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# **Supporting information**

# Concise total syntheses of ericifolione and its analogues enabled by a biomimetic inverse-electron-demand Diels-Alder reaction

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## Abbreviations

TLC	thin-layer chromatography		
NMR	nuclear magnetic resonance		
HRMS	high resolution mass spectroscopy		
ESI	electron spray ionization		
THF	tetrahydrofuran		
EtOAc	ethyl acetate		
NaOAc	sodium acetate		
iPr	isopropyl		
DCM	dichloromethane		
TFA	trifluoroacetic acid		
PTSA	p-toluenesulfonic acid		
IEDDA	inverse electron demand diels-alder		
PPPs	polycyclic polymethylated phloroglucinols		

#### Materials and methods

All reactions were conducted in a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Reagents were purchased at high commercial quality, and used without further purification. Thinlayer chromatography (TLC) was conducted with 0.25 mm Tsingdao silica gel plates (60F-254) and visualized by exposure to UV light (254 nm) or stained with potassium permanganate. Silica gel (ZCX-II, 200-300 mesh) used for flash column chromatography was purchased from Qing Dao Hai Yang Chemical Industry Co. of China. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Brüker Advance 500 (<sup>1</sup>H: 500 MHz, <sup>13</sup>C: 126 MHz). Chemical shifts reported in parts per million relative to CDCl<sub>3</sub> (<sup>1</sup>H NMR: 7.26 ppm, <sup>13</sup>C NMR: 77.16 ppm) or TMS (0.00 ppm). Mass spectrometric data were obtained using ABI-Q Star Elite high resolution mass spectrometer. The oil bath was used for the reactions that require heating. The ice bath was used for the reactions in 0 °C. Yields referred to chromatographically purified products unless otherwise stated. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad singlet.

#### The synthetic procedures

1. Preparation of syncarpic acid 9 or 9'



**4-Acetyl-5-hydroxy-2,2,6,6-tetramethylcyclohex-4-ene-1,3-dione 12.** Preparation of syncarpic acid **9** or **9**' is following a known procedure [1]. Sodium methoxide (7.18 g, 133 mmol) was slowly dissolved in anhydrous methanol (60 mL) at 0 °C. To this clear solution, acetylphloroglucinol **11** (2.77 g, 16.5 mmol) was added carefully and stirred for 10 min under nitrogen atmosphere. Then methyl iodide (32.1 g, 14.1 mL, 228 mmol) was slowly added. After finishing addition, the ice bath was removed and the mixture was stirred at room temperature for 24 h. The crude mixture was quenched with 2

N HCl (60 mL) and MeOH was removed under reduced pressure. The residue was extracted with  $CH_2Cl_2$  (5 × 60 mL) and the combined organic layers were washed with brine, dried over  $Na_2SO_4$  and concentrated *in vacuo*. The resultant crude ketone (3.40 g, 92%, yellow or brown solid) was used directly in the next step.

Syncarpic acid 9'. A 100 mL flask was charged with 6 N HCl (30 mL) and 12 (3.18 g, 14.2 mmol). The reaction mixture was stirred vigorously and refluxed for 24 h. The mixture was cooled to room temperature and extracted with EtOAc (5 × 50 mL). The combined organic layers were washed with brine (30 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under reduced pressure. The resultant crude product was purified by a short flash column chromatography (silica gel, hexane: EtOAc = 1: l) to afford 9 and 9' (2.07 g, 80% yield, yellow or brown solid).

#### 2. Preparations of ericifolione and analogues



#### **General procedure:**

To a 25 mL round-bottom flask equipped with a stir bar was added syncarpic acid **9'** (55 mg, 0.3 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (3 mL). The flask was placed under nitrogen before aldehydes **10** (10 equiv.) and L-proline (4 mg, 0.1 equiv.) were added. The reaction mixture was stirred at  $5\sim10$  °C for 30 minutes, then purified by a 3 cm long flash chromatography (silica gel, CH<sub>2</sub>Cl<sub>2</sub>) to afford the desired unsaturated triketone **7** as colorless oil. The unsaturated triketone was dissolved in THF (3 mL) immediately and stirred at  $20\sim25$  °C for  $3\sim12$  hours under argon atmosphere after addition of NaOAc (49 mg, 2 equiv. based on syncarpic acid **9'**). The solvent was removed in *vacuo* and resultant residue was purified by flash chromatography on silica gel (Hexanes/EtOAc = 50:1 to 20:1) to afford the desired product in 39-89% yields for 2 steps.

## The Comparison of <sup>1</sup>H and <sup>13</sup>C NMR Data of Natural and Synthetic ericifolione



ericifolione (1a)

<sup>1</sup> H chemical shift/δ ppm	<sup>1</sup> H Chemical shift /δ	$\Delta \delta/ppm^a$	<sup>13</sup> C chemical shift/δ	<sup>13</sup> C Chemical shift /δ	$\Delta \delta/ppm^a$
(Natural sample, 400	ppm (Synthetic		ppm (Natural sample,	ppm (Synthetic sample,	
MHz) <sup>a</sup>	sample, 500 MHz) <sup>b</sup>		100 MHz) <sup>a</sup>	126 MHz) <sup>b</sup>	
9.01 (1H, s, OH)	δ 9.00 (s, 1H)	-0.01	212.0 (s, C-3)	212.0	0.0
5.55 (1H, d, <i>J</i> = 2.5 Hz,	5.55 (d, <i>J</i> = 2.4 Hz,	0.00	211.4 (s, C-13)	211.4	0.0
H-9)	1H)				

2.81 (1H, dd, $J = 8.3$ ,	2.82 (dd, J = 10.2, 1.5	+0.01	197.8 (s, C-5)	197.8	0.0
1.4 Hz, H-7)	Hz, 1H)				
1.87 (2H, m, H-8, H-24)	1.95 – 1.80 (m, 2H)	+0.01	196.9 (s, C-11)	197.0	+0.1
1.74 (1H, m, H-21)	1.78-1.70 (m, 1H)	0.00	175.0 (s, C-15)	175.0	0.0
1.52 (6H, s, H-18, H-29)	1.51 (s, 6H)	-0.01	167.4 (s, C-1)	167.4	0.0
1.44 (3H, s, H-17)	1.44 (s, 3H)	0.00	116.7 (s, C-6)	116.8	+0.1
1.40 (3H, s, H-28)	1.39 (s, 3H)	-0.01	107.1 (s, C-10)	107.3	+0.2
1.39 (6H, s, H-19, H-30)	1.38 (s, 6H)	-0.01	79.4 (d, C-9)	79.5	+0.1
1.35-1.40 (2H, m, <i>J</i> =	1.37 – 1.40 (m, 1H)		56.2 (s, C-12)	56.3	+0.1
6.8 Hz, H-20)	1.27-1.30 (m, 1H)				
1.35 (3H, s, H-27)	1.35 (s, 3H)	0.00	55.2 (s, C-4)	55.3	+0.1
1.34 (3H, s, H-16)	1.34 (s, 3H)	_	48.6 (s, C-14)	48.7	+0.1
(not assigned)					
1.07 (3H, d, <i>J</i> = 6.4 Hz,	1.06 (d, J = 6.5 Hz,	-0.01	47.3 (s, C-2)	47.4	+0.1
H-23)	3H)				
0.99 (3H, d, <i>J</i> = 6.8 Hz,	0.99 (d, <i>J</i> = 6.6 Hz,	0.00	44.7 (t, C-20)	44.9	+0.2
H-22)	3H)				
0.95 (3H, d, <i>J</i> = 6.8 Hz,	0.94 (d, <i>J</i> = 6.8 Hz,	-0.01	41.4 (d, C-8)	41.6	+0.2
H-25)	3H)				
0.75 (3H, d, <i>J</i> = 6.8 Hz,	0.75 (d, $J = 6.8$ Hz,	0.00	27.2 (d, C-7)	27.4	+0.2
H-26)	3H)				
			26.7 (d, C-24)	26.7 (2C)	0.0
			26.7 (s, C-28)		0.0
			25.4 (s, C-17)	25.5	+0.1
			25.3 (d, C-21)	25.5	+0.2
			25.1 (s, C-29)	25.2	+0.1
			25.0 (d, C-18)	25.1	+0.1
			24.9 (s, C-27)	25.0	+0.1
			24.5 (s, C-19)	24.6	+0.1
			24.3 (s, C-22)	24.4	+0.1
			23.8 (s, C-25)	23.9	+0.1
			23.7 (s) (C-30 or C-	23.8	+0.1
			16)		
			21.3 (s) (C-30 or C-	21.5	+0.2
			16)		
			21.0 (s, C-23)	21.2	+0.2
			19.6 (s, C-26)	19.7	+0.1

 $^{a}\Delta\delta$ /ppm refers to the relative difference of each signal between the synthetic and natural samples.

# Reference

[1] H.X. Liu, K. Chen, Y. Yuan, et al., Org. Biomol. Chem. 14 (2016) 7354-7360.

#### <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra data of compounds 1a-1f



ericifolione (1a): 72% yield for 2 steps, 54 mg, yellowish oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  9.00 (s, 1H), 5.55 (d, J = 2.4 Hz, 1H), 2.82 (dd, J = 10.2, 1.5 Hz, 1H), 1.95 – 1.80 (m, 2H), 1.78-1.70 (m, 1H), 1.51 (s, 6H), 1.44 (s, 3H), 1.39 (s, 3H), 1.38 (s, 6H), 1.37 – 1.40 (m, 1H), 1.35 (s, 3H), 1.34 (s, 3H), 1.27-1.30 (m, 1H), 1.06 (d, J = 6.5 Hz, 3H), 0.99 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.75 (d, J = 6.8 Hz, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  212.0, 211.4, 197.8, 197.0, 175.0, 167.4, 116.8, 107.3, 79.5, 56.3, 55.3, 48.7, 47.4, 44.9, 41.6, 27.4, 26.7 (2C), 25.5, 25.5, 25.2, 25.1, 25.0, 24.6, 24.4, 23.9, 23.8, 21.5, 21.2, 19.7. HRMS calculated for C<sub>30</sub>H<sub>45</sub>O<sub>6</sub> (M + H<sup>+</sup>): 501.3216, found: 501.3232.



**4-ethyl-2-(2-hydroxy-3,3,5,5-tetramethyl-4,6-dioxocyclohex-1-en-1-yl)-3,6,6,8,8-pentamethyl-2,3,4,8-tetrahydro-5H-chromene-5,7(6H)-dione (1b):** 39% yield for 3 steps, 26 mg, pale solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.85 (s, 1H), 5.45 (d, J = 1.7 Hz, 1H), 2.47 (dd, J = 9.8, 3.1 Hz, 1H), 2.21 (q, J = 7.1 Hz, 1H), 1.75 – 1.64 (m, 1H), 1.50 (s, 3H), 1.49 (s, 3H), 1.47 (s, 3H), 1.44 (s, 3H), 1.42 (dd, J = 7.0, 2.9 Hz, 1H), 1.38 (s, 6H), 1.35 (s, 3H), 1.34 (s, 3H), 1.05 (t, J = 7.4 Hz, 3H), 0.84 (d, J = 7.2 Hz, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  212.0, 211.3, 198.6, 197.4, 175.3, 167.2, 114.2, 107.2, 78.5, 56.4, 55.3, 48.7, 47.5, 38.4, 31.3, 27.8, 27.4, 25.6, 25.4, 25.1, 24.9, 24.6, 21.2, 13.0, 12.2. HRMS calculated for C<sub>26</sub>H<sub>37</sub>O<sub>6</sub> (M +H<sup>+</sup>): 445.2590, found: 445.2588.



**3-ethyl-2-(2-hydroxy-3,3,5,5-tetramethyl-4,6-dioxocyclohex-1-en-1-yl)-6,6,8,8-tetramethyl-4-propyl-2,3,4,8-tetrahydro-5***H***-chromene-<b>5,7(6***H***)-dione (1c):** 58% yield for 2 steps, 41 mg, yellowish oil. <sup>1</sup>**H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.87 (s, 1H), 5.48 (d, J = 1.4 Hz, 1H), 2.78 (d, J = 7.6 Hz, 1H), 1.83 (d, J = 9.3 Hz, 1H), 1.61-1.54 (m, 2H), 1.49 (s, 3H), 1.49 (s, 3H), 1.45 (s, 3H), 1.40 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H), 1.32-1.42 (m, 3H), 0.98 (t, J = 6.5 Hz, 3H), 0.86-0.94 (m, 4H). <sup>13</sup>**C NMR** (125 MHz, CDCl<sub>3</sub>)  $\delta$  212.0, 211.3, 198.5, 197.3, 175.2, 167.5, 114.4, 107.2, 78.9, 56.4, 55.4, 48.7, 47.5, 39.2, 36.8, 32.2, 27.5, 25.4, 25.2, 25.1, 24.8, 24.1, 21.0, 20.6, 19.0, 14.1, 12.5. **HRMS** calculated for C<sub>28</sub>H<sub>41</sub>O<sub>6</sub> (M + H<sup>+</sup>): 473.2903, found: 473.2902.



**4-butyl-2-(2-hydroxy-3,3,5,5-tetramethyl-4,6-dioxocyclohex-1-en-1-yl)-6,6,8,8-tetramethyl-3-propyl-2,3,4,8-tetrahydro-5***H***-chromene-<b>5,7(6***H***)-dione (1d):** 84% yield for 2 steps, 63 mg, yellowish oil. <sup>1</sup>**H** NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.91 (s, 1H), 5.48 (d, J = 1.9 Hz, 1H), 2.70 (dd, J = 7.0, 2.5 Hz, 1H), 1.95 (d, J = 10.7 Hz, 1H), 1.50 (s, 3H), 1.50 (s, 3H), 1.45 (s, 3H), 1.42 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H), 1.30 – 1.50 (m, 7H), 1.24 – 1.14 (m, 2H), 0.94 0.92-1.00 (m, 1H), (t, J = 7.0 Hz, 3H), 0.82 (t, J = 7.2 Hz, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  212.1, 211.3, 198.5, 197.2, 175.2, 167.6, 114.5, 107.3, 79.1, 56.5, 55.4, 48.8, 47.5, 36.8, 34.4, 33.3, 29.7, 28.3, 27.5, 25.6, 25.4, 25.2, 25.0 (2C), 24.1, 22.7, 21.0, 20.7, 14.2 (2C). HRMS calculated for C<sub>30</sub>H<sub>45</sub>O<sub>6</sub> (M + H<sup>+</sup>): 501.3216, found: 501.3226.



**3-butyl-2-(2-hydroxy-3,3,5,5-tetramethyl-4,6-dioxocyclohex-1-en-1-yl)-6,6,8,8-tetramethyl-4-pentyl-2,3,4,8tetrahydro-5***H***-chromene-5,7(6***H***)-dione (1e): 51% yield for 2 steps, 41 mg, yellowish oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.89 (s, 1H), 5.47 (d,** *J* **= 1.6 Hz, 1H), 2.78 – 2.66 (dd,** *J* **= 7.8, 2.5 Hz, 1H), 1.92 (d,** *J* **= 10.9 Hz, 1H), 1.61 – 1.51 (m, 2H), 1.49 (s, 3H), 1.49 (s, 3H), 1.45 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.43 (s, 3H), 1.43-1.31 (m, 6H), 1.31 – 1.08 (m, 5H), 0.96-0.87 (m, 4H), 0.82 (t,** *J* **= 7.1 Hz, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 212.1, 211.3, 198.5, 197.2, 175.2, 167.5, 114.5, 107.2, 79.0, 56.5, 55.3, 48.7, 47.5, 37.1, 34.6, 33.2, 31.8, 29.7, 27.5, 27.1, 25.6, 25.5, 25.4, 25.2, 24.9, 24.8, 24.2, 22.7, 22.7, 21.0, 14.2, 13.9. HRMS calculated for C<sub>32</sub>H<sub>49</sub>O<sub>6</sub> (M +H<sup>+</sup>): 529.3529, found: 529.3538.** 



**3-benzyl-2-(2-hydroxy-3,3,5,5-tetramethyl-4,6-dioxocyclohex-1-en-1-yl)-6,6,8,8-tetramethyl-4-phenethyl-2,3,4,8-tetrahydro-5H-chromene-5,7(6H)-dione (1f):** 89% yield for 2 steps, 79 mg, yellowish oil. <sup>1</sup>**H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.00 (s, 1H), 7.32 – 7.15 (m, 5H), 7.14 – 7.07 (m, 3H), 6.93 (d, *J* = 6.9 Hz, 2H), 5.67 (d, *J* = 1.7 Hz, 1H), 2.76 – 2.71

(m, 2H), 2.71 - 2.62 (m, 1H), 2.47 (d, J = 11.1 Hz, 1H), 2.37 - 2.30 (m, 1H), 2.14 (dd, J = 13.4, 11.2 Hz, 1H), 1.93 - 1.84 (m, 1H), 1.73 - 1.62 (m, 1H), 1.53 (s, 3H), 1.51 (s, 3H), 1.49 (s, 6H), 1.43 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  212.0, 211.1, 198.0, 197.2, 175.3, 167.7, 141.7, 138.8, 128.9, 128.9, 128.7, 128.4, 126.7, 125.8, 114.0, 107.0, 78.8, 56.5, 55.4, 48.8, 47.6, 38.9, 36.5, 33.4, 32.9, 32.5, 27.1, 25.5, 25.5, 25.5, 25.3, 25.3, 23.8, 21.4. HRMS calculated for C<sub>38</sub>H<sub>45</sub>O<sub>6</sub> (M + H<sup>+</sup>): 597.3216, found: 597.3224.



Methyl 3-((2R,3S,4S)-2-(2-hydroxy-3,3,5,5-tetramethyl-4,6-dioxocyclohex-1-en-1-yl)-3-(2-methoxy-2-oxoethyl)-6,6,8 ,8-tetramethyl-5,7-dioxo-3,4,5,6,7,8-hexahydro-2H-chromen-4-yl)propanoate (1h): 63% yield for 2 steps, 53 mg, yellowish oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.90 (s, 1H), 5.51 (d, J = 1.9 Hz, 1H), 3.70 (s, 3H), 3.64 (s, 3 H), 2.69 (ddd, J = 16.0, 8.2, 3.9 Hz, 2H), 2.58 (d, J = 9.9 Hz, 1H), 2.48 (ddd, J = 16.1, 9.9, 6.1 Hz, 1H), 2.2 9 (dd, J = 15.9, 3.4 Hz, 1H), 2.07 – 1.97 (m, 2H), 1.81 – 1.71 (m, 1H), 1.51 (s, 3H), 1.48 (s, 3H), 1.47 (s, 3H), 1.44 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  211. 57, 210.78, 197.83, 197.09, 175.30, 173.48, 171.95, 167.94, 112.97, 106.24, 77.54, 56.32, 55.23, 52.14, 51.66, 48.69, 47.41, 33.94, 33.76, 32.06, 31.74, 29.61, 27.22, 25.52, 25.22, 24.97, 24.79, 24.43, 24.33, 21.04. HRMS calculated for C<sub>30</sub>H<sub>41</sub>O<sub>10</sub> (M + H<sup>+</sup>): 561.2700, found: 561.2712.

# Copies of <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra





















. 9

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 f2 (ppm)