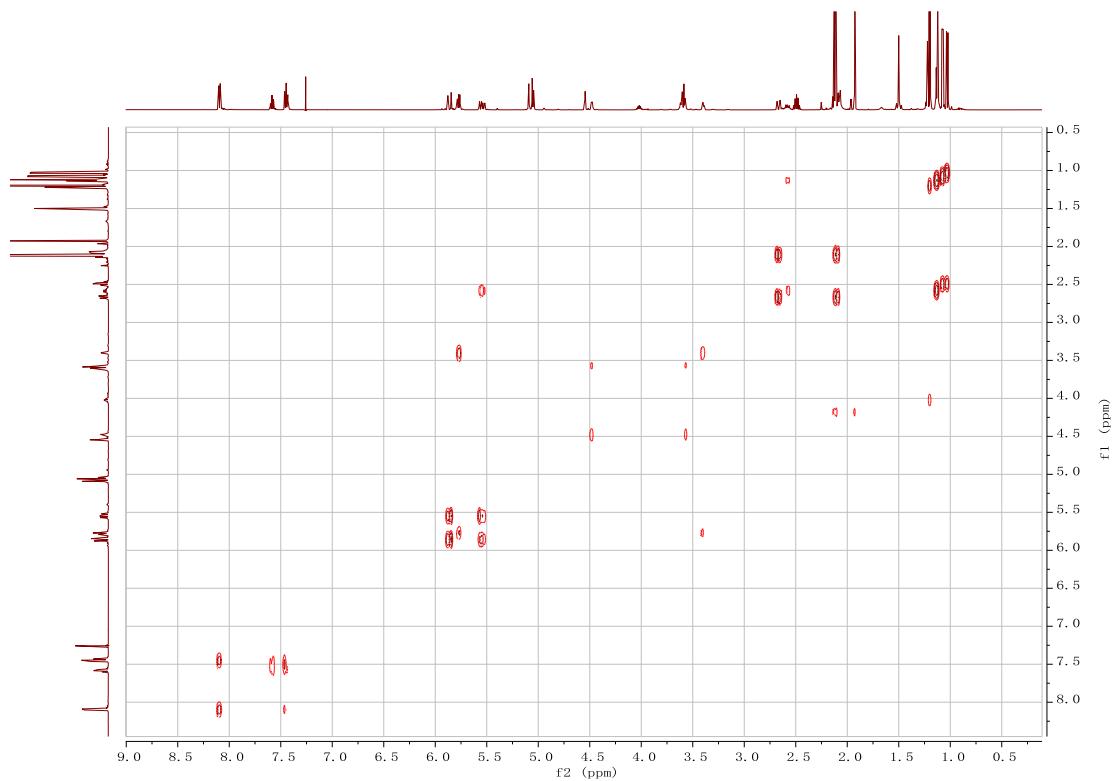


Figure S63. ¹H-¹H COSY spectrum of euphjatrophane F (7)

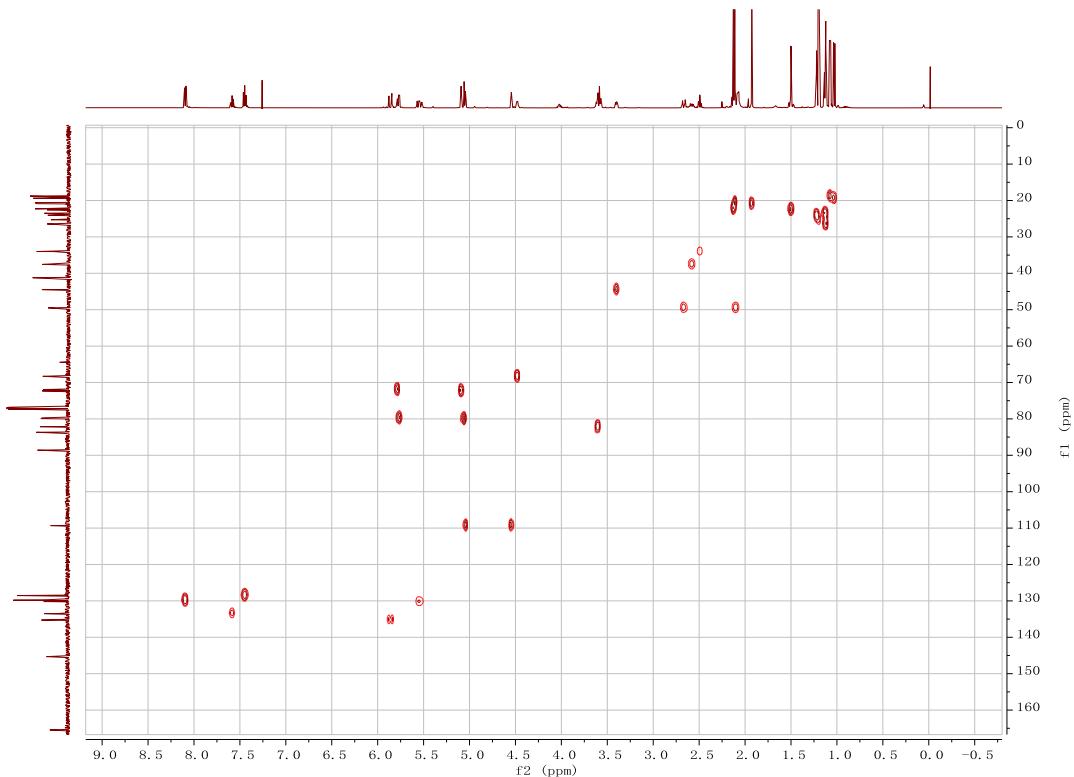


Figure S64. HSQC spectrum of euphjatrophane F (7)

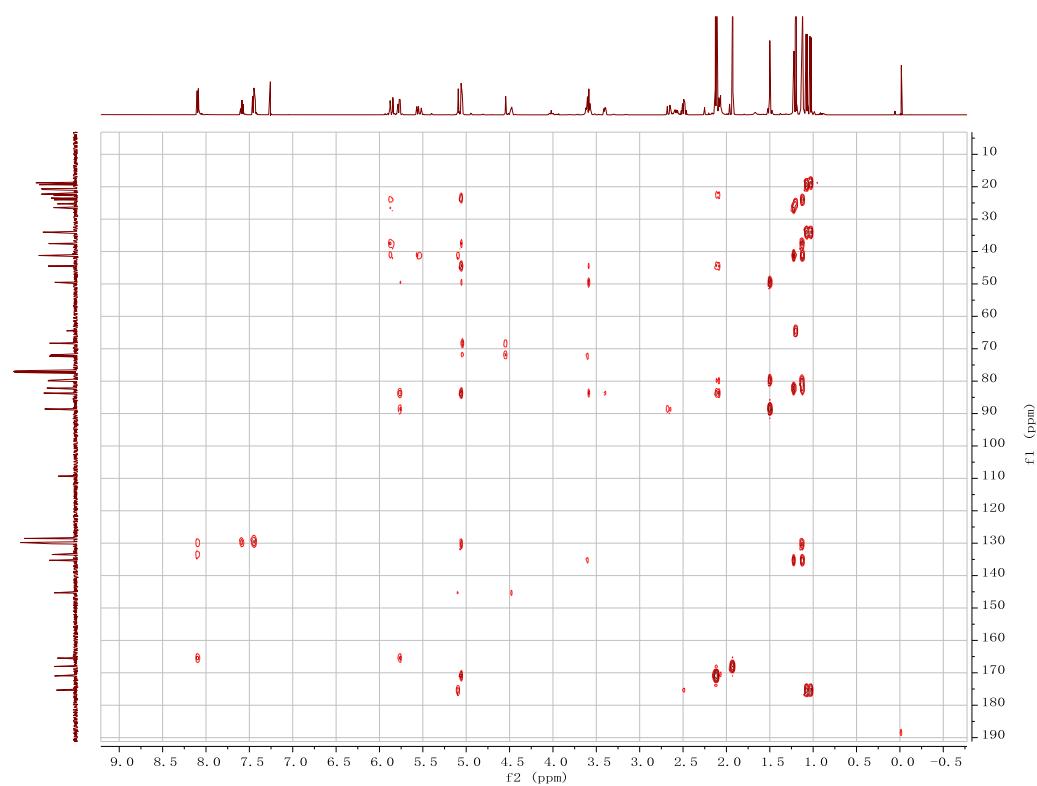


Figure S65. HMBC spectrum of euphatropane F (7)

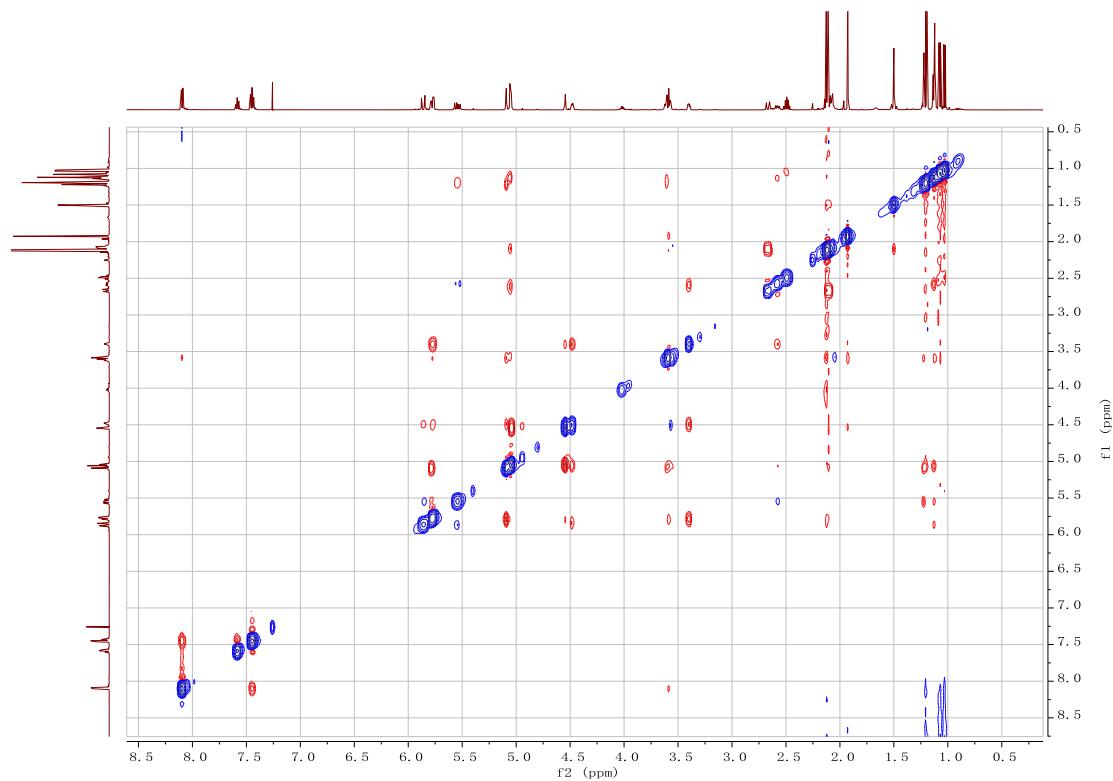


Figure S66. ROESY spectrum of euphatropane F (7)

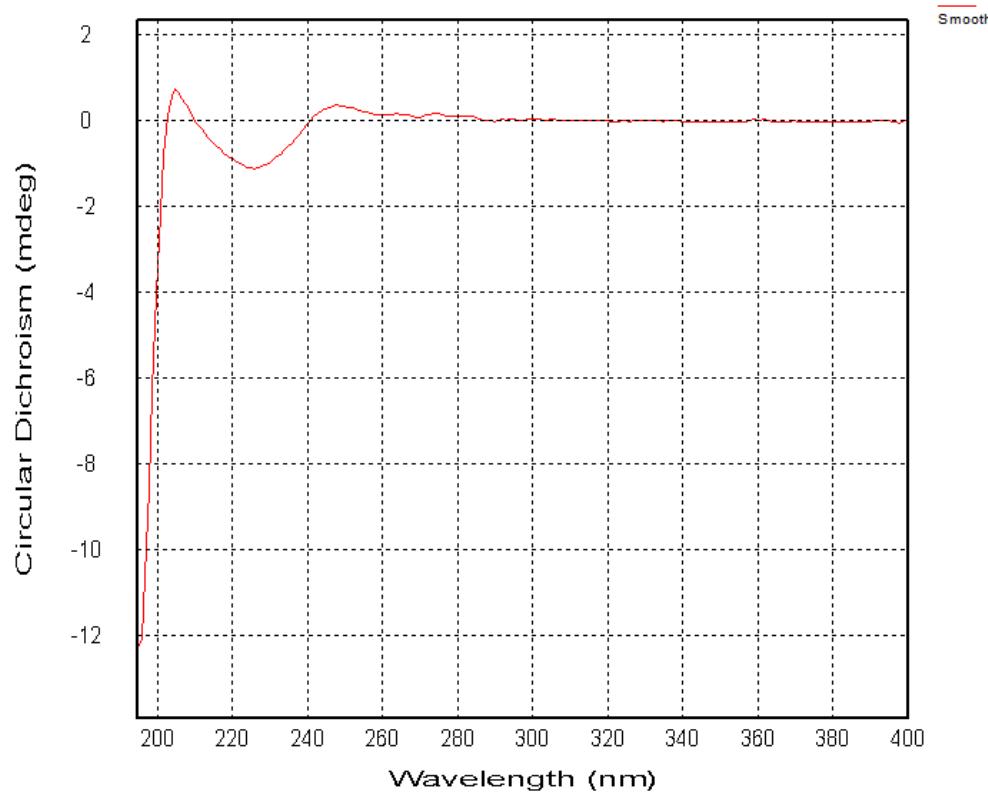


Figure S67. CD spectrum of euphatropane F (7)

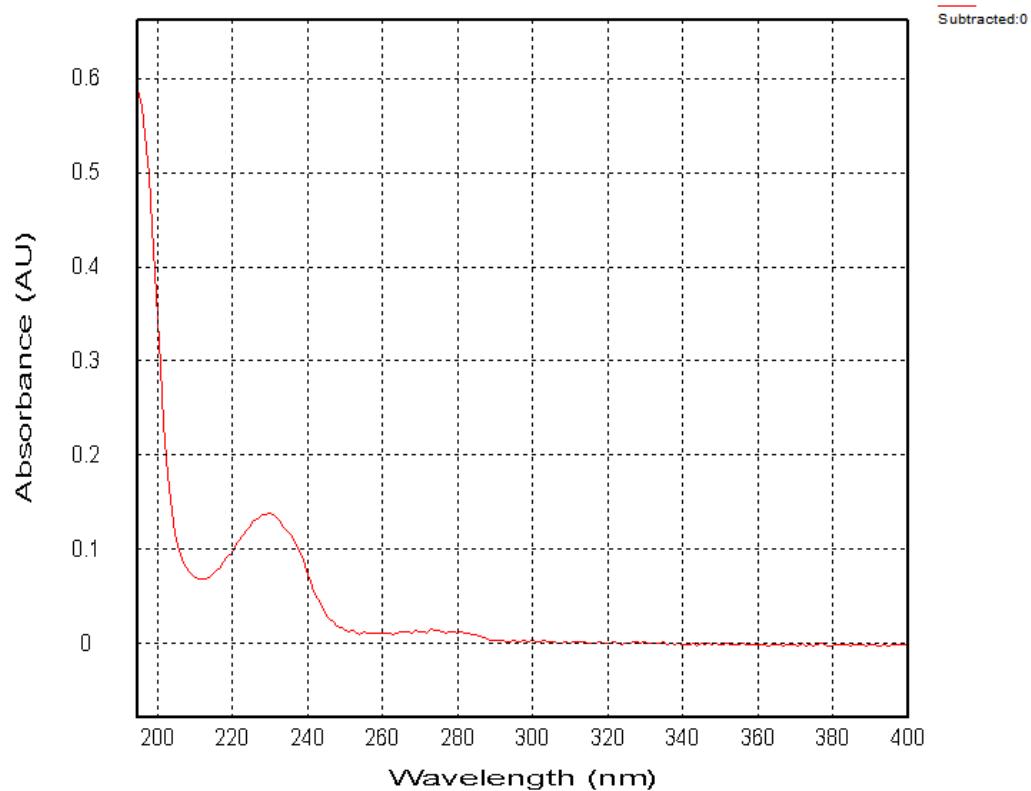


Figure S68. UV spectrum of euphatropane F (7)

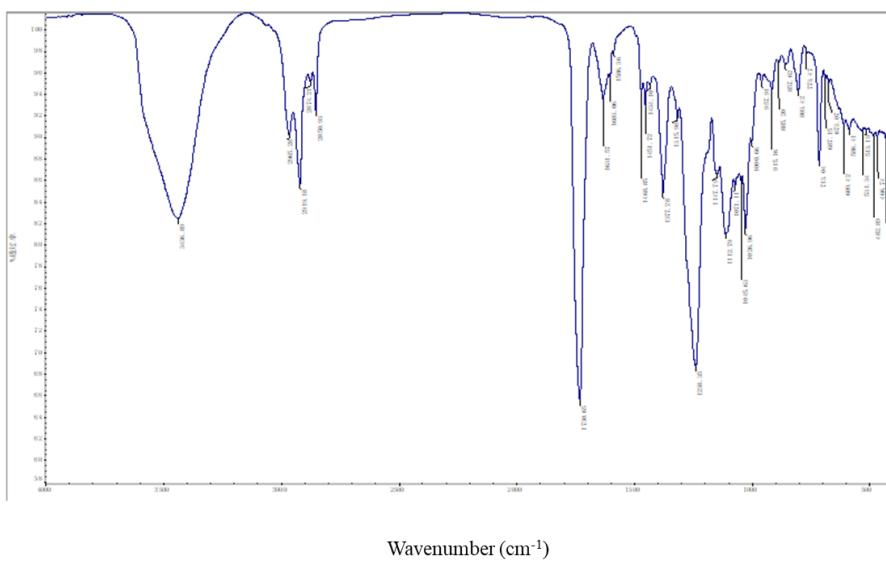
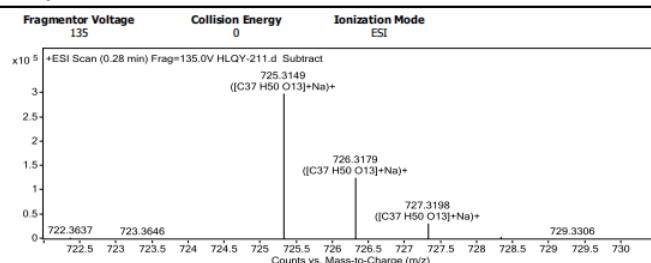


Figure S69. IR spectrum of euphatropane F (7)

Qualitative Analysis Report

Data Filename	HLQY-211.d	Sample Name	HLQY-211
Sample Type	Sample	Position	P1-C1
Instrument Name	Instrument 1	User Name	
Acq Method	s.m	Acquired Time	7/13/2020 3:06:49 PM
IRM Calibration Status	Success	DA Method	Default.m
Comment			
Sample Group		Info.	
Acquisition SW	6200 series TOF/6500 series		
Version	Q-TOF B.05.01 (B5125.2)		

User Spectra



Peak List

m/z	z	Abund	Formula	Ion
683.3043	1	12952.36		
720.3589	1	28360.97		
721.3622	1	12745.93		
725.3149	1	298945.53	C37 H50 O13	(M+Na)+
726.3179	1	125976.79	C37 H50 O13	(M+Na)+
727.3198	1	31686.18	C37 H50 O13	(M+Na)+
741.2883	1	35291.52		
742.292	1	12583.82		
748.3903	1	45541.17		
749.3931	1	18295.9		

Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	0	30

Formula Calculator Results

Formula	Calculated Mass	Calculated Mz	Mz	Diff. (mDa)	Diff. (ppm)	DBE
C37 H50 O13	702.3251	725.3144	725.3149	-0.50	-0.69	13.0000

-- End Of Report --

Figure S70. (+)-HRESIMS spectrum of euphatropane F (7)

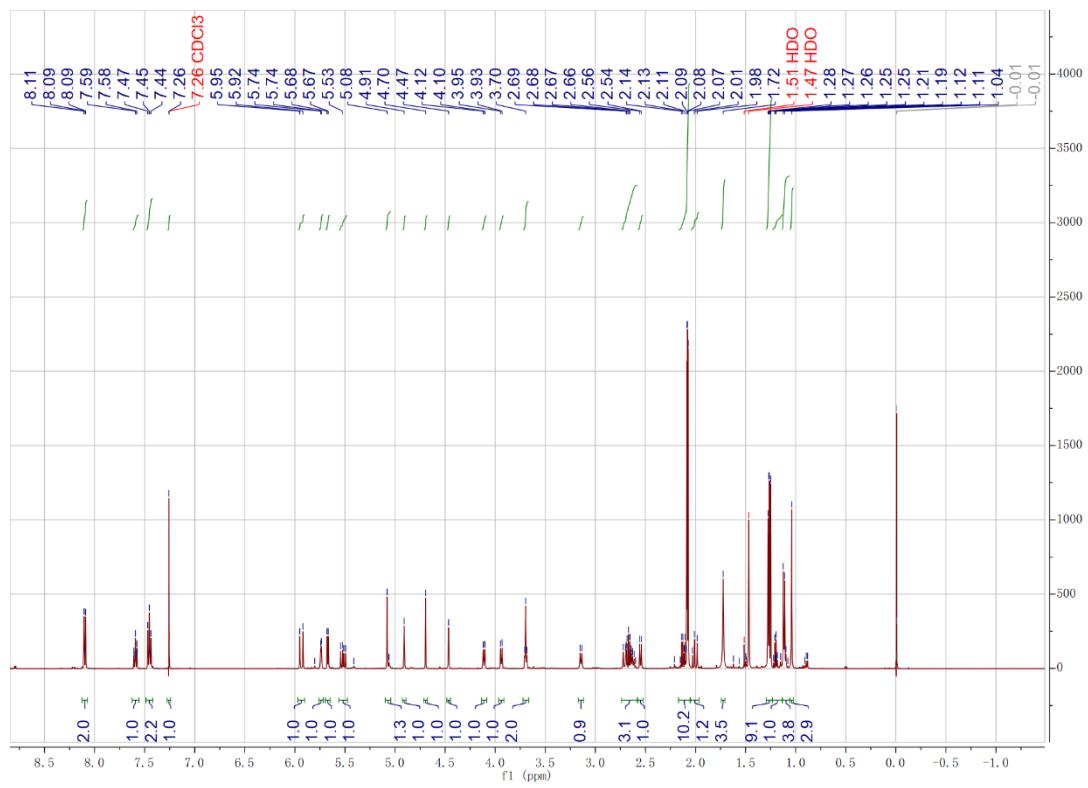


Figure S71. ^1H NMR spectrum of euphatropane G (**8**)

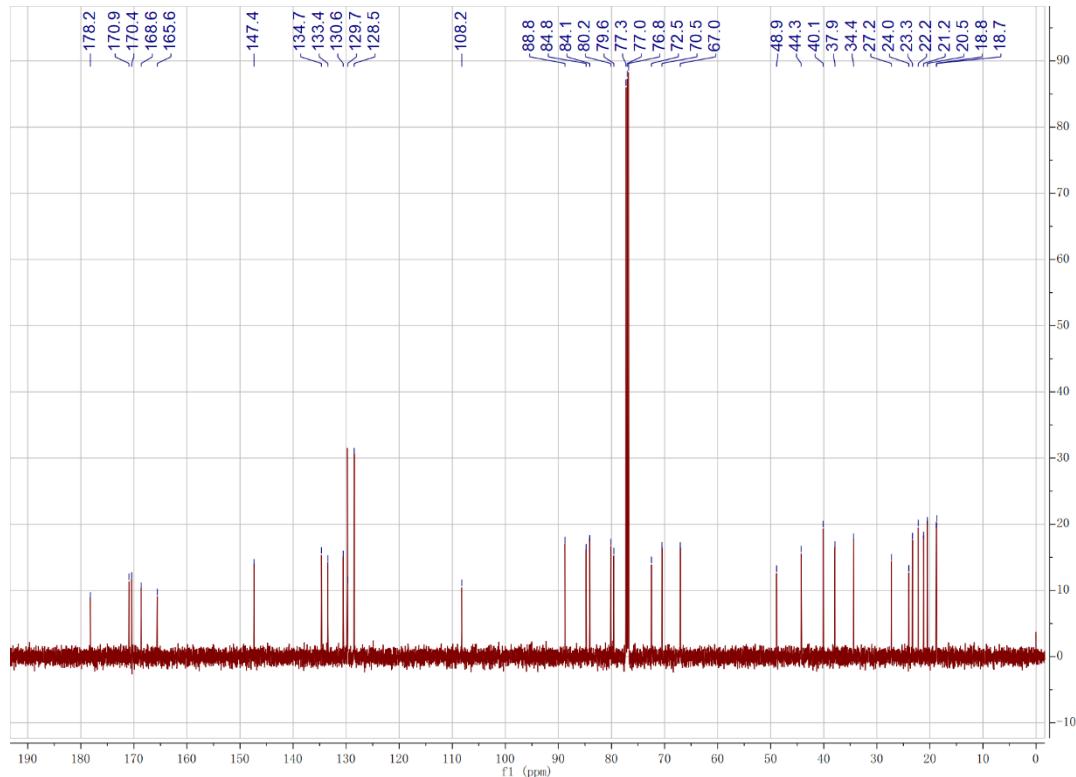


Figure S72. ^{13}C NMR spectrum of euphatropane G (**8**)

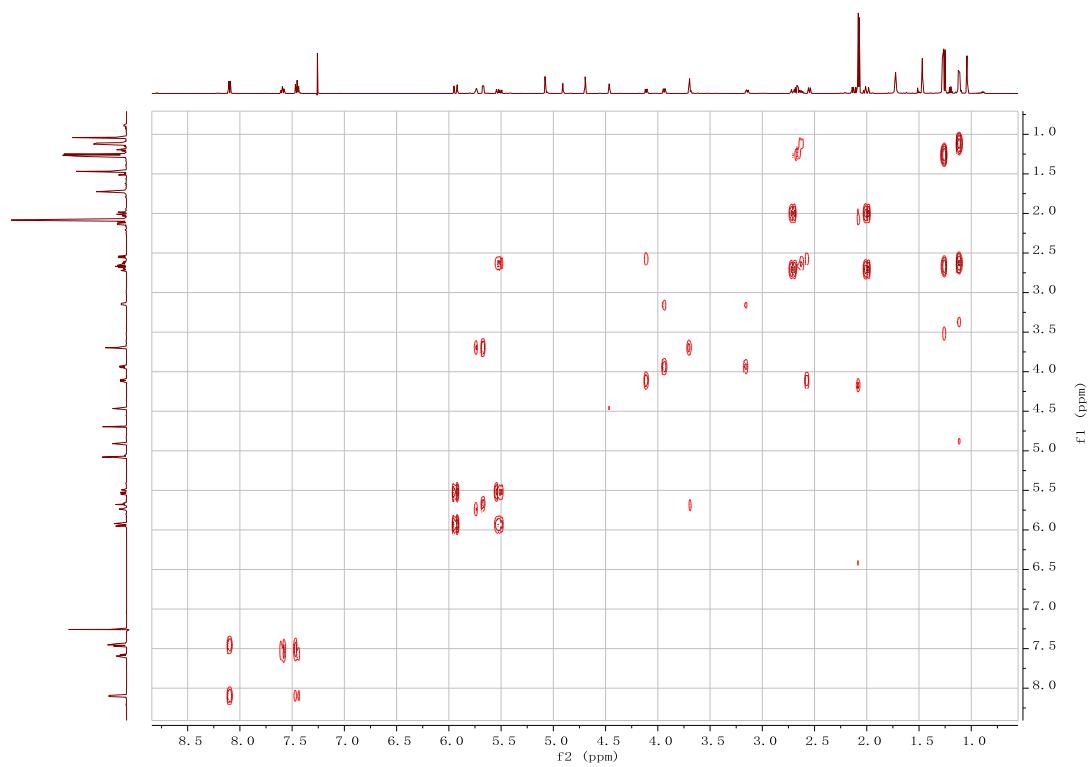


Figure S73. ^1H - ^1H COSY spectrum of euphjatrophane G (**8**)

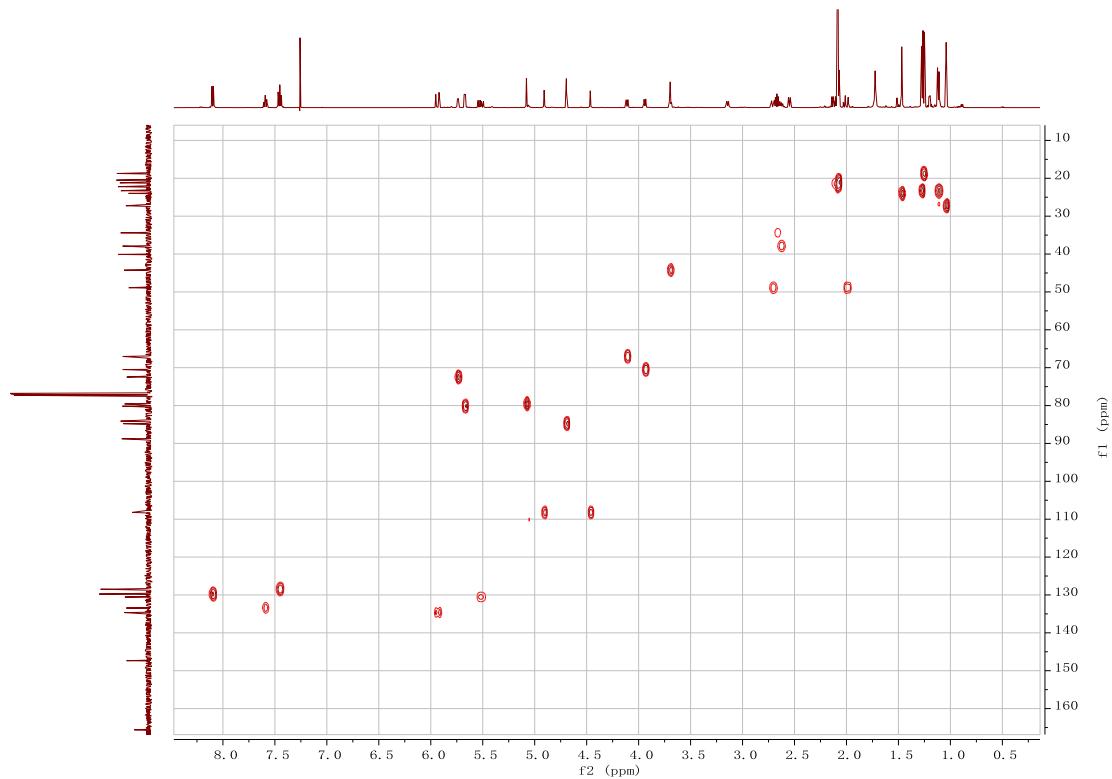


Figure S74. HSQC spectrum of euphjatrophane G (**8**)

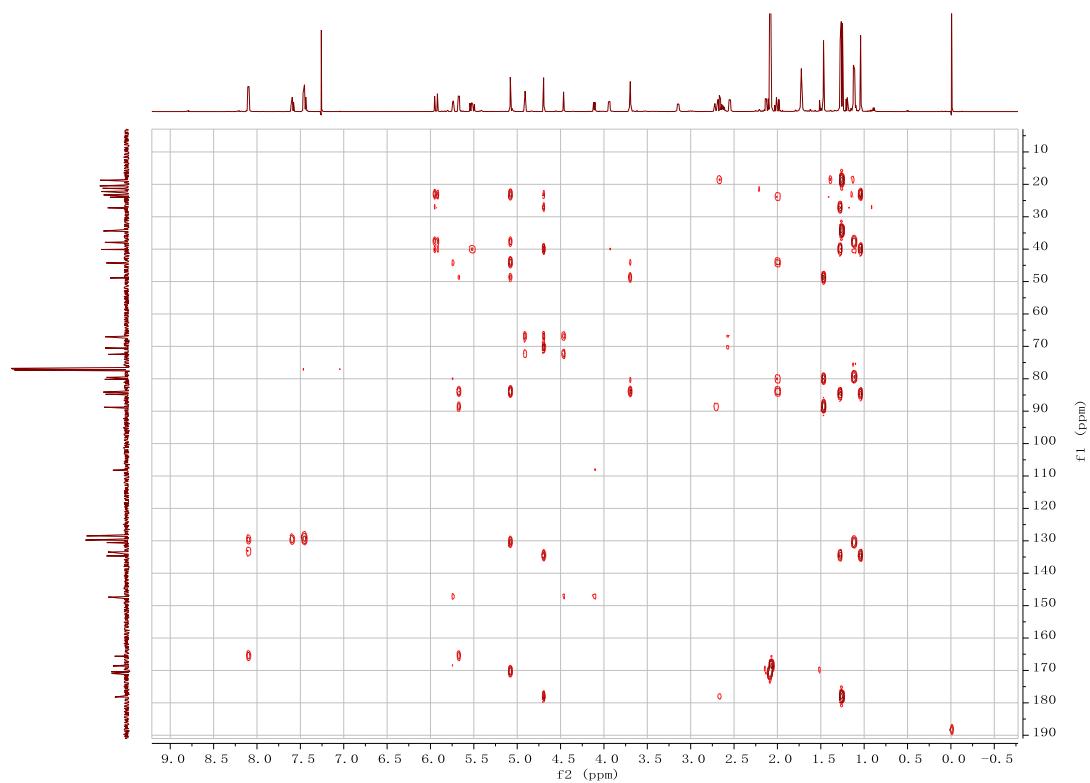


Figure S75. HMBC spectrum of euphatropane G (8)

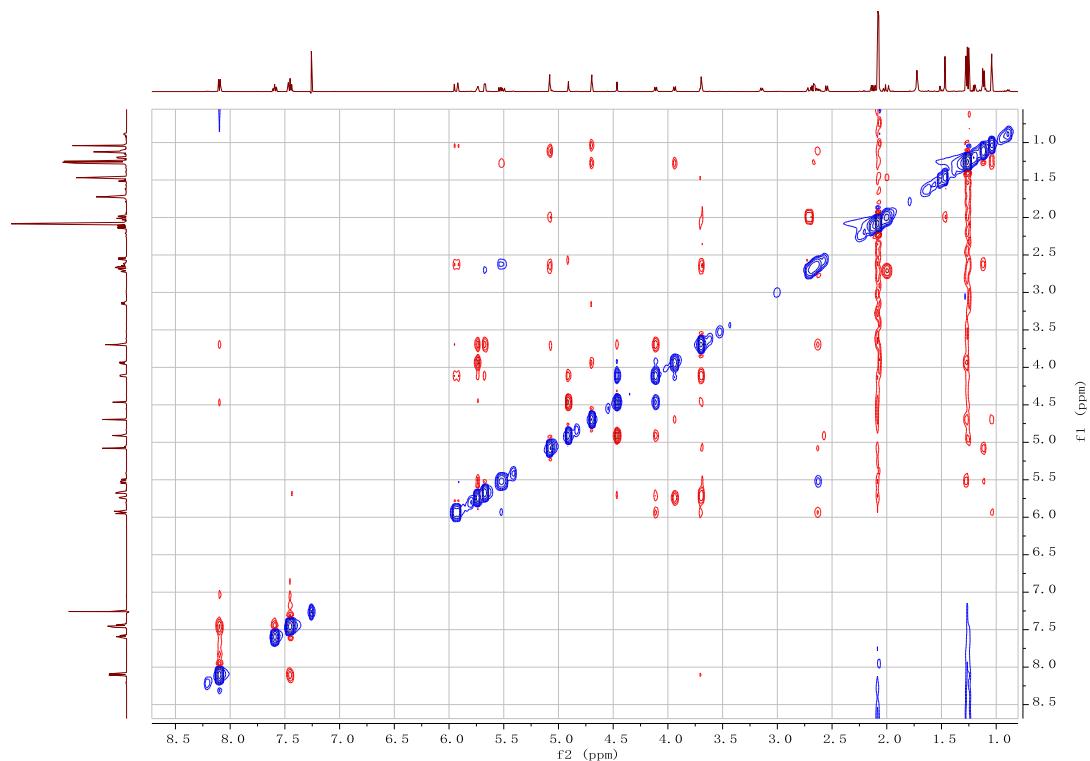


Figure S76. ROESY spectrum of euphatropane G (8)

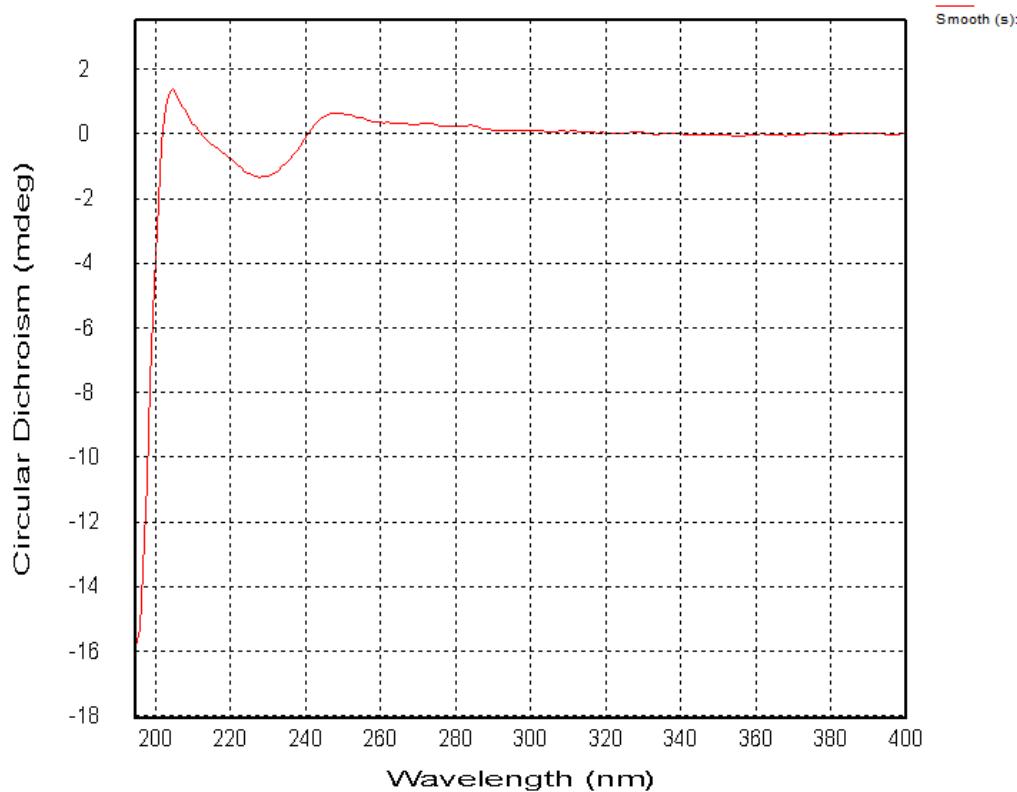


Figure S77. CD spectrum of euphatropane G (**8**)

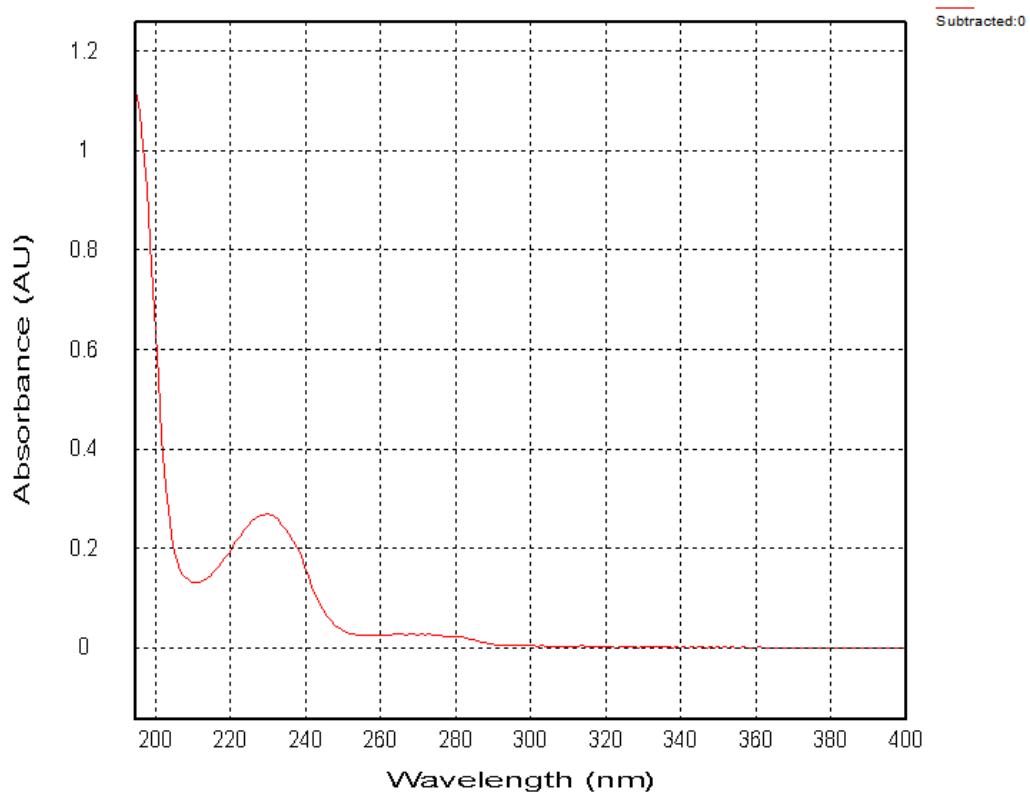


Figure S78. UV spectrum of euphatropane G (**8**)

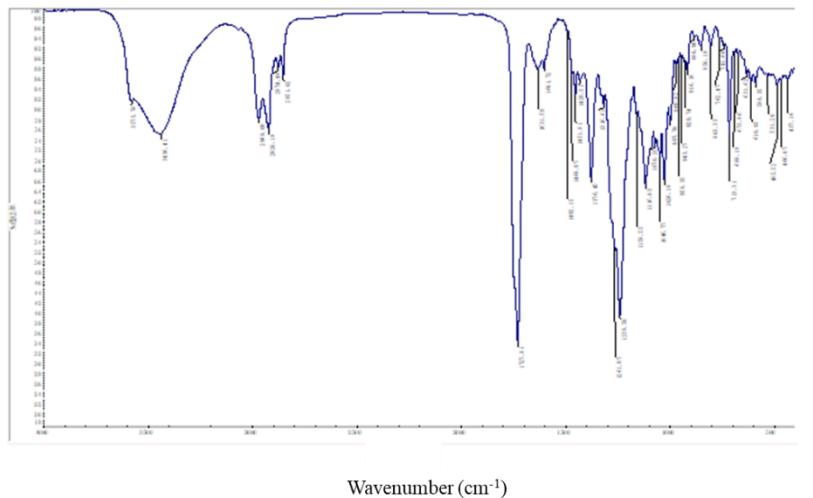
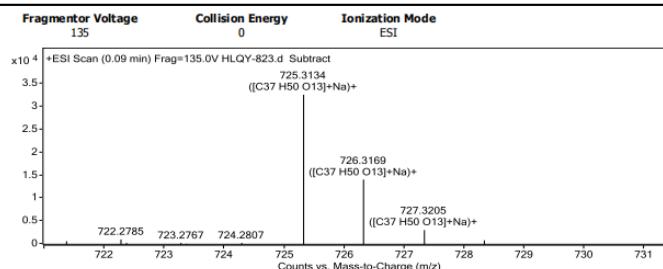


Figure S79. IR spectrum of euphjatrophane G (8)

Qualitative Analysis Report

Data Filename	HLQY-823.d	Sample Name	HLQY-823
Sample Type	Sample	Position	P1-C3
Instrument Name	Instrument 1	User Name	
Acq Method	s.m	Acquired Time	7/13/2020 3:09:11 PM
IRM Calibration Status	Success	DA Method	Default.m
Comment			
Sample Group		Info.	
Acquisition SW	6200 series TOF/6500 series		
Version	Q-TOF 8.05.01 (B5125.2)		

User Spectra



Formula Calculator Element Limits

Element	Min	Max				
C	3	60				
H	0	120				
O	0	30				
Formula Calculator Results						
Formula	CalculatedMass	CalculatedMz	Mz	Diff. (mDa)	Diff. (ppm)	DBE
C37 H50 O13	702.3251	725.3144	725.3134	1.00	1.38	13.0000

-- End Of Report --

Figure S80. (+)-HRESIMS spectrum of euphjatrophane G (8)

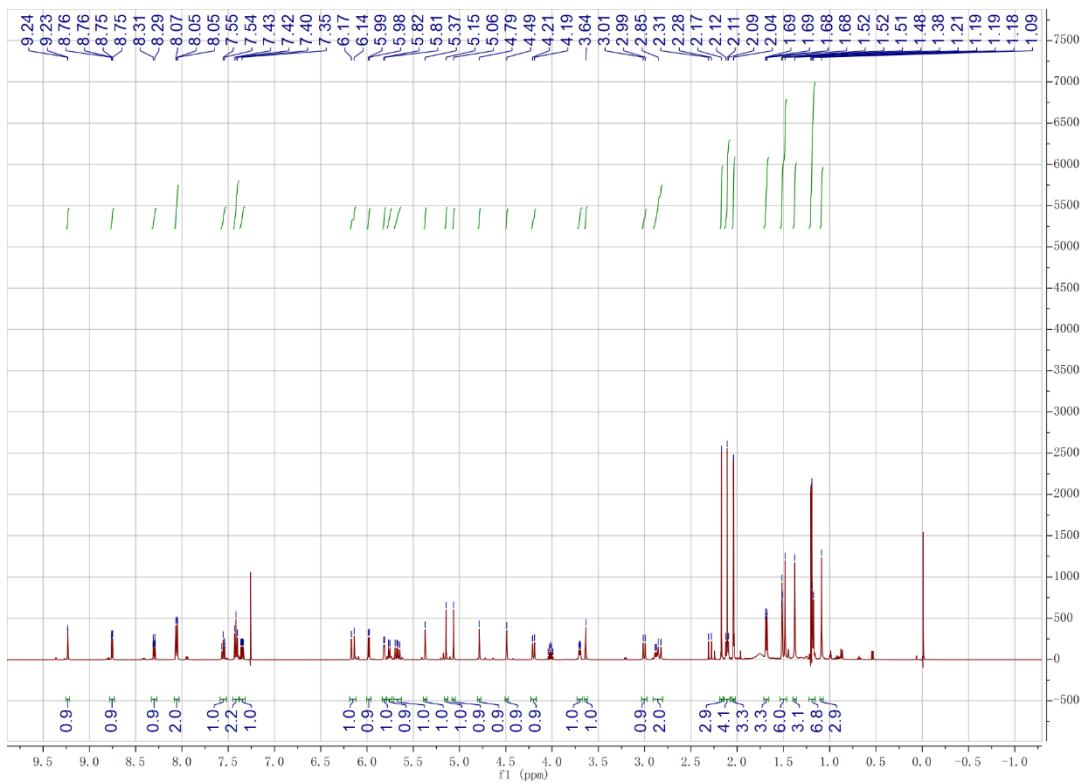


Figure S81. ^1H NMR spectrum of euphepepluone K (9)

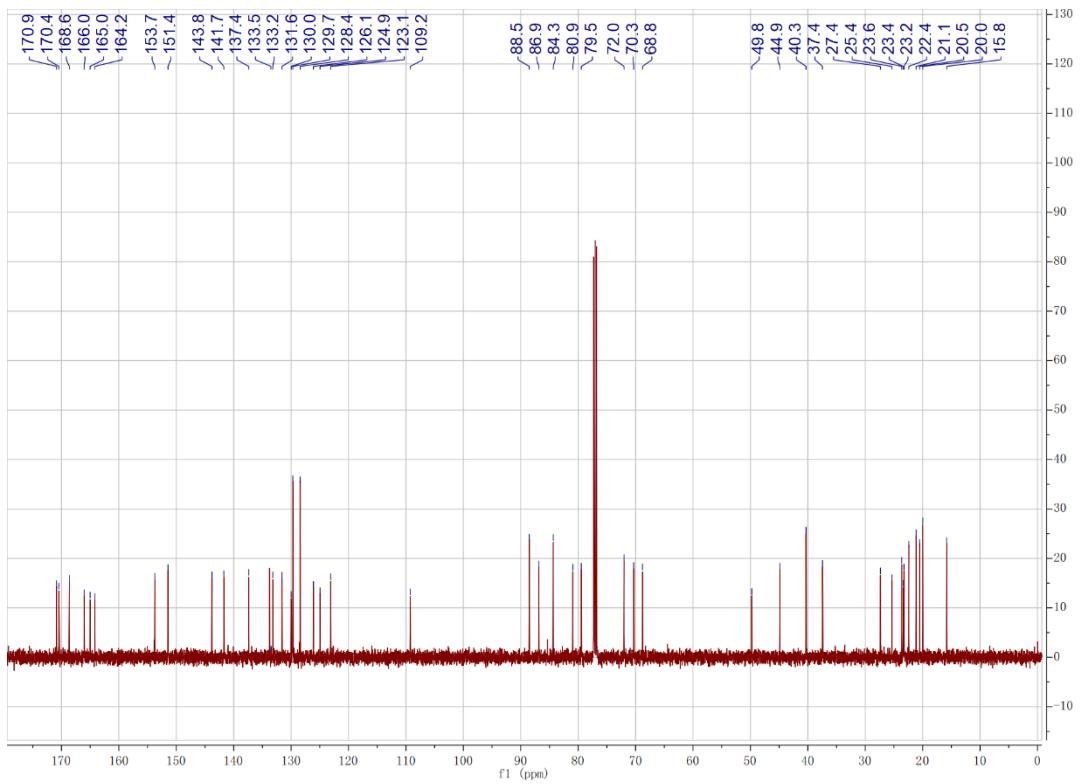


Figure S82. ^{13}C NMR spectrum of euphepepluone K (9)

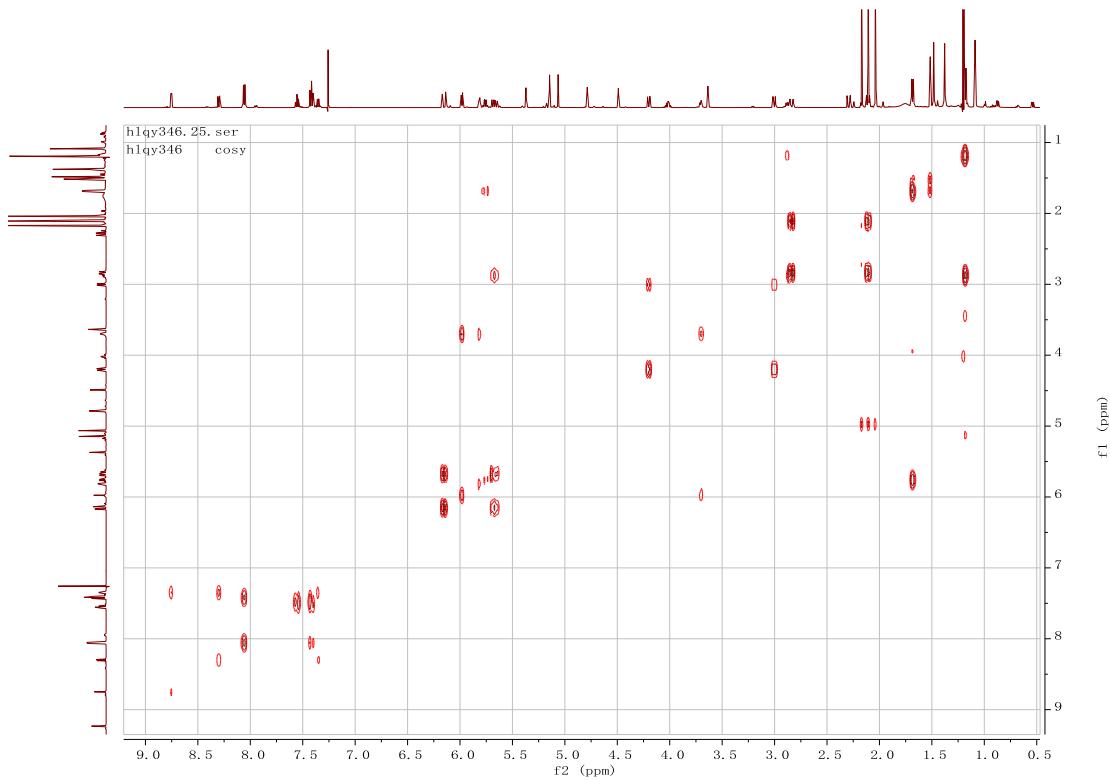


Figure S83. ¹H-¹H COSY spectrum of euphepepluone K (9)

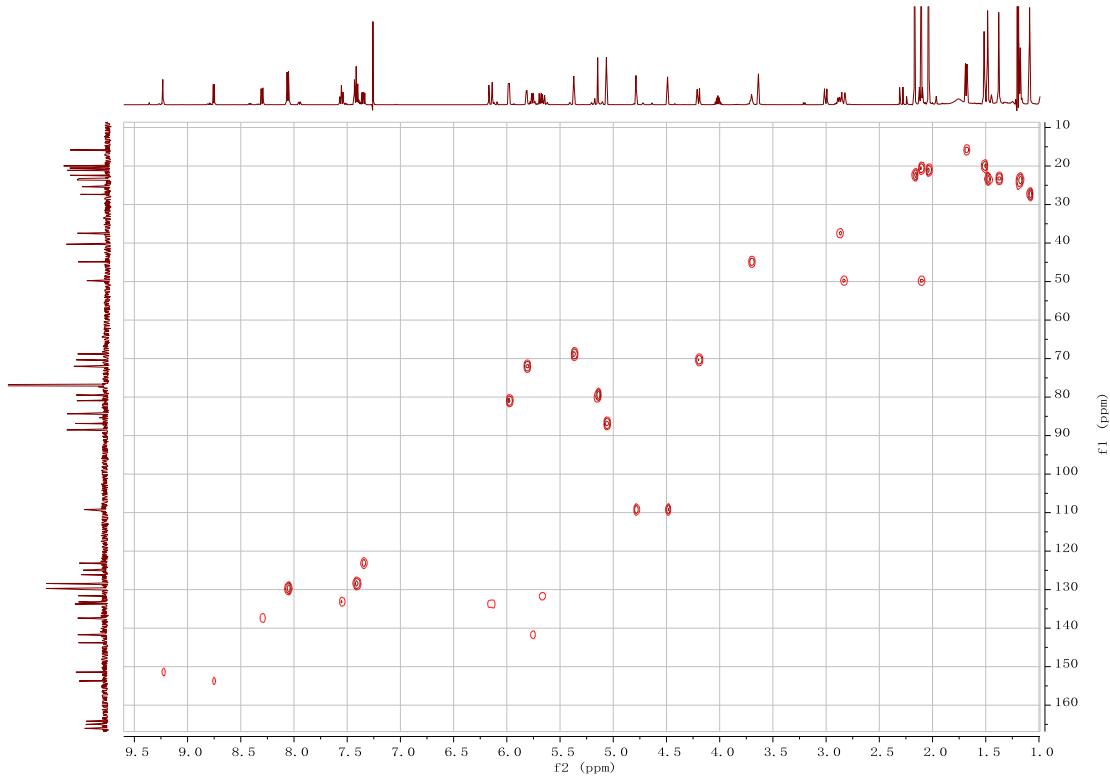


Figure S84. HSQC spectrum of euphepepluone K (9)

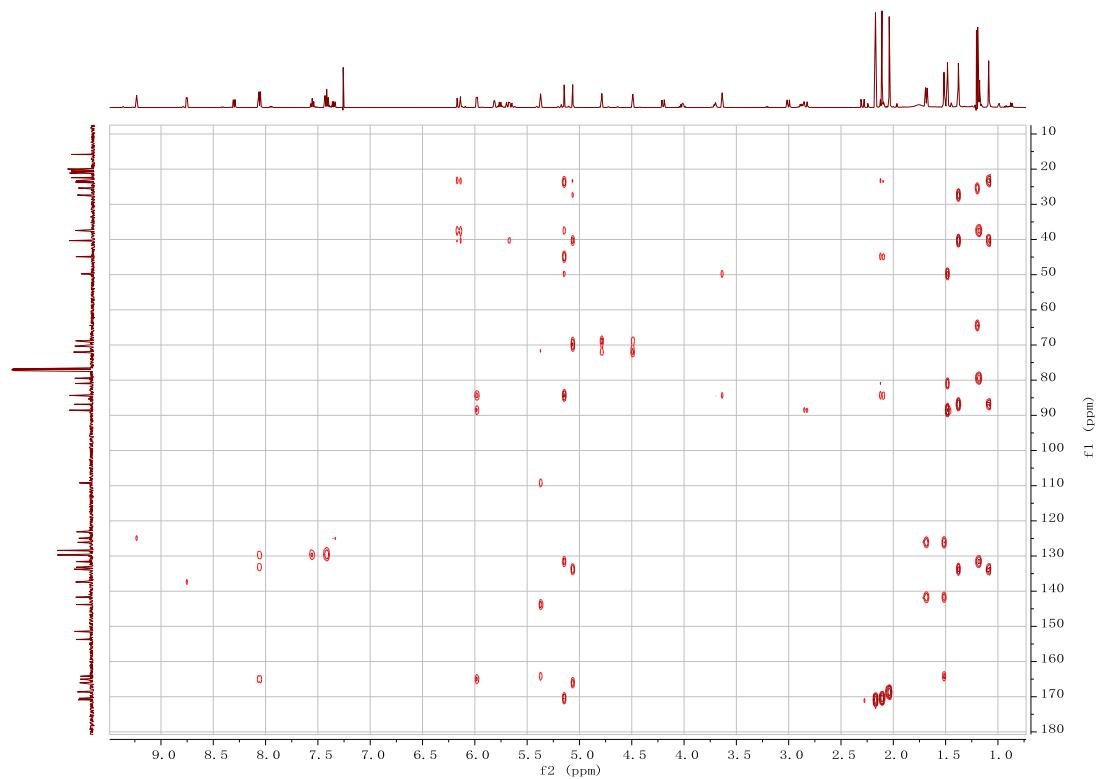


Figure S85. HMBC spectrum of euphepluone K (**9**)

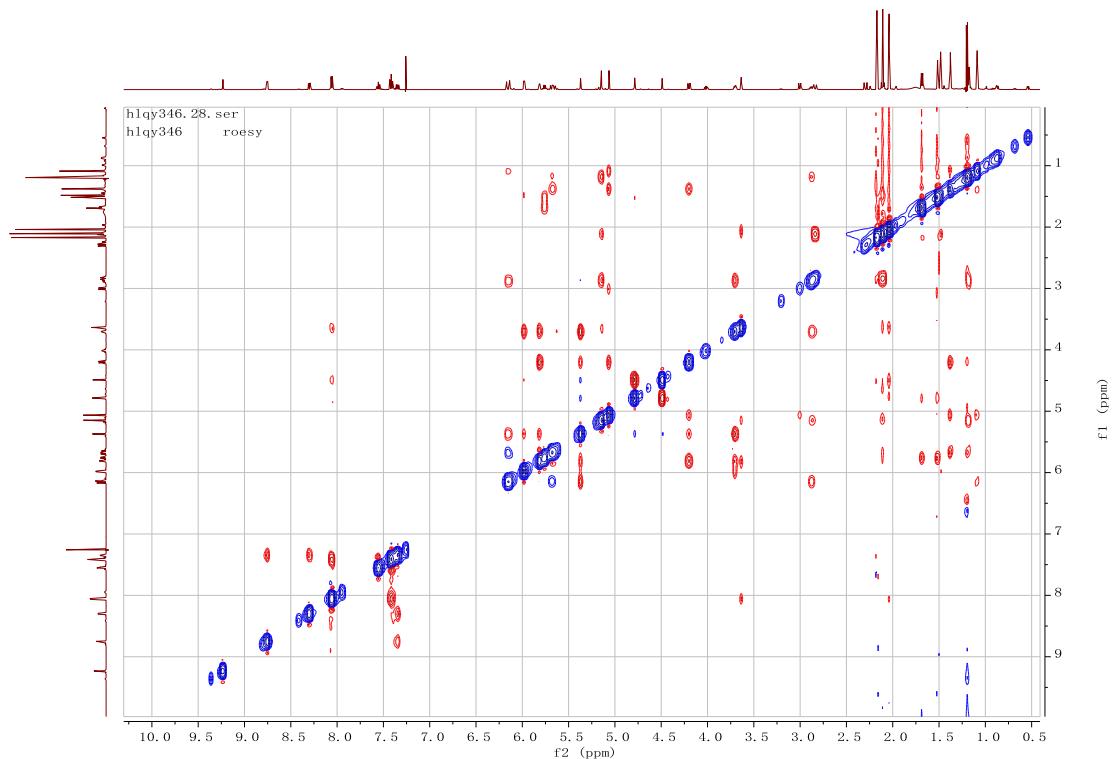


Figure S86. NOESY spectrum of euphepluone K (**9**)

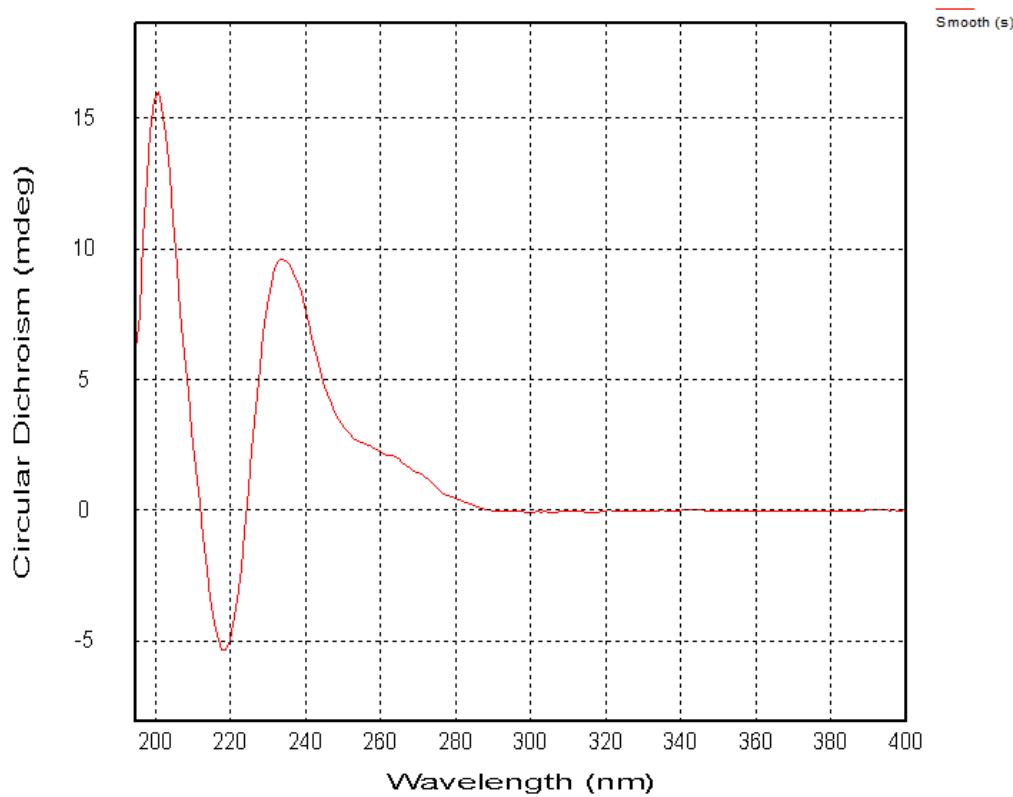


Figure S87. CD spectrum of euphepluone K (9)

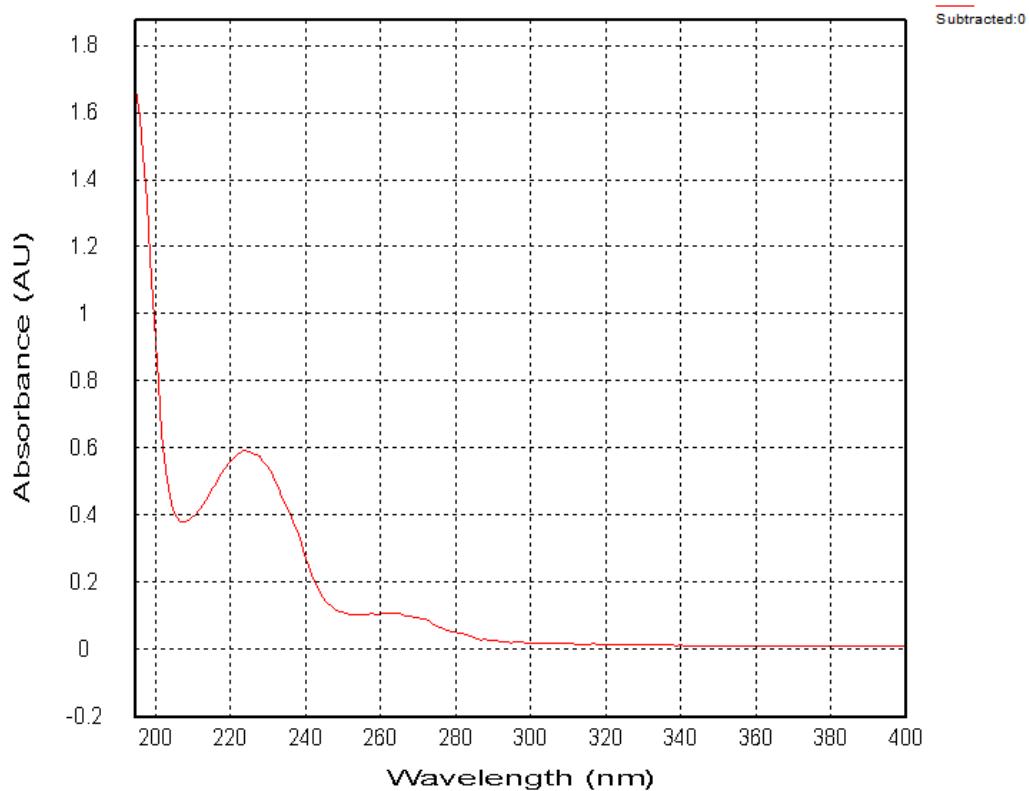


Figure S88. UV spectrum of euphepluone K (9)

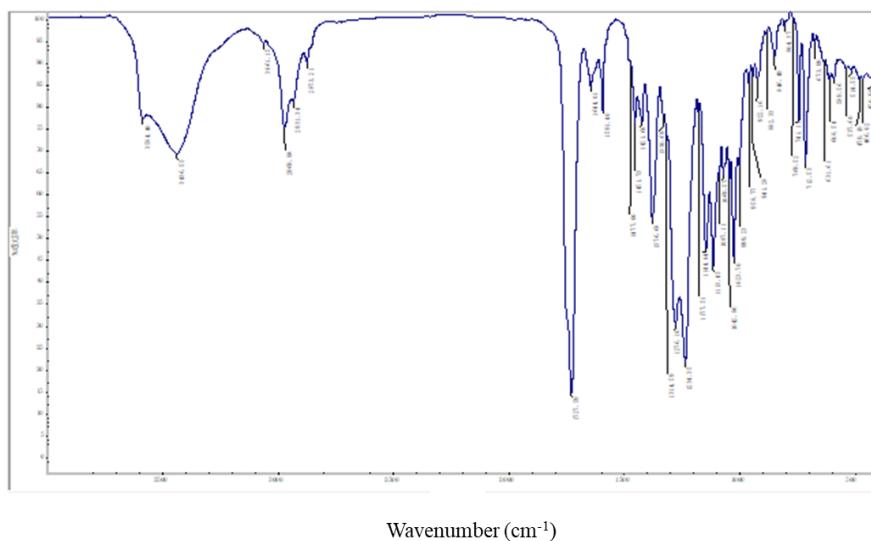
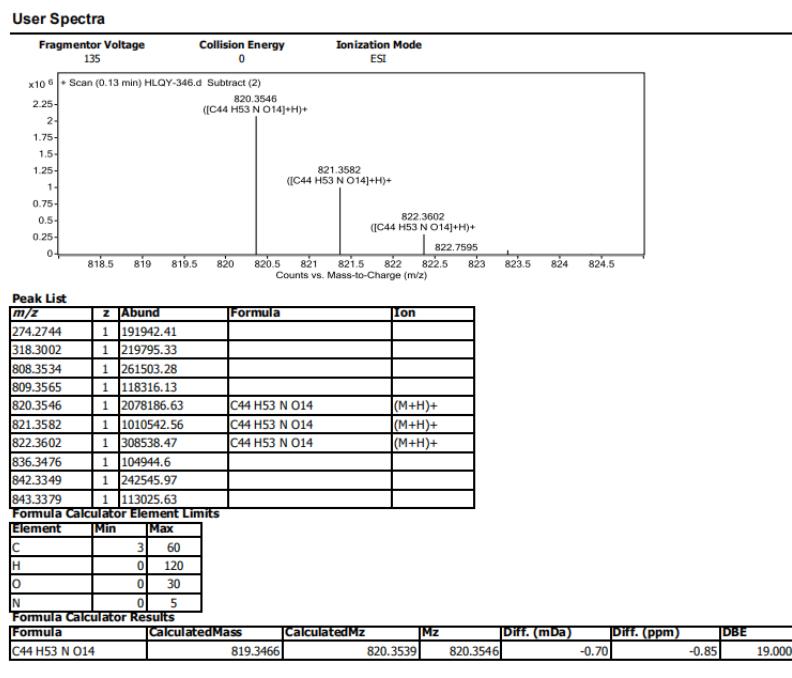


Figure S89. IR spectrum of euphepepluone K (9)

Qualitative Analysis Report

Data Filename	HLQY-346.d	Sample Name	HLQY-346
Sample Type	Sample	Position	P1-A5
Instrument Name	Instrument 1	User Name	
Acq Method	s.m	Acquired Time	8/31/2020 4:02:24 PM
IRM Calibration Status	Success	DA Method	Default.m
Comment			
Sample Group	Info.		
Acquisition SW	6200 series TOF/6500 series		
Version	Q-TOF B.05.01 (B5125.2)		



--- End Of Report ---

Figure S90. (+)-HRESIMS spectrum of euphepepluone K (9)

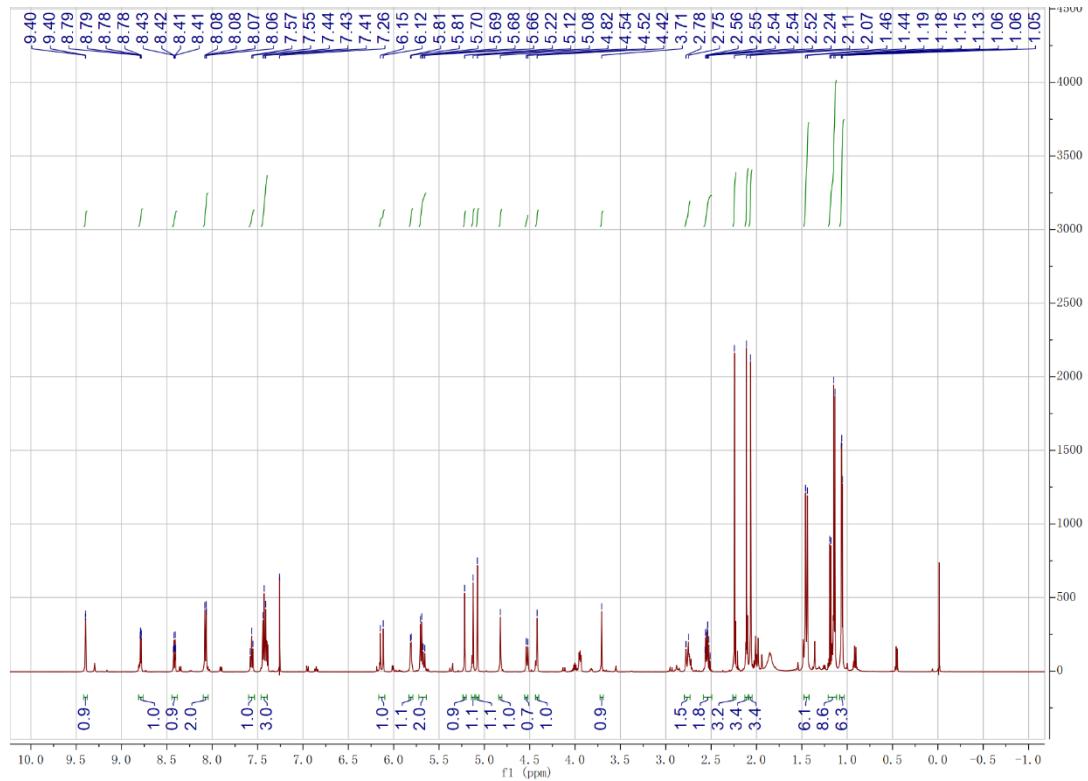


Figure S91. ^1H NMR spectrum of euphepepluone L (**10**)

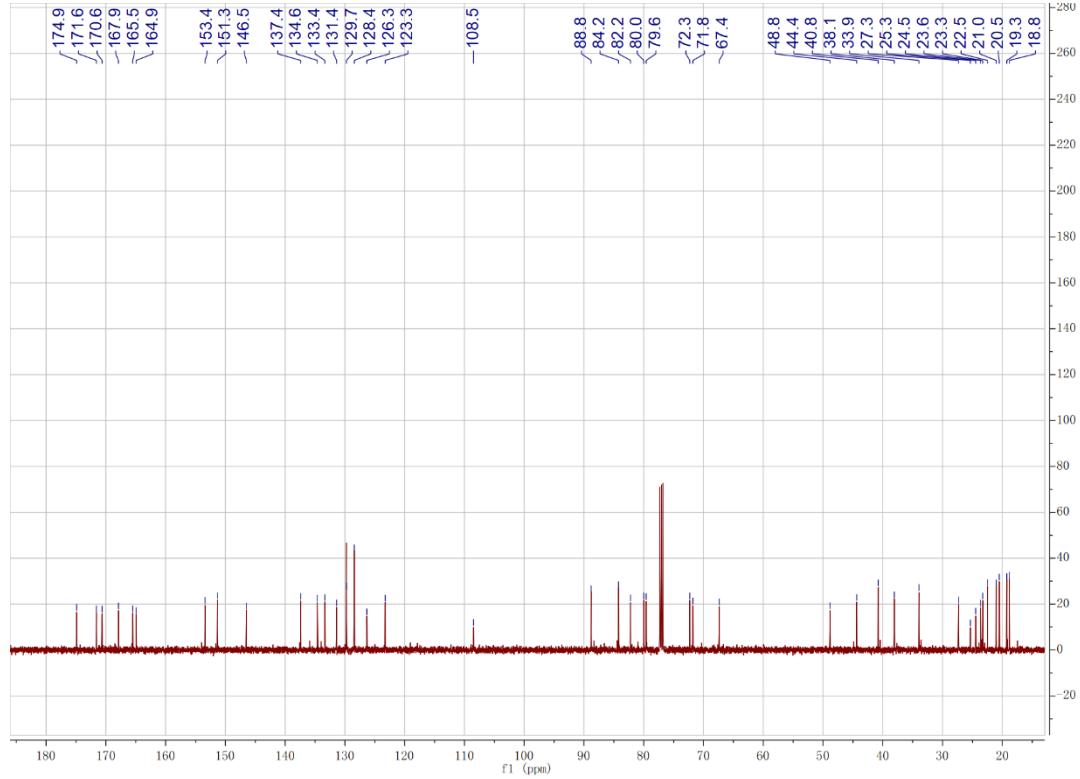


Figure S92. ^{13}C NMR spectrum of euphepluone L (**10**)

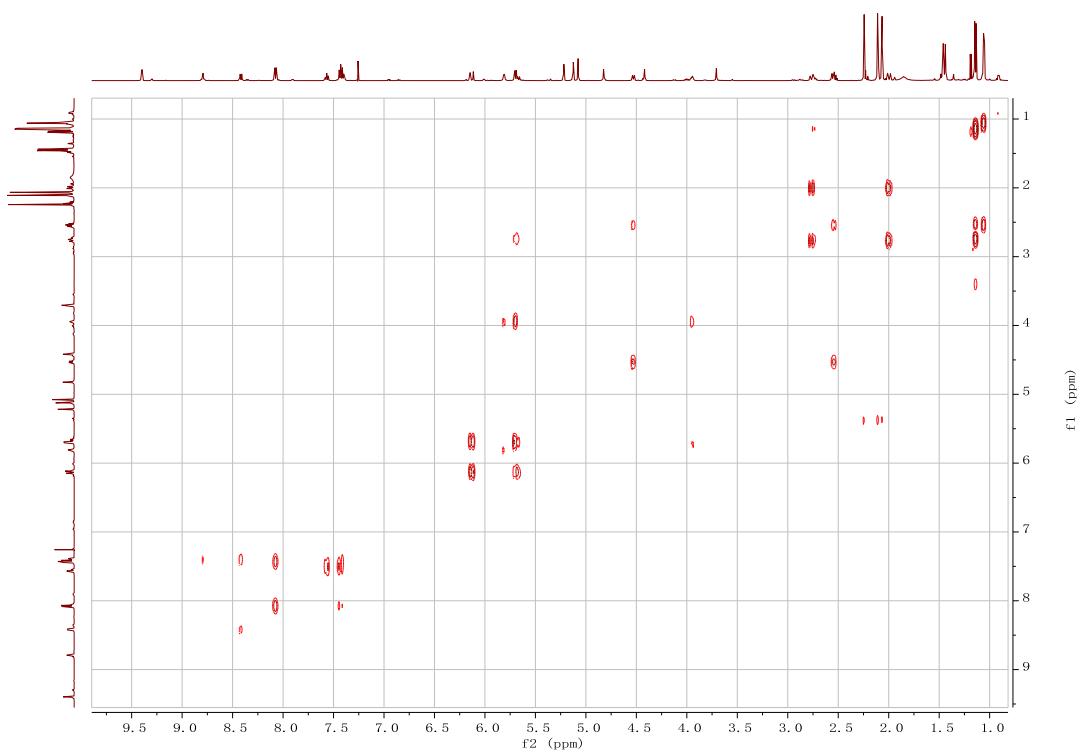


Figure S93. ¹H-¹H COSY spectrum of euphepepluone L (**10**)

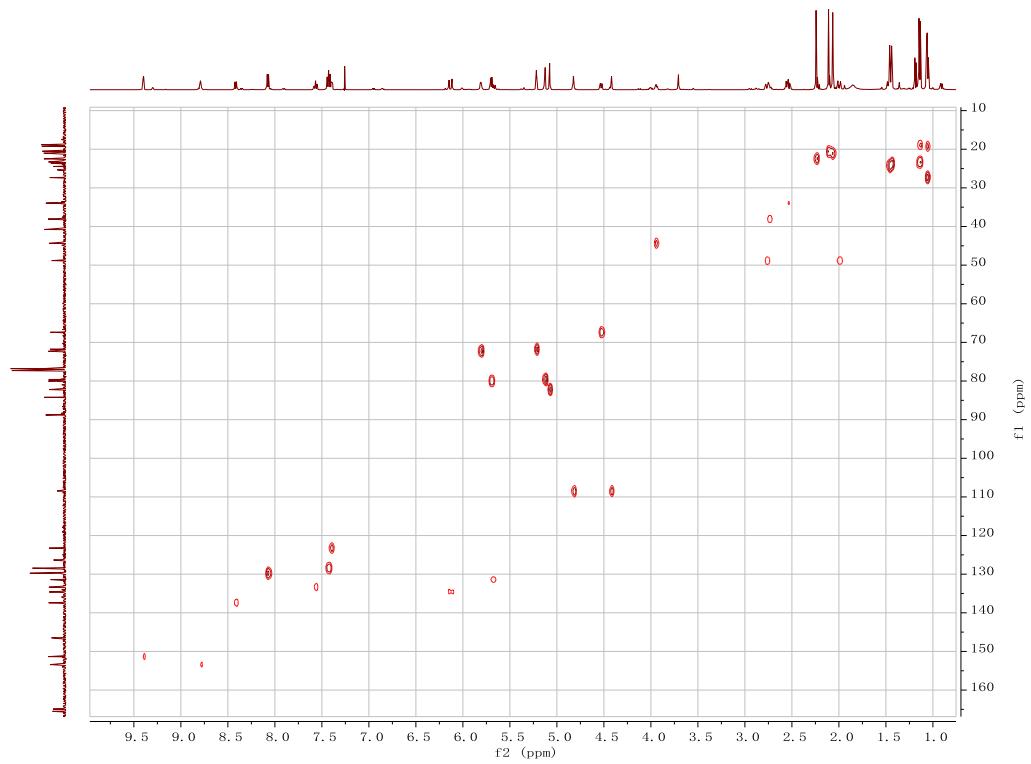


Figure S94. HSQC spectrum of euphepepluone L (**10**)

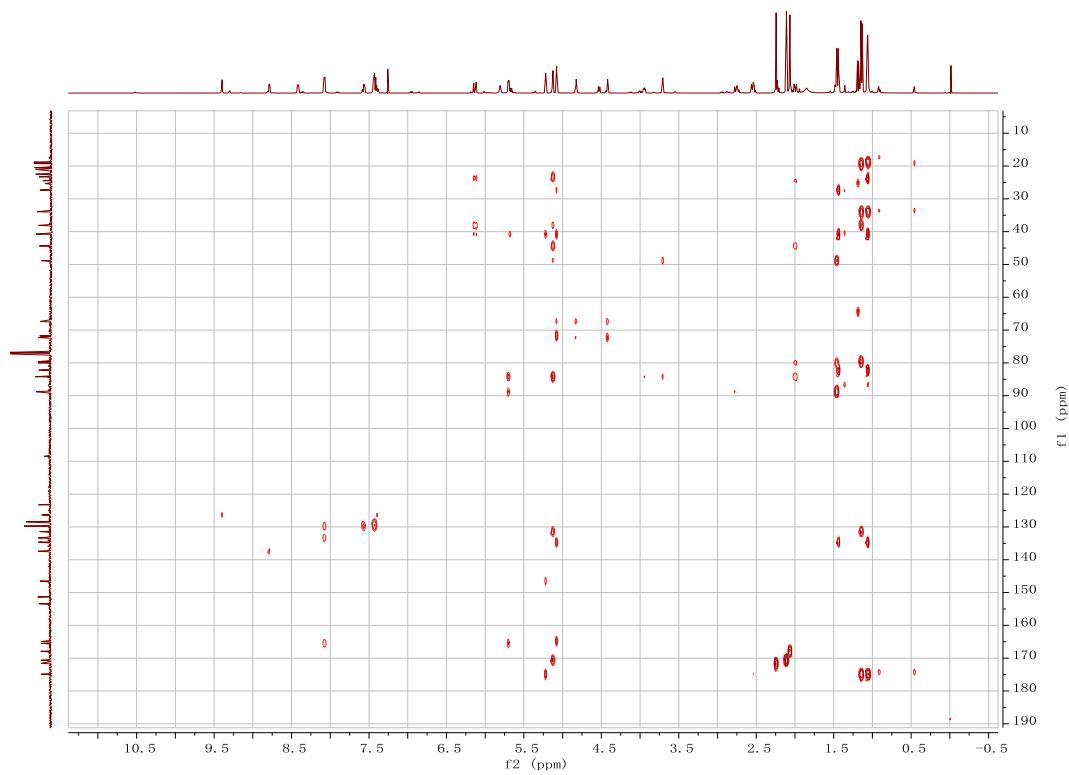


Figure S95. HMBC spectrum of euphepepluone L (**10**)

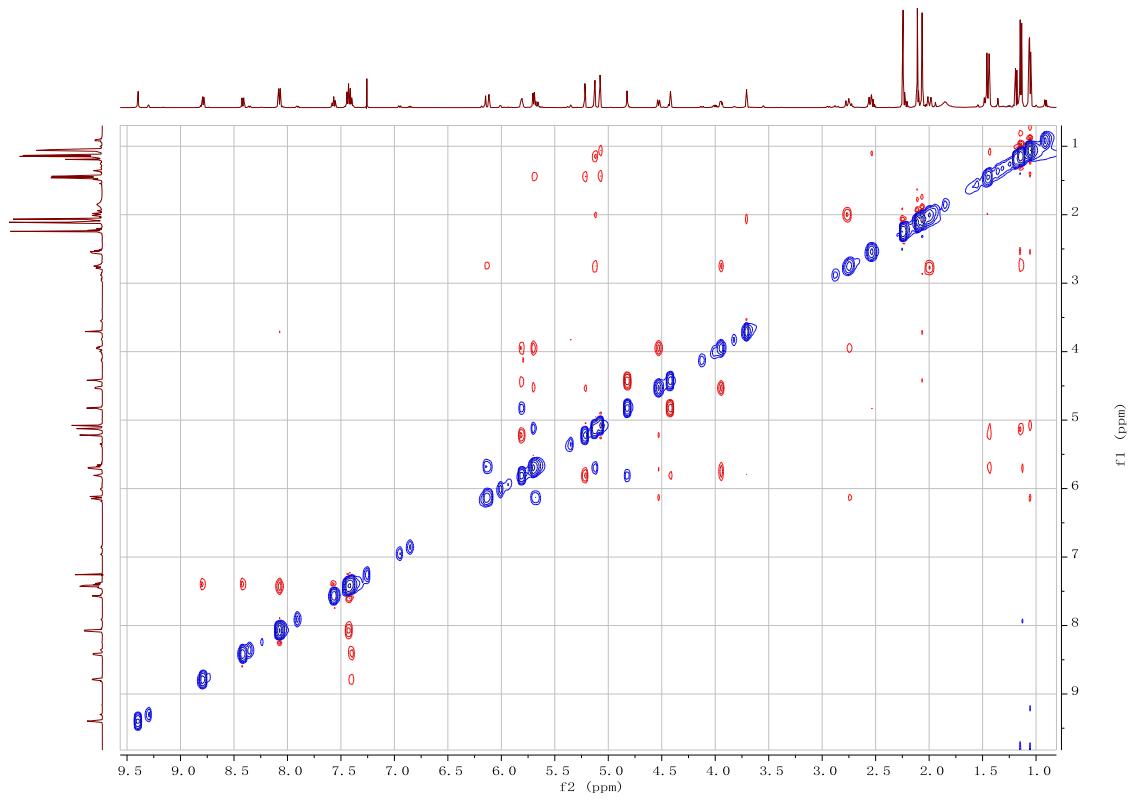


Figure S96. ROESY spectrum of euphepepluone L (**10**)

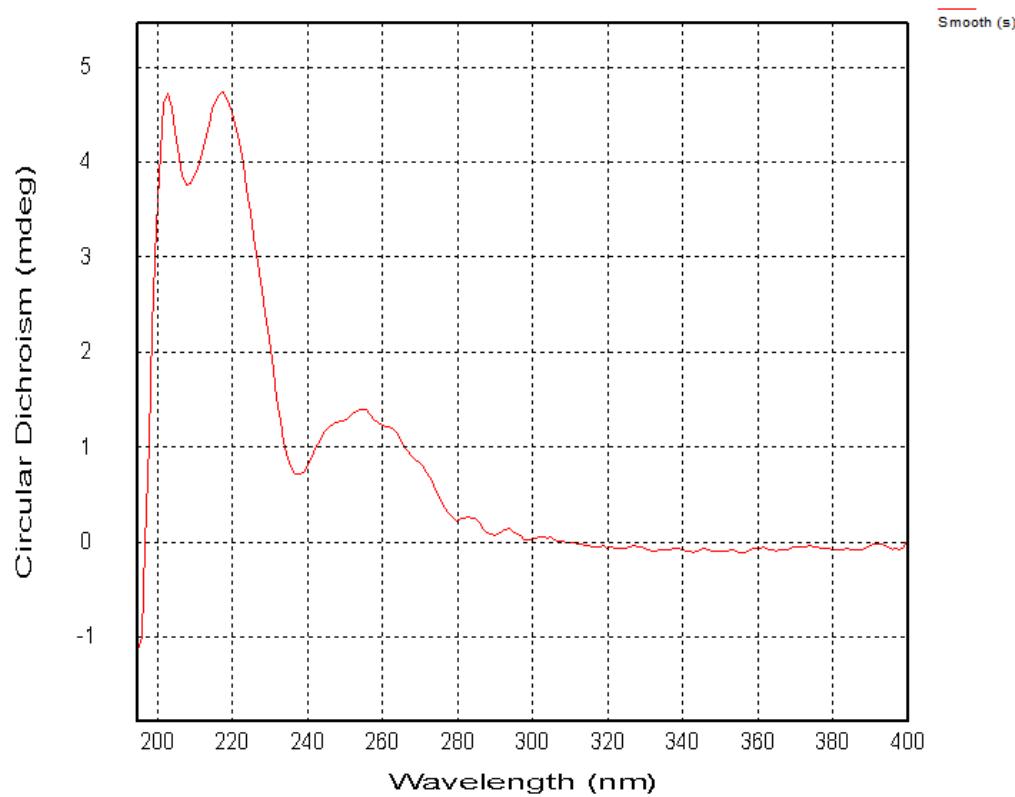


Figure S97. CD spectrum of euphepepluone L (**10**)

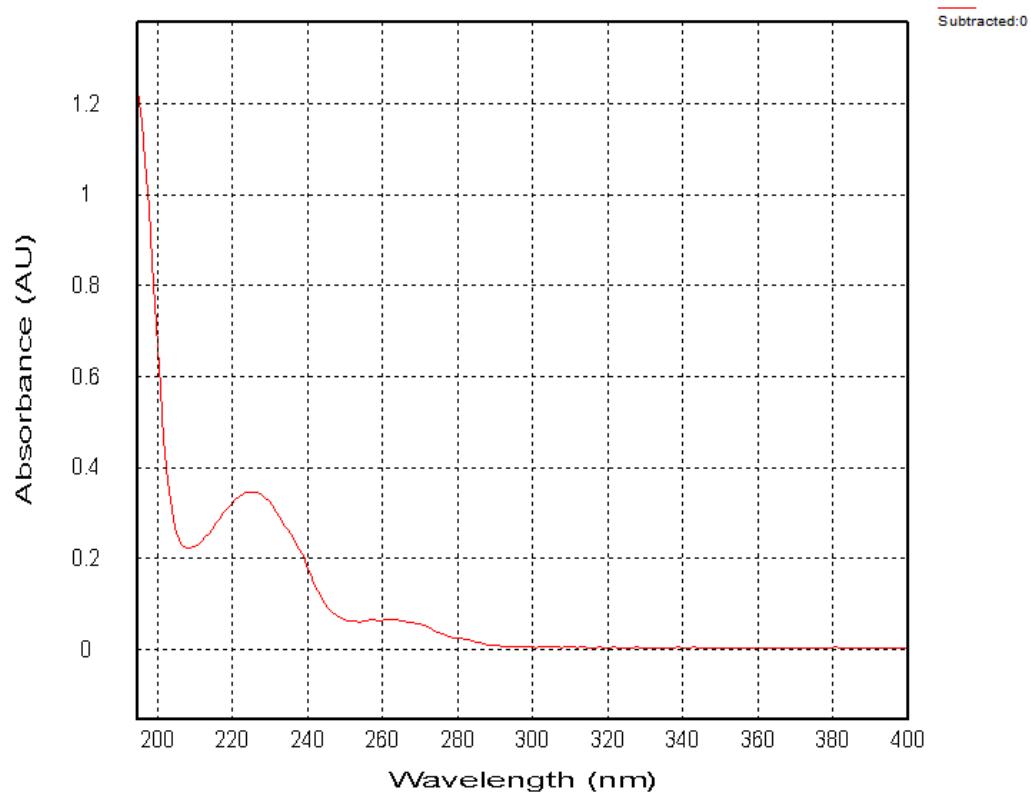


Figure S98. UV spectrum of euphepepluone L (**10**)

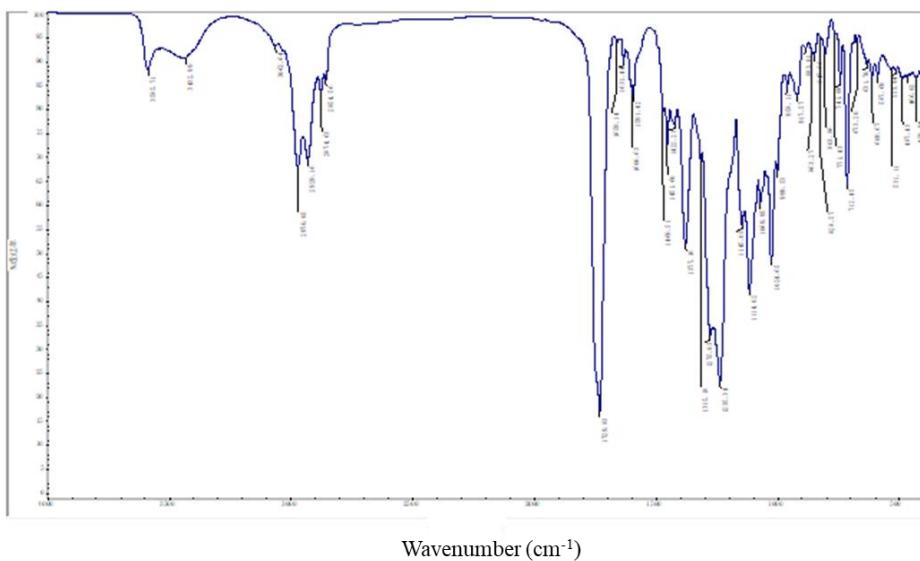
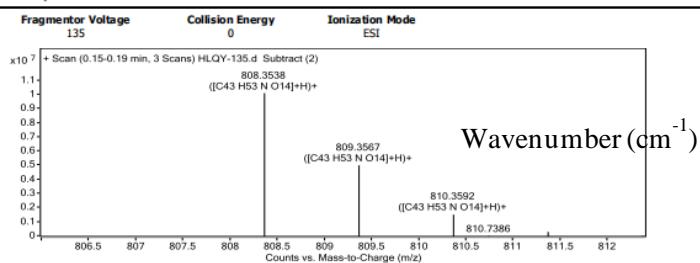


Figure S99. IR spectrum of euphepepluone L (**10**)

Qualitative Analysis Report

Data Filename	HLQY-135.d	Sample Name	HLQY-135
Sample Type	Sample	Position	P1-A7
Instrument Name	Instrument 1	User Name	
Acq Method	s.m	Acquired Time	8/31/2020 4:05:00 PM
IRM Calibration Status	Success	DA Method	Default.m
Comment			
Sample Group	Info.		
Acquisition SW	6200 series TOF/6500 series		
Version	Q-TOF B.05.01 (B5125.2)		

User Spectra



Peak List

m/z	z	Abund	Formula	Ion
138.0546	1	250957.7		
274.2237	1	210272.61		
318.2999	1	236259.41		
764.327	1	226453.28		
808.3538	1	10106264	C43 H53 N O 14	(M+H)+
809.3567	1	5025067.5	C43 H53 N O 14	(M+H)+
810.3592	1	1573988.63	C43 H53 N O 14	(M+H)+
811.3621	1	325669.66	C43 H53 N O 14	(M+H)+
830.3345	1	541736.94		
831.3375	1	253886.89		

Formula Calculator Element Limits

Element	Min	Max
C	3	60
H	0	120
O	0	30
N	0	5

Formula Calculator Results

Formula	CalculatedMass	CalculatedMz	Mz	Diff. (mDa)	Diff. (ppm)	DBE
C43 H53 N O 14	807.3466	808.3539	808.3538	0.10	0.12	18.0000

--- End Of Report ---

Figure S100. (+)-HRESIMS spectrum of euphepepluone L (**10**)

Table S1. ^1H and ^{13}C NMR Data of Euphepepluones G, K, and L in CDCl_3^a

position	Euphepepluone G		Euphepepluone K		Euphepepluone L	
	δ_{H} (J in Hz)	δ_{C}	δ_{H} (J in Hz)	δ_{C}	δ_{H} (J in Hz)	δ_{C}
1a	2.66 d (14.2)	50.3	2.84 d (14.5)	49.9	2.76 d (13.9)	49.0
1b	2.13 dd (14.0, 9.9)		2.11 d (14.5)		2.00 d (13.9)	
2		88.5		88.7		88.9
3	5.86 d (5.7)	80.5	5.98 d (5.9)	81.1	5.71 d (6.3)	80.1
4	3.36 t (4.4)	44.7	3.71 dd (5.5, 4.1)	45	3.94 dd (6.1, 4.3)	44.5
5	5.74 d (2.6)	71.8	5.82 d (3.5)	72.1	5.81 d (3.5)	72.4
6		144.2		143.9		146.6
7a	5.23 s	68.5	5.38 s	68.9	4.54 s	67.5
7b						
8a	4.03 d (11.0)	70.1	4.21 s	70.4	5.22 s	71.9
8b						
9	4.72 s	86.1	5.07 s	87.1	5.09 s	82.4
10		40.1		40.4		40.9
11	5.91 d (16.0)	134	6.15 d (15.9)	133.8	6.13 d (15.8)	134.7
12	5.57 dd (16.0, 9.5)	131.1	5.67 dd (16.0, 9.7)	131.7	5.69 dd (15.7, 9.7)	131.5
13	2.67 m	37.6	2.88 m	37.6	2.74 m	38.2
14	5.09 s	79.4	5.15 s	79.6	5.13 s	79.7
15		84.1		84.5		84.3
16	1.51 s	22.7	1.48 s	23.5	1.46 s	24.6
17a	4.87 s	109.4	4.79 s	109.4	4.83 s	108.6
17b	4.49 s		4.49 s		4.42 s	
18	1.00 s	27.3	1.09 s	27.5	1.07 s	27.4
19	1.28 s	23.3	1.38 s	23.4	1.44 s	23.8
20	1.13 d (7.0)	23.7	1.18 d (7.1)	23.8	1.14 d (6.9)	23.4
OAc-2						
C=O		170.7		171.0		171.7
	2.14 s	22.4	2.17 s	22.5	2.25 s	22.6
OAc-3						
C=O						
OAc-5						
C=O		168.6		168.8		168.0
	1.99 s	21.2	2.04 s	21.2	2.07 s	21.1
OAc-7						
C=O						
OAc-8						
C=O						
OAc-9						
C=O		171.9		170.6		170.7
	2.04 s	20.6				
OAc-14						
C=O		170.5,		170.6		170.7
	2.07 s	20.7	2.11 s	20.6	2.11	20.6

OAc-15

C=O

OBz-3

C=O		165.0		165.1		165.6
1'		130.1		130.1		129.7
2',6'	8.07 d (8.2)	129.8	8.06 d (8.4)	129.8	8.08 d (8.0)	129.9
3',5'	7.43 t (7.3)	128.5	7.42 t (8.0)	128.5	7.43 t (7.8)	128.6
4'	7.56 t (7.2)	133.3	7.56 t (7.4)	133.3	7.57 t (7.4)	133.5

OPrp-7

C=O		172.0
1''	2.36 m	27.6
2''	1.17d (14.0)	9.1

OTig-7

C=O		164.3
1''		126.2
2''	5.77 m	141.9
3''	1.69 dd (7.3, 1.4)	16.0
4''	1.52 s	20.1

OiBu-8

C=O			175.0
1''		2.54 m	34.1
2''		1.14 d (7.0)	18.9
3''		1.06 d (6.9)	19.4

ONic-9

C=O		165.9		164.9
2'''	9.25 d (1.4)	151.1	9.41 br s	151.1
3'''		125.3		126.6
4'''	8.34 dt (8.0, 1.7)	138.0	8.44 dt (7.9, 1.8)	137.9
5'''	7.39 dd (7.9, 4.9)	123.4	7.43 m	123.5
6'''	8.77 dd (4.7, 1.3)	153.4	8.79 d (4.8)	153.2

a: Yang, Y.; Zhou, M.; Wang, D.; Liu, X.; Ye, X.; Wang, G.; Lin, T.; Sun, C.; Ding, R.; Tian, W.; Chen, H. F., Jatrophane Diterpenoids from Euphorbia peplus as Multidrug Resistance Modulators with Inhibitory Effects on the ATR-Chk-1 Pathway. *J Nat Prod* **2021**, 84 (2), 339-351.