

*Supporting Information*

**Short and Scalable Synthesis of Cynandione A**

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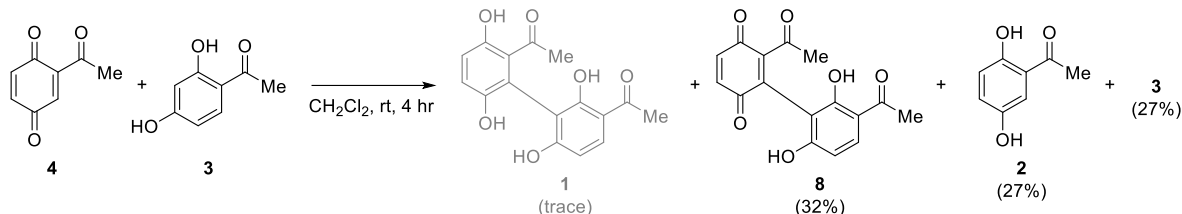
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## 1. General methods

All chemicals were of reagent-grade and were used as purchased. All reactions were performed under an inert atmosphere of dry nitrogen using distilled dry solvents. The reactions were monitored by thin-layer chromatography (TLC) using silica gel 60 F-254 plates (40 x 10 mm). Compounds on the TLC plates were visualized under UV light and by spraying with either potassium permanganate or anisaldehyde solutions. Flash column chromatography was conducted on silica gel 60 (230–400 mesh). Melting points were measured using a Buchi M-560 melting point apparatus without correction.  $^1\text{H}$  and  $^{13}\text{C}$  nuclear magnetic resonance (NMR) spectra were recorded on a JEOL 600 MHz Fourier transform spectrometers at ambient temperature. The chemical shifts were reported in ppm ( $\delta$ ) units relative to the reference peak of the solvent ( $^1\text{H}$  NMR:  $\text{CD}_3\text{OD}-d_4$  (3.30 ppm) or  $\text{DMSO}-d_6$  (2.50 ppm);  $^{13}\text{C}$  NMR:  $\text{CD}_3\text{OD}-d_4$  (49.00 ppm) or  $\text{DMSO}-d_6$  (40.00ppm)). The NMR peak multiplicities are designated as: s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublets), dt (doublet of triplets), td (triplet of doublets), and br (broad signal). The Fourier transform infrared (FT-IR) spectra were obtained using an Agilent Cary 630 spectrometer. The high-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) mass spectrometry.

## 2. Experimental procedures and data analysis

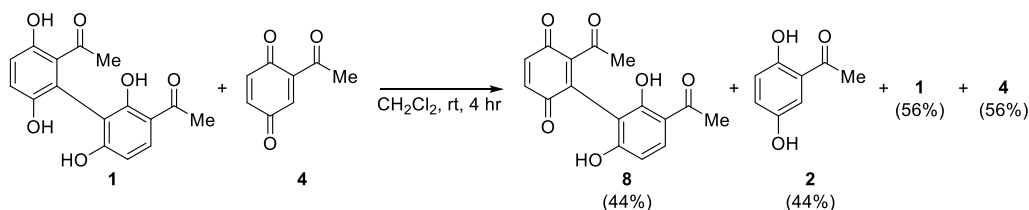
- The initial trial for the synthesis of **1** (Scheme 3 in the main text).



A solution of **4** (80 mg, 0.53 mmol, 1.0 equiv) and **3** (81 mg, 0.53 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (3 ml) was stirred at room temperature for 4 h, then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to yield **8** (51 mg, 32%), **2** (22 mg, 27%) and **3** (22 mg, 27%).

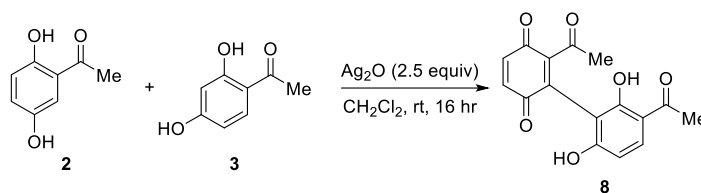
**Compound 8**: orange solid; mp 172–173 °C; <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ 7.85 (d, *J* = 8.9 Hz, 1H), 7.06 (d, *J* = 10.2 Hz, 1H), 6.99 (d, *J* = 10.3 Hz, 1H), 6.50 (d, *J* = 8.9 Hz, 1H), 2.55 (s, 3H), 2.25 (s, 3H); <sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>) δ 204.0, 199.6, 186.2, 185.9, 162.4, 161.9, 145.1, 137.4, 136.8, 136.6, 134.9, 112.7, 108.1, 106.9, 30.6, 26.7.; IR (neat, cm<sup>-1</sup>) ν<sub>max</sub> 3242, 1699, 1608, 1300, 1058, 849, 695; HRMS (ESI): calcd. for C<sub>16</sub>H<sub>11</sub>O<sub>6</sub> [M-H]<sup>-</sup> 299.05501, found 299.05368.

- The redox reaction between **1** and **4**

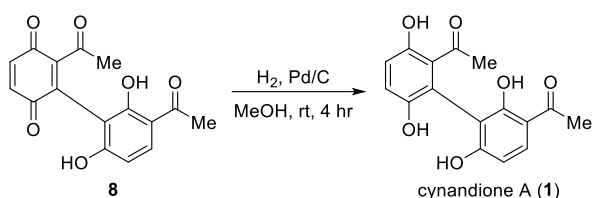


A solution of **1** (91 mg, 0.30 mmol, 1.0 equiv) and **4** (45 mg, 0.30 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (2 ml) was stirred at room temperature for 4 h, then concentrated under reduced pressure to obtain the crude residue. The yield of each compound was determined by <sup>1</sup>H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

- Synthesis of **1** via a tandem oxidation/regioselective arylation strategy (Scheme 4 in the main text).



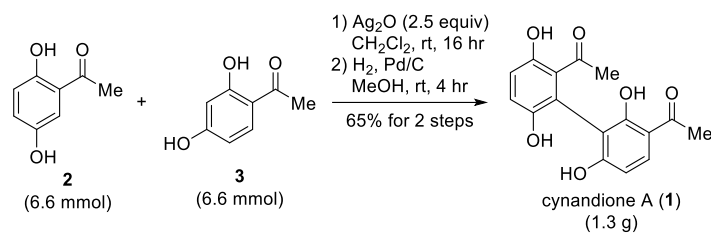
To a solution of **2** (300 mg, 2.0 mmol, 1.0 equiv) and **3** (300 mg, 2.0 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (8 ml),  $\text{Ag}_2\text{O}$  (1.14 g, 2.5 equiv) was added at room temperature. After stirring for 16 h, the mixture was filtered through a pad of Celite and rinsed with  $\text{CH}_2\text{Cl}_2$ . The filtrate was then concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 3:1, *v/v*) to yield **8** (361 mg, 61%).



To a solution of **8** (100 mg, 0.33 mmol, 1.0 equiv) in MeOH (5 ml), Pd/C (10 mg) was added and bubbled with  $\text{H}_2(\text{g})$  for 30 min, then stirred for 4 h under an atmosphere of  $\text{H}_2(\text{g})$  at room temperature. The mixture was then filtered through a pad of Celite, rinsed with MeOH, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/acetone = 3:1, *v/v*) to yield **1** (89 mg, 88%).

cynandione A (**1**): yellow solid; mp 201–202 °C;  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO}-d_6$ )  $\delta$  9.31 (s, 1H), 7.71 (d,  $J = 8.9$  Hz, 1H), 6.74 (d,  $J = 8.7$  Hz, 1H), 6.69 (d,  $J = 8.7$  Hz, 1H), 6.44 (d,  $J = 8.9$  Hz, 1H), 2.54 (s, 3H), 2.21 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO}-d_6$ )  $\delta$  203.7, 203.5, 163.0, 162.8, 148.5, 147.5, 132.7, 130.7, 118.7, 117.9, 116.3, 112.8, 112.0, 108.0, 31.2, 26.6; IR (neat,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$  3490, 3356, 3076, 1664, 1500, 1308, 1149, 1049, 803; HRMS (ESI): calcd. for  $\text{C}_{16}\text{H}_{13}\text{O}_6$   $[\text{M}-\text{H}]^-$  301.07066, found 301.06924.

- The gram-scale synthesis of **1** (Scheme 5 in the main text).



To a solution of **2** (1.0 g, 6.6 mmol, 1.0 equiv) and **3** (1.0 g, 6.6 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (15 ml), Ag<sub>2</sub>O (3.81 g, 2.5 equiv) was added and stirred for 16 h at room temperature. The mixture was then filtered through a pad of Celite, rinsed with CH<sub>2</sub>Cl<sub>2</sub>, and concentrated under reduced pressure. To a solution of the crude residue in MeOH (10 ml), Pd/C (200 mg) was added and bubbled with H<sub>2</sub>(g) for 30 min, then stirred for 4 h under an atmosphere of H<sub>2</sub>(g) at room temperature. The mixture was then filtered through a pad of Celite, rinsed with MeOH, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/acetone = 3:1, v/v) to yield **1** (1.3 g, 65% for two steps).

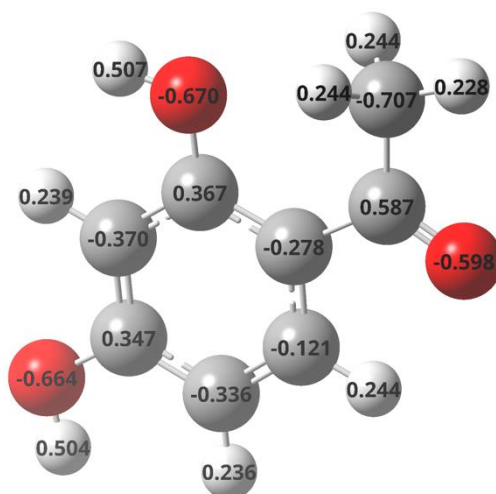
### 3. Data comparison of natural and synthetic cynandione A (1)

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR of the natural and synthetic **1**.

| $^1\text{H}$ NMR                                   |   | $^{13}\text{C}$ NMR                                |   |
|--|---|--|---|
| Natural<br>(800 MHz,<br>DMSO- $d_6$ ) <sup>1</sup> | Synthetic<br>(600 MHz,<br>DMSO- $d_6$ ) | Natural<br>(200 MHz,<br>DMSO- $d_6$ ) <sup>1</sup> | Synthetic<br>(150 MHz,<br>DMSO- $d_6$ ) |
| 12.86 (s, 1H)                                      | -                                       | 203.7  | 203.7                                   |
| 10.31 (s, 1H)                                      | -                                       | 203.6  | 203.5                                   |
| 9.31 (s, 1H)                                       | 9.31 (s, 1H)                            | 163.0  | 163.0                                   |
| 8.49 (s, 1H)                                       | -                                       | 162.8  | 162.8                                   |
| 7.68 (d, 1H)                                       | 7.71 (d, 1H)                            | 148.5  | 148.5                                   |
| 6.72 (d, 1H)                                       | 6.74 (d, 1H)                            | 147.5  | 147.5                                   |
| 6.67 (d, 1H)                                       | 6.69 (d, 1H)                            | 132.7  | 132.7                                   |
| 6.43 (d, 1H)                                       | 6.44 (d, 1H)                            | 130.7  | 130.7                                   |
| 2.50 (s, 3H)                                       | 2.54 (s, 3H)                            | 118.7  | 118.7                                   |
| 2.19 (s, 3H)                                       | 2.21 (s, 3H)                            | 117.9  | 117.9                                   |
|  |   | 116.3  | 116.3                                   |
|  |   | 112.8  | 112.8                                   |
|  |   | 112.0  | 112.0                                   |
|  |   | 108.0  | 108.0                                   |
|  |   | 31.2   | 31.2                                    |
|  |   | 26.7   | 26.6                                    |

#### 4. The natural bond orbital (NBO) charge analysis of **3**.

For the natural bond orbital (NBO) charge analysis<sup>1</sup> of **3**, density functional theory (DFT) calculations were performed using the Gaussian 16 program suite.<sup>2</sup> Geometry optimization of **3** was carried out by employing the M06-2X hybrid density functional,<sup>3</sup> the Def2-TZVP basis set,<sup>4</sup> and the implicit solvation model based on density (SMD)<sup>5</sup> to simulate the dichloromethane solvent. Such theoretical methods have shown reliable results in computational investigations related to the synthesis of various natural products.<sup>6</sup> From the optimized geometry, vibrational frequencies were calculated to ensure that there were no imaginary frequencies and the structure was properly optimized. NBO atomic charges were then calculated using the same level of theory, as shown in Figure S1.



**Figure S1.** The NBO charge analysis of **3**.



## 5. References

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## 6. Copies of spectra ( $^1\text{H}$ and $^{13}\text{C}$ NMR)

