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# Facile construction of 3-hydroxyphenanthrene-1,4-diones: key intermediates to tanshinone I and its A-ring-modified analogue

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ABSTRACT

A mild synthetic approach was established allowing for a convenient construction of tricyclic hydroxyphenanthraquinones, the key precursor for total synthesis of tanshinone I. This tandem process includes decarboxylative radical alkylation, intramolecular C–H arylation and one-pot O-demethylation and aromatization. Variously substituted phenylpropanoic acids were well tolerated in this approach, and synthesis of tanshinone I (**1**) was finally successful in six straight steps in 19% overall yields from commercially available 5-bromovanillin.



## 1. Introduction

Tanshinones represent a series of chromophore-containing abietane-derived diterpenes isolated exclusively from *Salvia miltiorrhiza* Bunge (*Danshen* in Chinese), one of the most famous traditional Chinese medicines (TCMs) for the treatment of cardiovascular disease, heart failure as well as inflammatory diseases including chronic hepatitis and arthritis.[1] Among the tanshinone family, tanshinone I (**1**), tanshinone IIA (**2**), cryptotanshinone (**3**) and neo-tanshinlactone (**4**) (Fig. 1) are the major bioactive constituents exhibiting various pharmacological activities, such as cardioprotection, antibacterial, anti-inflammatory, antioxidant, anti-platelet aggregation and anticancer properties.[2,3] Recently, an increasing attention has been drawn to tanshinone I due to its unique in vitro and in vivo anticancer activities.[4,5] Synthetically, several methods towards total synthesis of **1** have been reported since the early 1960s (Scheme 1), including semi-synthesis from podocarpic acid,[6] photochemical aromatic annulation,[7] Diels–Alder reaction[8] and base-induced photochemical cyclization.[9] However, all of these methods suffered from low yields, not readily available starting materials, harsh reaction conditions, and, most importantly, the impracticality of generating diversified structural analogues of tanshinone I for structure–activity relationship study. Therefore, mild and facile synthetic approaches to access tanshinone I and its analogues are still wanted.

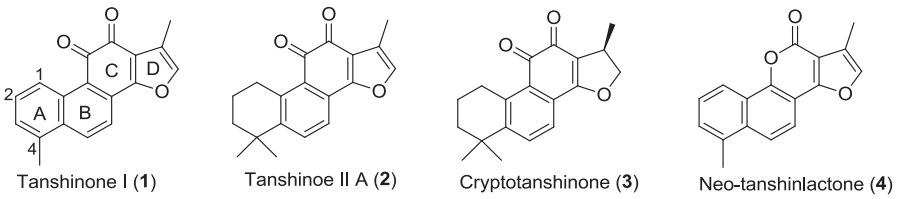


**Fig. 1.** Structures of four bioactive tanshinones isolated from *Danshen*.

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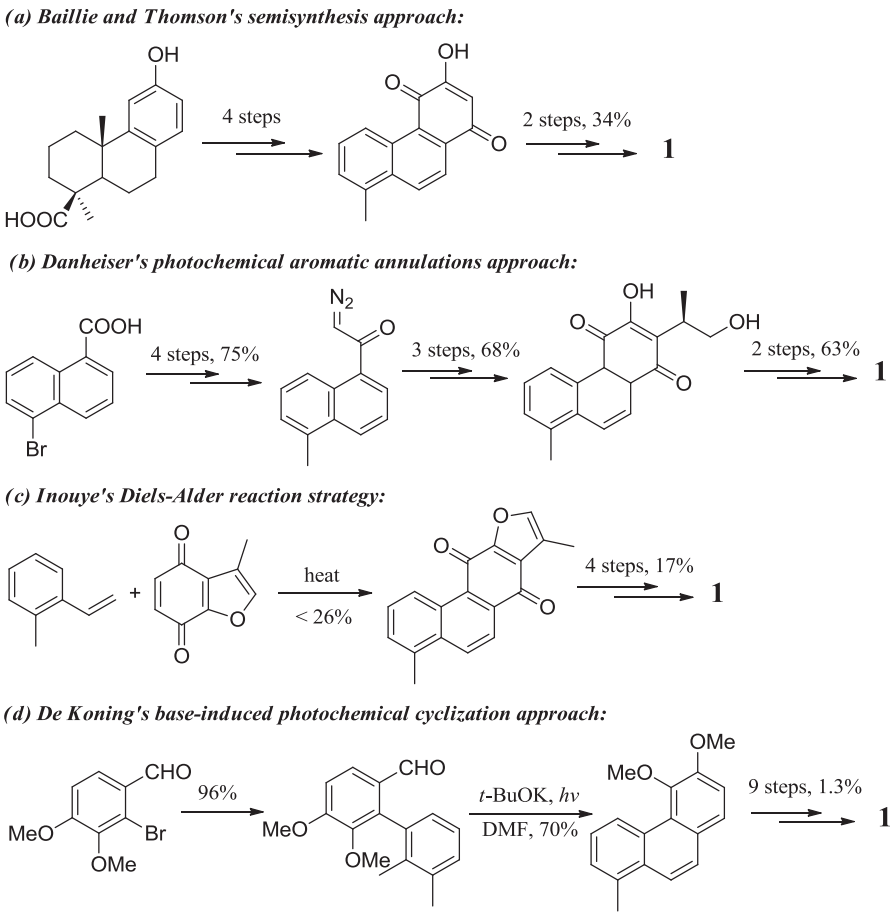



**Scheme 1.** Reported approaches for the synthesis of tanshinone I (**1**).

In our synthetic efforts towards biologically active natural products,[10–13] we developed an efficient method to assemble benzo[*a*]anthraquinones from bromoquinones and arylpropionic acid through a tandem three-step reaction approach, including silver-catalyzed decarboxylic radical alkylation, palladium-catalyzed cyclization and DBU-assisted aromatization.[11] As an application of this method, we also synthesized a series of naphtho[2,3-*a*]carbazole-5,13-diones as well as indole- or benzofuran-fused benzo[*a*]carbazole-1,4-diones from indol-3-propanoic acid through a similar one-pot reaction protocol.[12,13] Inspired by these results, we envisioned that this tandem three-step reaction strategy might be utilized to construct the A/B/C tricyclic phenanthraquinone fragment of tanshinone I (**1**), which would eventually lead to a facile total synthesis of **1**. Herein, we describe, for the first time, the application of this radical strategy to the synthesis of this key tricyclic precursor, and subsequent assembly of tanshinone I and its 4-demethylated analogues.

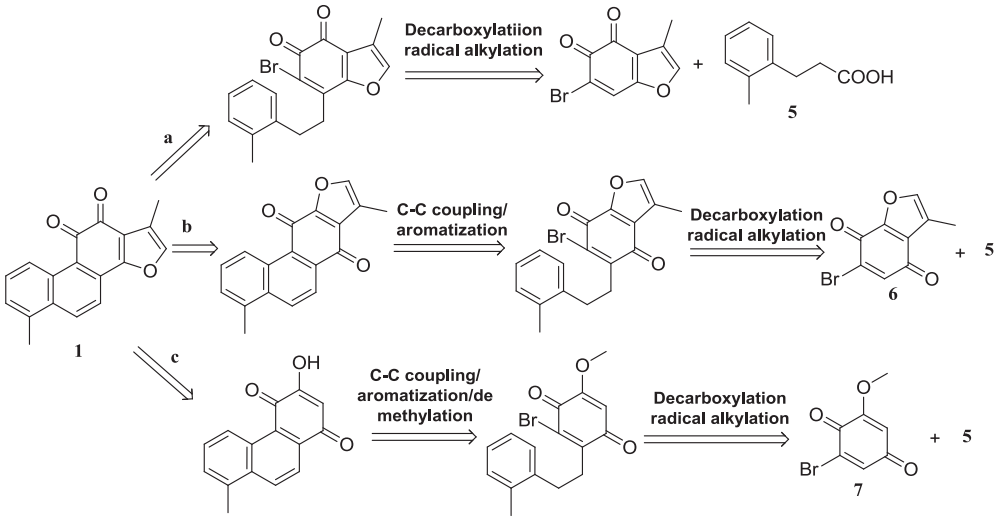
## 2. Results and discussion

The retrosynthetic analysis of **1** was outlined in Scheme 2. Three possible approaches (path a, b and c) were proposed using different bromoquinone substrates during the synthesis. All of these paths included the decarboxylative radical alkylation of bromoquinones with tolylpropionic acid followed by intracellular C–C coupling and aromatization reactions as key steps to construct the A/B/C rings of **1**. In both paths a and b, the furan ring was introduced prior to the formation of ring B through the bromoquinone intermediate, whereas in path c, the furan ring was constructed after the formation of A/B/C ring system.

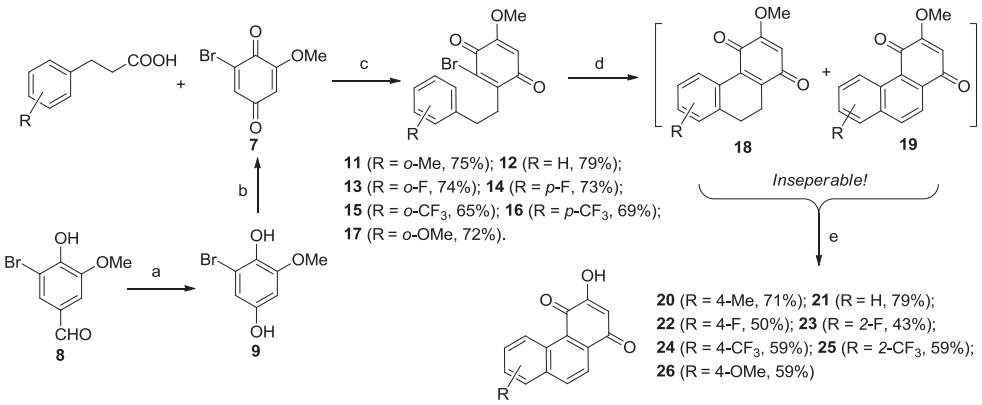
In view of the relative instability of 6-bromo-3-methyl benzofuran-4,5-dione in path a,[14] we decided to start our synthetic effort based on path b with 6-bromo-3-methylbenzofuran-4,7-dione (**6**) as the key intermediate. Unfortunately, treating a mixture of bromoquinone **6** and acid **5** with $AgNO_3$ and $(NH_4)_2S_2O_8$ at rt delivered no desired product. Elevating the reaction temperature to 80 °C resulted in decomposition of the substrate. The failure of this radial alkylation reaction was likely ascribed to the instability of the furan ring of **6**. In this regard, we switched our synthetic effort of **1** to path c with bromoquinone **7** as the substrate.

As depicted in Scheme 3, by following a literature procedure,[15] Baeyer–Villiger oxidation of 5-bromovanillin (**8**) with sodium percarbonate followed by hydrolysis of the ester function afforded 1,4-hydroquinone **9**. Subsequent oxidation of **9** with $FeCl_3$ provided bromoquinone **7** in 89% overall yield (two steps). Initially, the commercially available 3-phenylpropanoic acid was used as a model substrate to test the feasibility of the radical reaction with **7**. To our delight, decarboxylative radical alkylation of 3-phenylpropanoic acid with **7** in the presence of 0.3 equiv of $AgNO_3$ and 2 equiv of $(NH_4)_2S_2O_8$ went through smoothly and delivered the desired intermediate **12** in 45% yield. It should be noted that this alkylation reaction of **7** selectively occurred at the carbon neighbouring to bromo- other than the carbon close to methoxy group due to the electronic effects of these two substituents.[12,13]

To further optimize the reaction conditions to achieve better yield, a number of silver catalysts, variant reagent ratios as well as other reaction parameters were screened. As summarized in Table 1, all the silver catalysts initiated the radical alkylation, while $Ag_2CO_3$ and $Ag_3PO_4$ proved to be more promising to provide

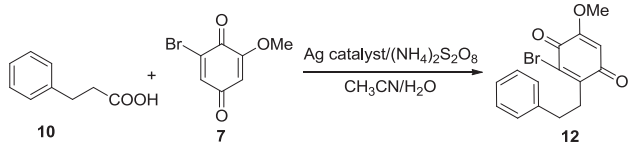



**Scheme 2.** Our retrosynthetic analysis of tanshinone I (**1**).




**Scheme 3.** Synthesis of 3-hydroxyphenanthrene-1,4-diones **20**–**26**. Reagents and conditions: (a) sodium percarbonate, THF/$H_2O$, rt, 90%; (b) $FeCl_3$, MeOH/$H_2O$, rt, 99%; (c) $Ag_3PO_4$ (30%), $(NH_4)_2S_2O_8$ (2 equiv), $CH_3CN/H_2O$, 85 °C, 65–79%; (d) $Pd(OAc)_2$, $PPh_3$, $K_2CO_3$, toluene, 110 °C; (e) NaOH, $O_2$, ethanol/$H_2O$, 95 °C, 43–79% (two steps).

**Table 1**
Optimization of radical alkylation reaction condition for **12**




| Entry | Ag catalysts | Molar ratio (10/7/Ag catalyst/oxidant) | $T$ (°C) | Time (h) | Yield[a] (%) |
|---|---|---|---|---|---|
| **1** | $AgNO_3$ | 1.5/1.0/0.3/2.0 | 80 | 2.5 | 45 |
| **2** | $Ag_2CO_3$ | 1.5/1.0/0.3/2.0 | 80 | 2.5 | 58 |
| **3** | AgOAc | 1.5/1.0/0.3/2.0 | 80 | 2.5 | 37 |
| **4** | $Ag_3PO_4$ | 1.5/1.0/0.3/2.0 | 80 | 2.5 | 62 |
| **5** | $AgBF_4$ | 1.5/1.0/0.3/2.0 | 80 | 2.5 | 50 |
| **6** | $AgClO_4$ | 1.5/1.0/0.3/2.0 | 80 | 2.5 | 49 |
| **7** | AgOTf | 1.5/1.0/0.3/2.0 | 80 | 2.5 | 48 |
| **8** | $Ag_3PO_4$ | 1.5/1.0/0.6/2.0 | 80 | 2.0 | 63 |
| **9** | $Ag_3PO_4$ | 1.5/1.0/0.1/2.0 | 80 | 2.0 | 33 |
| **10** | $Ag_3PO_4$ | 1.0/1.5/0.3/2.0 | 80 | 2.0 | 45 |
| **11** | $Ag_3PO_4$ | 1.5/1.0/0.3/2.0 | 85 | 1.0 | 61 |
| **12** | $Ag_3PO_4$ | 2.0/1.0/0.3/2.0 | 85 | 0.8 | 79 |

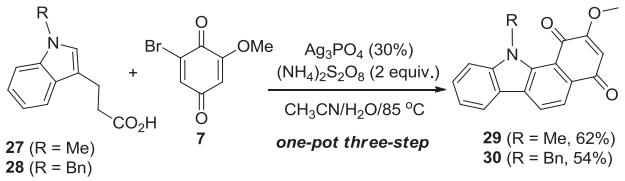
[a] Isolated yields.

product **12** in 58% and 62% yields, respectively (entries 2 and 4). The best result (79% for **12**) was achieved by using 0.3 equiv of $Ag_3PO_4$, 2 equiv of $(NH_4)_2S_2O_8$ as well as 2/1 molar ratio of compounds **10** and **7** at 85 °C (entry 12).

With the optimized reaction conditions in hand, we then set out to explore the substrate scope. A number of arylpropionic acids were employed with various substituents at the *para*- or *ortho*-positions of the phenyl ring, including methyl, fluoro, trifluoromethyl and methoxyl groups. It was found that all reactions under the optimized conditions occurred smoothly and furnished the corresponding products **11**–**17** in 65–79% yields (Scheme 3), indicating that various substitutions on the phenyl ring were well tolerated in the alkylation reaction.

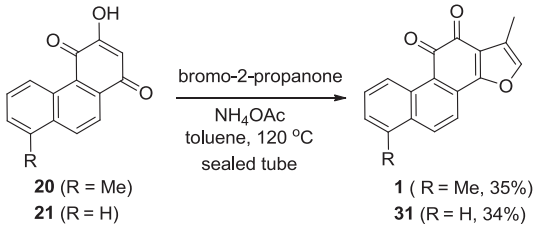
Next, we turned our attention to the intramolecular cyclization of bromoquinone **11** through a $Pd(OAc)_2$-catalyzed C–H arylation to construct the A/B/C tricyclic skeleton of **1** (Scheme 3). By following our previously developed C–C coupling procedure,[11] treating **11** with $Pd(OAc)_2$ (0.45 equiv), $PPh_3$ (0.8 equiv) and $K_2CO_3$ (3 equiv) in refluxing toluene for 12 h yielded the desired cyclization product **18** as the major product, together with a small amount of dehydrogenated aromatic product **19** that was inseparable from **18** by flash chromatography. To our delight, after many attempts, we found that the reaction mixture, without further isolation, was directly treated with aqueous NaOH solution (1 N) under $O_2$ atmosphere in refluxing EtOH to complete the dehydrogenation and O-demethylation in one pot affording the aromatic product **20** in 71% yield as the sole product (two steps). On the basis of this encouraging result, a series of tricyclic hydroxyquinones **21**–**26** were successfully synthesized in 43–79% yields in a similar fashion. To further verify this method, indole-3-propionic acids **27** and **28** were used to replace tolylpropionic acids and subjected to the optimized radical alkylation. Benzo

[*a*]carbazole-1,4-diones **29** and **30** were obtained directly in 62% and 54% yields, respectively. The high efficiency of this one-pot three-step process (radical alkylation–cyclization–aromatization) is due to the high reactivity of indole-3-propionic acid substrates, a phenomenon similar to our previous report (Scheme 4).[12]




**Scheme 4.** Synthesis of compounds **29** and **30**.

With the key precursor **20** successfully prepared, we decided to complete the synthesis of tanshinone I (**1**) by using the reported Feist–Bénary reaction (Scheme 5).[16] Although this one-step synthetic reaction has been claimed in a patent using $NH_4OAc$/HOAc in refluxing EtOH/toluene,[17] repeating this procedure only led to a complex with trace amount of desired product **1** in our laboratory. Extensive investigations indicated that the solvent played a key impact factor for the conversion of **20** to **1**. Using anhydrous toluene as the solvent, treating **20** with bromo-2-propanone and $NH_4OAc$ at 120 °C in a sealed tube for 10 h successfully provided tanshinone I (**1**) in 35% yield as the major product, together with recovered **20** (30%). Similarly, 4-demethylated analogue **31** was also achieved in 34% yield under the same reaction condition from the precursor **21**.




**Scheme 5.** Synthesis of **1** and its analogue **31**.

## 3. Conclusion

In summary, we have developed a mild synthetic approach allowing for a convenient construction of tricyclic hydroxyphenanthraquinone **20**, the key precursor for total synthesis of tanshinone I (**1**). This tandem process includes decarboxylative radical alkylation, intramolecular C–H arylation and one-pot O-demethylation and aromatization. Variously substituted phenylpropanoic acids were tolerated very well in this approach, and one-pot synthesis of benzo[*a*]carbazole-1,4-diones **29** and **30** was achieved directly in the radical alkylation reaction. Finally, synthesis of tanshinone I (**1**) and its 4-demthylated analogue **31** was completed by following a modified Feist–Bénary reaction. Compared to the currently available procedures for total synthesis of tanshinone I,[6–9] our protocol started from commercially available starting material (5-bromovanillin), and furnished the natural product in six straight steps in 19% overall yields. Our success in the efficient construction of tricyclic phenanthraquinone compounds provides new synthetic potential to easily access novel tanshinone I derivatives.

## 4. Experimental section

### 4.1. General

All reactions were performed in glassware containing a Teflon-coated stir bar. All reagents were obtained from commercial sources and used without further purifications. Melting points were determined by a X-4 digital display microscopic melting point apparatus and are uncorrected. $^1H$ and $^{13}C$ NMR spectra were recorded with tetramethylsilane as an internal reference. Low- and high resolution mass spectra were obtained in the EI (70 eV) mode. Flash column chromatography on silica gel (200–300 mesh) was used for the routine purification of reaction products. The column output was monitored by TLC on silica gel (100–200 mesh) precoated on glass plates (10×50 cm), and spots were visualized by UV light at 254 nm.

*4.1.1. 2-Bromo-6-methoxycyclohexa-2,5-diene-1,4-dione (**7**).* This compound was prepared according to a literature procedure.[15] $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.21 (d, $J$=2.4 Hz, 1H), 5.97 (d, $J$=2.4 Hz, 1H), 3.86 (s, 3H).

### 4.2. General procedure for compounds 11–17, 29 and 30 through silver-catalyzed radical alkylation

A vigorously stirred mixture of various substituted propanoic acid (1.0 mmol), 2-bromo-6-methoxy-[1,4]-benzoquinone (217 mg, 0.5 mmol), $Ag_3PO_4$ (63 mg, 0.15 mmol) and acetonitrile (5 mL) was placed in a preheated oil bath at 85 °C, and a solution of $(NH_4)_2S_2O_8$ (228 mg, 1.0 mmol) in water (3 mL) was added over a period of 5 min under $N_2$ by means of a syringe. The resulting mixture was stirred at the same temperature. After completion of the reaction, as indicated by TLC, the reaction was quenched with ice and extracted with $CH_2Cl_2$ (3×20 mL). The combined organic solution was washed with brine, dried over anhydrous $Na_2SO_4$, filtered and evaporated to give a solid residue. The residue was further purified using chromatography developed by $CH_2Cl_2$ to afford the desired products.

*4.2.1. 3-Bromo-5-methoxy-2-(2-methylphenethyl)cyclohexa-2,5-diene-1,4-dione (**11**).* Yellow solid (75%), mp 149–152 °C. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.20–7.12 (m, 4H), 5.96 (s, 1H), 3.85 (s, 3H), 2.94–2.90 (m, 2H), 2.78–2.74 (m, 2H), 2.42 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 183.7, 174.9, 158.4, 149.1, 138.7, 136.3, 133.2, 130.5, 129.2, 126.7, 126.2, 107.5, 56.8, 32.1, 31.4, 19.4. MS (EI) 334 ($M^+$); HRMS (EI) calcd for $C_{16}H_{15}BrO_3$ ($M^+$) 334.0205, found 334.0188.

*4.2.2. 3-Bromo-5-methoxy-2-phenethylcyclohexa-2,5-diene-1,4-dione (**12**).* Yellow solid (79%), mp 138–140 °C. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.32–7.20 (m, 5H), 5.96 (s, 1H), 3.85 (s, 3H), 3.00–2.96 (m, 2H), 2.80–2.76 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 183.7, 174.9, 158.3, 149.0, 140.5, 133.4, 128.6 (4), 126.5, 107.4, 56.8, 33.9, 33.3. MS (EI) 320 ($M^+$); HRMS (EI) calcd for $C_{15}H_{13}BrO_3$ ($M^+$) 320.0048, found 320.0025.

*4.2.3. 3-Bromo-2-(2-fluorophenethyl)-5-methoxycyclohexa-2,5-diene-1,4-dione (**13**).* Yellow solid (74%), mp 134–137 °C. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.23–7.17 (m, 2H), 7.07–6.98 (m, 2H), 5.95 (s, 1H), 3.85 (s, 3H), 3.03–2.99 (m, 2H), 2.88–2.84 (m, 2H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 183.7, 174.9, 161.3 (d, $J$=245.5 Hz), 158.3, 148.7, 133.6, 130.9 (d, $J$=4.8 Hz), 128.4 (d, $J$=8.2 Hz), 127.2 (d, $J$=16.0 Hz), 124.2 (d, $J$=3.7 Hz), 115.4 (d, $J$=22.0 Hz), 107.5, 56.8, 31.6, 27.3. MS (EI) 338 ($M^+$); HRMS (EI) calcd for $C_{15}H_{12}BrFO_3$ ($M^+$) 337.9954, found 337.9950.

*4.2.4. 3-Bromo-2-(4-fluorophenethyl)-5-methoxycyclohexa-2,5-diene-1,4-dione (**14**).* Yellow solid (73%), mp 130–132 °C. $^1H$ NMR

(400 MHz, $CDCl_3$): δ 7.23–7.18 (m, 2H), 7.01–6.95 (m, 2H), 5.96 (s, 1H), 3.85 (s, 3H), 2.97–2.93 (m, 2H), 2.78–2.74 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 183.6, 174.8, 161.7 (d, *J*=244.2 Hz), 158.4, 148.8, 136.1, 133.5, 130.0 (2), 115.5, 115.3, 107.4, 56.8, 33.3, 33.0. MS (EI) 338 ($M^+$); HRMS (EI) calcd for $C_{15}H_{12}BrFO_3$ ($M^+$) 337.9954, found 337.9957.

*4.2.5. 3-Bromo-5-methoxy-2-(2-(trifluoromethyl)phenethyl)cyclohexa-2,5-diene-1,4-dione (**15**).* Yellow solid (65%), mp 143–145 °C. $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J*=7.9 Hz, 1H), 7.52–7.48 (m, 1H), 7.43 (d, *J*=7.5 Hz, 1H), 7.35–7.31 (m, 1H), 5.98 (s, 1H), 3.86 (s, 3H), 3.05–2.94 (m, 4H). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 183.7, 174.9, 158.4, 148.5, 139.2, 133.8, 132.1, 131.5, 128.7 (q, *J*=29.9 Hz), 126.7, 126.1 (q, *J*=5.7 Hz), 124.6 (q, *J*=274.3 Hz), 107.52, 56.9, 33.0, 30.4. MS (EI) 388 ($M^+$); HRMS (EI) calcd for $C_{16}H_{12}BrF_3O_3$ ($M^+$) 387.9922, found 387.9919.

*4.2.6. 3-Bromo-5-methoxy-2-(4-(trifluoromethyl)phenethyl)cyclohexa-2,5-diene-1,4-dione (**16**).* Yellow solid (69%), mp 124–126 °C. $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J*=8.1 Hz, 2H), 7.38 (d, *J*=8.1 Hz, 2H), 5.97 (s, 1H), 3.86 (s, 3H), 3.01–2.96 (m, 2H), 2.86–2.82 (m, 2H). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 183.6, 174.7, 158.5, 148.5, 144.6, 133.7, 128.9 (3), 125.6, 124.4 (q, *J*=272.3 Hz), 107.4 (2), 56.9, 33.6, 32.8. MS (EI) 388 ($M^+$); HRMS (EI) calcd for $C_{16}H_{12}BrF_3O_3$ ($M^+$) 387.9922, found 387.9904.

*4.2.7. 3-Bromo-5-methoxy-2-(2-methoxyphenethyl)cyclohexa-2,5-diene-1,4-dione (**17**).* Yellow solid (72%), mp 161–163 °C. $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.19 (m, 1H), 7.13 (dd, *J*=7.4, 1.7 Hz, 1H), 6.87 (m, 1H), 6.82 (d, *J*=8.2 Hz, 1H), 5.93 (s, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 2.99 (dd, *J*=8.7, 6.6 Hz, 2H), 2.83 (dd, *J*=8.8, 6.5 Hz, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 183.6, 175.0, 158.2, 157.6, 149.7, 133.0, 130.2, 128.7, 127.9, 120.6, 110.3, 107.4, 56.8, 55.4, 31.5, 28.8. MS (EI) 350 ($M^+$); HRMS (EI) calcd for $C_{16}H_{15}BrO_4$ ($M^+$) 350.0154, found 350.0154.

*4.2.8. 2-Methoxy-11-methyl-1H-benzo[a]carbazole-1,4(11H)-dione (**29**).* Red solid (62%), mp 236–239 °C. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 8.60 (d, *J*=7.9 Hz, 1H), 8.29 (d, *J*=7.8 Hz, 1H), 7.90 (d, *J*=7.9 Hz, 1H), 7.73 (d, *J*=8.3 Hz, 1H), 7.64–7.60 (m, 1H), 7.37–7.33 (m, 1H), 6.30 (s, 1H), 3.91 (s, 3H), 3.89 (s, 3H). $^{13}C$ NMR (125 MHz, DMSO-$d_6$): δ 184.7, 179.7, 161.7, 144.7, 138.8, 130.8, 129.8, 128.3, 125.6, 121.2, 121.1, 120.9, 117.5, 117.2, 110.9, 107.9, 56.6, 35.4. MS (EI) 291 ($M^+$); HRMS (EI) calcd for $C_{18}H_{13}NO_3$ ($M^+$) 291.0895, found 291.0896.

*4.2.9. 11-Benzyl-2-methoxy-1H-benzo[a]carbazole-1,4(11H)-dione (**30**).* Red solid (54%), mp 189–192 °C. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 8.67 (d, *J*=7.9 Hz, 1H), 8.33 (d, *J*=7.8 Hz, 1H), 7.93 (d, *J*=8.0 Hz, 1H), 7.67 (d, *J*=8.4 Hz, 1H), 7.58–7.54 (m, 1H), 7.38–7.34 (m, 1H), 7.18–7.15 (m, 3H), 6.84 (dd, *J*=7.8, 1.5 Hz, 2H), 6.26 (s, 1H), 5.88 (s, 2H), 3.86 (s, 3H). $^{13}C$ NMR (125 MHz, DMSO-$d_6$): δ 184.9, 180.5, 161.4, 144.8, 138.5, 138.1, 131.5, 130.9, 128.8 (3), 127.4, 126.8 (2), 126.5, 122.2, 121.7, 121.6, 118.3, 118.2, 112.1, 108.3, 57.1, 50.4. MS (EI) 367 ($M^+$); HRMS (EI) calcd for $C_{24}H_{17}NO_3$ ($M^+$) 367.1208, found 367.1215.

### 4.3. General procedure for compounds 20–26 through intracellular C–H arylation followed by one-pot O-demethylation and aromatization

A mixture of various bromoquinones (0.5 mmol), $Pd(OAc)_2$ (51 mg, 0.225 mmol), $PPh_3$ (105 mg, 0.4 mmol), $K_2CO_3$ (207 mg, 1.5 mmol) and anhydrous toluene (5 mL) was refluxed under $N_2$ for 12 h. The reaction mixture was diluted with water (20 mL) and extracted with $CH_2Cl_2$ (3×20 mL). The combined organic solution was washed with brine, dried over anhydrous $Na_2SO_4$, filtered and evaporated to give a solid residue. Without further purification, the residue was dissolved in ethanol (5 mL), and the resulting solution was heated at 95 °C in the presence of aqueous NaOH solution (1 N, 10 mL) under $O_2$ atmosphere ($O_2$ balloon) for 30 min. After cooling to rt, the reaction mixture was acidified with 2 N HCl (6 mL) and extracted with EtOAc (3×20 mL). The combined organic solution was washed with brine, dried over anhydrous $Na_2SO_4$, filtered and evaporated to give a solid residue. The residue was further purified using chromatography developed by 10% methanol in $CH_2Cl_2$ to afford the desired products.

*4.3.1. 3-Hydroxy-8-methylphenanthrene-1,4-dione (**20**).* Orange solid (71%), mp 209–212 °C. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.29 (d, *J*=8.8 Hz, 1H), 8.48 (d, *J*=8.8 Hz, 1H), 8.09 (d, *J*=8.8 Hz, 1H), 7.69–7.65 (m, 1H), 7.54 (d, *J*=6.9 Hz, 1H), 6.11 (s, 1H), 2.70 (s, 3H). $^{13}C$ NMR (125 MHz, DMSO-$d_6$): δ 184.8, 184.1, 160.7, 135.2, 134.6, 132.3, 131.7, 129.9, 129.7, 128.9, 125.5, 124.8, 121.3, 107.8, 19.5. MS (EI) 238 ($M^+$); HRMS (EI) calcd for $C_{15}H_{10}O_3$ ($M^+$) 238.0630, found 238.0630.

*4.3.2. 3-Hydroxyphenanthrene-1,4-dione (**21**).* Red solid (79%). $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 9.42 (d, *J*=8.9 Hz, 1H), 8.37 (d, *J*=8.5 Hz, 1H), 8.08 (d, *J*=8.0 Hz, 1H), 8.07 (d, *J*=8.2 Hz, 1H), 7.83–7.79 (m, 1H), 7.74–7.70 (m, 1H), 6.15 (s, 1H). $^{13}C$ NMR (125 MHz, DMSO-$d_6$): δ 185.0, 183.9, 160.2, 135.7, 135.6, 132.6, 130.3, 129.3, 129.1, 128.3, 126.6, 125.2, 121.5, 108.0. MS (EI) 224 ($M^+$); HRMS (EI) calcd for $C_{14}H_8O_3$ ($M^+$) 224.0473, found 224.0475.

*4.3.3. 8-Fluoro-3-hydroxyphenanthrene-1,4-dione (**22**).* Orange solid (50%), mp 227–239 °C. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 9.26 (d, *J*=8.9 Hz, 1H), 8.53 (d, *J*=8.8 Hz, 1H), 8.18 (d, *J*=8.8 Hz, 1H), 7.86–7.78 (m, 1H), 7.58 (dd, *J*=10.5, 7.8 Hz, 1H), 6.18 (s, 1H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ 184.7, 183.5, 160.2, 157.9 (d, *J*=252.5 Hz), 133.1, 130.5, 130.4 (d, *J*=4.0 Hz), 127.30 (d, *J*=7.1 Hz), 125.4 (d, *J*=16.2 Hz), 125.3, 123.1 (d, *J*=4.0 Hz), 122.3, 112.2 (d, *J*=19.2 Hz), 108.2. MS (EI) 242 ($M^+$); HRMS (EI) calcd for $C_{14}H_7FO_3$ ($M^+$) 242.0379, found 242.0384.

*4.3.4. 6-Fluoro-3-hydroxyphenanthrene-1,4-dione (**23**).* Orange solid (43%), mp 223–225 °C. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 11.71 (br s, 1H), 9.11 (d, *J*=12.7 Hz, 1H), 8.41 (d, *J*=8.2 Hz, 1H), 8.22–8.16 (m, 1H), 8.03 (d, *J*=8.6 Hz, 1H), 7.69–7.62 (m, 1H), 6.15 (s, 1H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ 184.7, 183.5, 163.0 (d, *J*=245.2 Hz), 159.9, 135.7, 133.2, 133.8, 132.1 (d, *J*=10.1 Hz), 130.2 (d, *J*=11.1 Hz), 124.5 (d, *J*=6.1 Hz), 121.0, 118.4 (d, *J*=26.3 Hz), 110.2 (d, *J*=25.3 Hz), 108.2. MS (EI) 242 ($M^+$); HRMS (EI) calcd for $C_{14}H_7FO_3$ ($M^+$) 242.0379, found 242.0376.

*4.3.5. 3-Hydroxy-8-(trifluoromethyl)phenanthrene-1,4-dione (**24**).* Yellow solid (59%), mp 193–195 °C. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 11.85 (br s, 1H), 9.72 (d, *J*=9.1 Hz, 1H), 8.51 (d, *J*=8.8 Hz, 1H), 8.29 (d, *J*=7.7 Hz, 1H), 8.20 (d, *J*=7.3 Hz, 1H), 7.95 (t, *J*=8.2 Hz, 1H), 6.20 (s, 1H). $^{13}C$ NMR (125 MHz, DMSO-$d_6$): δ 184.3, 183.4, 160.3, 132.5, 131.8, 130.4, 130.1, 130.0, 128.6, 127.1 (q, *J*=6.3 Hz), 126.0, 125.0 (q, *J*=30.0 Hz), 124.3 (q, *J*=274.7 Hz), 123.7, 108.2. MS (EI) 292 ($M^+$); HRMS (EI) calcd for $C_{15}H_7F_3O_3$ ($M^+$) 292.0347, found 292.0351.

*4.3.6. 3-Hydroxy-6-(trifluoromethyl)phenanthrene-1,4-dione (**25**).* Yellow solid (59%), mp 210–212 °C. $^1H$ NMR (300 MHz, DMSO-$d_6$): δ 11.77 (br s, 1H), 9.77 (s, 1H), 8.47 (d, *J*=8.5 Hz, 1H), 8.30 (d, *J*=8.5 Hz, 1H), 8.18 (d, *J*=8.6 Hz, 1H), 7.95 (d, *J*=8.7 Hz, 1H), 6.17 (s, 1H). $^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ 184.9, 184.0, 160.5, 137.1, 135.8, 133.6, 131.2, 130.1 (q, *J*=32.3 Hz), 128.4, 126.3, 124.8 (q, *J*=6.1 Hz), 124.7 (q, *J*=273.7 Hz), 124.3, 123.8, 108.7. MS (EI) 292

($M^+$); HRMS (EI) calcd for $C_{15}H_7F_3O_3$ ($M^+$) 292.0347, found 292.0344.

*4.3.7. 3-Hydroxy-8-methoxyphenanthrene-1,4-dione (**26**).* Red solid (59%), mp 185–187 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.97 (d, $J$=8.8 Hz, 1H), 8.59 (d, $J$=8.5 Hz, 1H), 8.03 (d, $J$=8.7 Hz, 1H), 7.70 (t, $J$=8.2 Hz, 1H), 7.16 (d, $J$=7.4 Hz, 1H), 6.13 (s, 1H), 4.01 (s, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 184.9, 183.7, 160.3, 155.0, 132.9, 130.9, 130.4, 129.0, 127.5, 124.8, 120.8, 118.4, 108.0, 106.7, 55.9. MS (EI) 254 ($M^+$); HRMS (EI) calcd for $C_{15}H_{10}O_4$ ($M^+$) 254.0579, found 254.0579.

### 4.4. General procedure for tanshinone I (1) and compound 31

A mixture of 3-hydroxyphenanthrene-1,4-diones (0.1 mmol), bromo-2-propanone (69 mg, 0.5 mmol), $NH_4OAc$ (8 mg, 0.1 mmol) and anhydrous toluene (5 mL) in a sealed tube was heated to 120 °C for 10 h in the dark. After cooling to rt, the reaction mixture was acidified with 1 N HCl (3 mL) and extracted with $CH_2Cl_2$ (3×20 mL). The combined organic solution was washed with brine, dried over anhydrous $Na_2SO_4$, filtered and evaporated to give a solid residue. The residue was further purified using chromatography developed by $CH_2Cl_2$ to afford the desired products.

*4.4.1. 1,6-Dimethylphenanthro[1,2-b]furan-10,11-dione (**1**).* Red solid (35%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 9.23 (d, $J$=8.8 Hz, 1H), 8.28 (d, $J$=8.8 Hz, 1H), 7.78 (d, $J$=8.8 Hz, 1H), 7.54 (t, $J$=8.1 Hz, 1H), 7.34 (d, $J$=7.2 Hz, 1H), 7.29 (s, 1H), 2.68 (s, 3H), 2.29 (s, 3H). $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ 183.5, 175.6, 161.2, 142.0, 135.2, 133.6, 133.0, 132.8, 130.7, 129.6, 128.4, 124.8, 123.1, 121.8, 120.5, 118.7, 19.9, 8.9. MS (EI) 276 ($M^+$); HRMS (EI) calcd for $C_{18}H_{12}O_3$ ($M^+$) 276.0786, found 276.0789.

*4.4.2. 1-Methylphenanthro[1,2-b]furan-10,11-dione (**31**).* Red solid (34%), mp 226–229 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 9.28 (d, $J$=8.8 Hz, 1H), 8.31 (d, $J$=8.5 Hz, 1H), 8.00 (d, $J$=8.2 Hz, 1H), 7.83 (d, $J$=8.5 Hz, 1H), 7.80 (s, 1H), 7.73 (t, $J$=7.7 Hz, 1H), 7.59 (t, $J$=7.2 Hz, 1H), 2.20 (s, 3H). $^{13}$C NMR (150 MHz, DMSO-$d_6$): $\delta$ 182.2, 174.8, 159.9, 143.2, 136.9, 134.0, 131.6, 130.6, 129.5, 129.4, 127.2, 125.8, 122.7, 120.8, 120.3, 118.9, 8.6. MS (EI) 262 ($M^+$); HRMS (EI) calcd for $C_{17}H_{10}O_3$ ($M^+$) 262.0630, found 262.0633.

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## Supplementary data

These data include all NMR spectra for the compounds described in this paper. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.03.019.

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