First total synthesis of salvianolic acid C, tournefolic acid A, and tournefolal

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DOI: http://dx.doi.org/10.3998/ark.5550190.0013.619

Abstract
First total synthesis of the natural product salvianolic acid C, tournefolal and tournefolic acid A has been described. The key benzofuran skeletons are prepared via selective iodination and Sonogashira reaction.

Keywords: Salvianolic acid C, benzofuran, Sonogashira coupling, iodination

Introduction

Salvia miltiorrhiza Bunge (Dan-shen) is widely used as a Chinese traditional medicine for the treatment of myocardial infarction, atherosclerosis, and thrombus.[1] The hydrosoluble salvianolic acids isolated from water-soluble part of Dan-shen are considered as the main pharmacological active ingredients for the activities of anti-oxidative, anticoagulant, antithrombotic, anti-HIV, anti-tumor, and so on.[2] Salvianolic acid C (**1**), one of the Salvianolic acids, is constituted of danshensu (**2**)[3] and 2-phenyl-benzofuran neolignan tournefolic acid A (**3**)[4] linked by ester bond. Recently, Liang et al.[5] have reported that salvianolic acid C (**1**) displays anti-proliferative activity against HepG2 cells with IC_{50} value of 20 μM through apoptosis, and the mechanism is concerned with inhibition of tubulin polymerization. Furthermore, neolignan tournefolic acid A (**3**) and tournefolal (**4**) express valuable anti-lipidperoxidative acitivity.[4] However, the low contents of salvianolic acid C (**1**), [6] tournefolic acid A (**3**) as well as tournefolal (**4**) limit for further pharmacological property research. In view of their importance, the development of a route for the synthesis of salvianolic acid C (**1**), tournefolic acid A (**3**) as well as tournefolal (**4**) are of importance.

The 2-phenyl-benzofuran skeleton of **1** is a privileged structure in medical chemistry. Several natural compounds containing 2-phenyl-benzofuran, such as XH-14,[7] obovaten,[8] and egonol,[9] show significant biological activities. Therefore, due to the importance of 2-phenyl-benzofuran derivatives, many methods for synthesis of these compounds have been developed.[10-13] However, salvianolic acid C (**1**), tournefolic acid A (**3**), and tournefolal (**4**) have substitutents at C-4, which are distinct from common natural neolignans having substitutents at C-5.

According to the literature,[4-6] although several groups have isolated salvianolic acid C (**1**), tournefolic acid A (**3**), and tournefolal (**4**) to study their biological activities, the total synthesis of them have not yet been reported. Our group has focused on total synthesis and pharmacological research of natural products for many years.[14] Herein, we wish to report a route first time on the total synthesis of salvianolic acid C (**1**), tournefolic acid A (**3**), and tournefolal (**4**). And the approach is also suitable for synthesis the C-4 substituted 2-phenyl-benzofuran compounds.

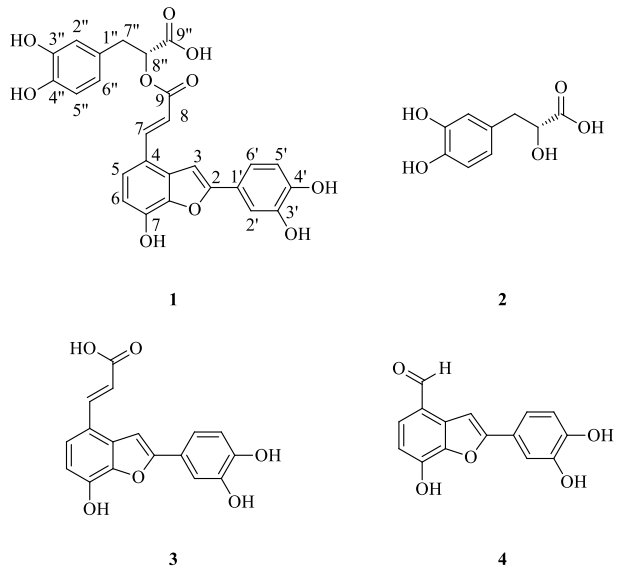
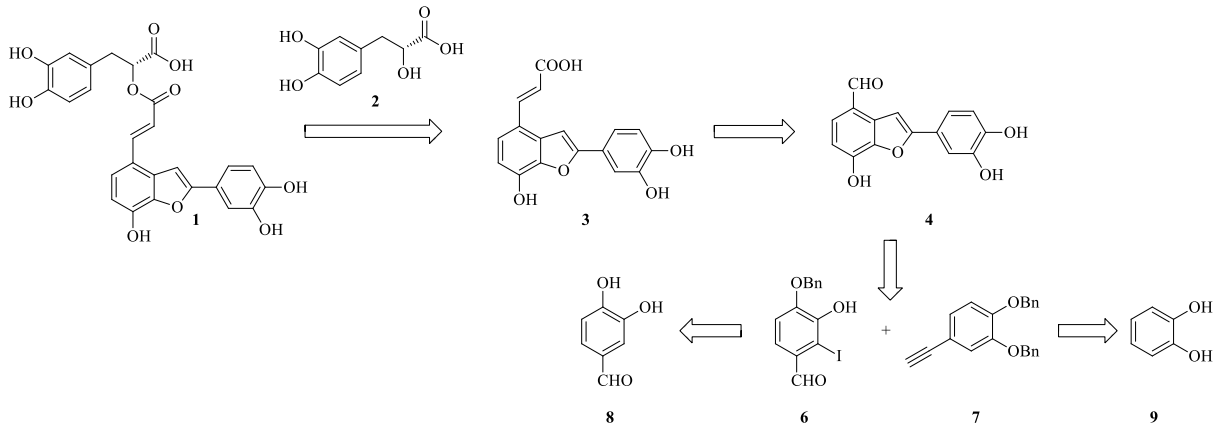


Figure 1. Salvianolic acid C (**1**), danshensu (**2**), tournefolic acid A (**3**), and tournefolal (**4**).

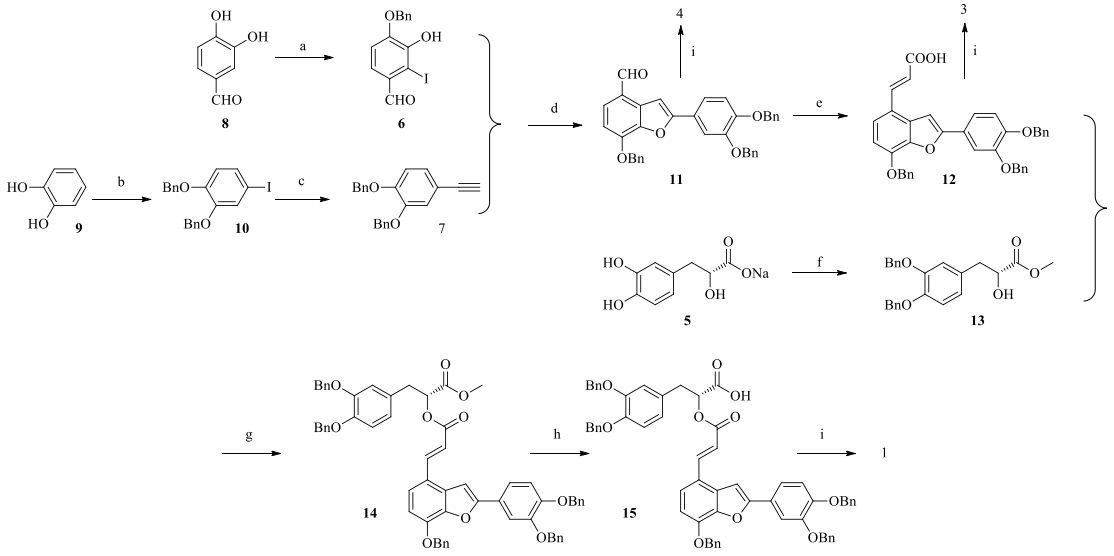
Results and Discussion

The retrosynthetic analysis of salvianolic acid C (**1**) is shown in Scheme 1. We hypothesized that **1** could be structured from tournefolic acid A (**3**) through esterification with danshensu (**2**). And **3** could be obtained by Knoevenagel condensation from **4**.[15] The key benzofuran intermediate tournefolal (**4**) could be synthesized by Sonogashira coupling of 3-hydroxy-2-iodobenzaldehyde (**6**) and the ethynylbenzene analogues (**7**). Compound (**6**) could be prepared from 4-dihydroxybenzaldehyde (**8**), and Compound (**7**) could be prepared from pyrocatechol (**9**). To investigate the feasibility of the analysis above, the related experiments were carried out.



Scheme 1. The retrosynthetic analysis of salvanolic acid C.

As illustrated in Scheme 2, the synthesis of the intermediate **6** was initiated with the selective benzylation at C-4(OH) of **8** by treatment with NaI, and $NaHCO_3$ at 40 ºC for 2 days,[16] followed by using iodine chloride to introduce iodine at C-2.[17] In order to avoid over iodination, the dose of iodine chloride should not exceed 1 eqiv. The other key building block **7**[18] was prepared via four steps including benzylation from **9**, iodination catalyzed by iodine and Ag_2SO_4, Sonogashira reaction with ethynyltrimethylsilane at r.t., and alkaline hydrolysis reaction. It was noted that the amount of iodine should be subjected to 0.75 eqiv to obtain **10** in a quantitative yield. If the dose was exceeded, the byproduct of over iodination would be generated.



Scheme 2. *Reagents and Conditions*: **a.** (i) $NaHCO_3$, NaI, BnCl, DMF, 40 ºC, 2 d, 67%; (ii) ICl, Py, DCM, 0 ºC–r.t., 12 h, 86%; **b.** (i) K_2CO_3, BnBr, DMF, r.t., 12 h, 96%; (ii) I_2, Ag_2SO_4, DCM / EtOH, r.t., 1 h, 95%; **c.** (i) Pd $(PPh_3)_2Cl_2$, CuI, TEA, r.t., 12 h, 90%; (ii) K_2CO_3, MeOH, r.t., 24

h, 94%; **d.** $PdCl_2(PPh_3)_2$, CuI, TEA, DMF, 65 °C, 12 h, 63%; **e.** piperidine, Py, 100 °C, 5 h, 85%; **f.** (i) BnBr, K_2CO_3, MeOH, reflux, 5 h; (ii) *p*-TsOH, MeOH, reflux, 4 h, 51%, in two steps; **g.** EDCI, DMAP, DMF, r.t., 2 d, 84%; **h.** Me_3SnOH, DCE, reflux, 24 h, 43%; **i.** BBr_3, DCM, -78 °C, 1 h.

The Sonogashira coupling[13] of **6** with **7** was catalyzed by $Pd(Ph_3P)_2Cl_2$ (3 mol%) and CuI (2 mol%) to afford benzofuran aldehyde **11** as a yellow solid in 63% yield. Compound **12** was prepared via Knoevenagel condensation of **11** with malonic acid in pyridine in 85% yield with excellent *E/Z* ratio (95:5). Compound **13**, which was prepared from Sodium Danshensu **5** via benzylation and methyl esterification, was esterified with **12** to produce **14** in 87% yield. Considering about the acrylic acid ester bond of **14**, we chose neutral reagent Me_3SnOH as the catalyst for demethylation to afford **15** in 43% yield.[14] Taking into account the tolerance of double-bond, the debenzylation of **15** was catalyzed by Lewis acid BBr_3 at -78 °C to afford **1**. And we succeeded in obtaining **1** through purification by Sephadex LH-20 in 40% yield. This method of debenzylation could be applied in the preparation of tournefolic acid A (**3**) and tournefolal (**4**) from compound **12** and **11**, respectively.

Conclusions

In summary, we have developed a method first time for the total synthesis of salvianolic acid C (**1**) (4.5% yield, in thirteen steps), tournefolic acid A (**3**) (12.1% yield, in nine steps), and tournefolal (**4**) (31.5% yield, in eight steps). This approach also can be applied to build the C-4 substituted 2-phenyl-benzofuran construction.

Experimental Section

General. Reagents and all solvents were analytically pure grade and were used without further purification. Column chromatography (CC) was performed on Sephadex LH-20, silica gel (200–300 mesh) and RP-18 (20–45 μm). ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian Mercury 300 spectrometer in the solvent indicated. Chemical shifts are reported in ppm relative to the internal reference. ESIMS were obtained on a Bruker Esquire 3000 Plus spectrometer, and HRESIMS on a Micromass Q-Tof Global mass spectrometer.

4-(Benzyloxy)-3-hydroxy-2-iodobenzaldehyde (6). (1) To a stirred solution of benzaldehyde **8** (4 g, 29.0 mmol) in DMF (50 mL) was added $NaHCO_3$ (3.65 g, 40.0 mmol), NaI (1.30 g, 8.7 mmol), and BnCl (7 mL). The mixture was stirred at 40 °C for 2 days. After cooling to r.t., 1 N HCl (50 mL) was added, and the solution was extracted with EtOAc (3 × 70 mL). The combined

organic layers were washed with brine, dried, filtered, and concentrated under reduced pressure. The crude product was purified by recrystallization from DCM/PE to afford a white solid 4-(benzyloxy)-3-hydroxy-benzaldehyde (4.4 g, 67%).
(2) To a stirred solution of 4-(benzyloxy)-3-hydroxybenzaldehyde (0.456 g, 2 mmol) and pyridine (2 mL) in anhydrous DCM (10 mL) was added ICl (1 M in DCM, 2 mL, 2 mmol). The mixture was stirred for 15 min at 0 °C, then warmed up to r.t. slowly, and stirred at r.t. overnight under Ar protection. After completion of the reaction, 1 N HCl (10 mL) was added, and the solution was extracted with DCM (3×20 mL). The combined organic extracts were washed with brine, dried, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (PE : EtOAc = 9 : 1) to afford a white solid **6** (0.615 g, 86%).
Compound 6. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.22 (s, 2H), 6.36 (s, 1H), 6.97 (d, *J* = 8.7 Hz, 1H), 7.41 (m, 5H), 7.52 (d, *J* = 8.7 Hz, 1H), 10.04 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 71.9, 88.6, 111.5, 123.9, 128.1(2C), 129.1, 129.2(2C) 135.1(2C), 146.2, 150.1, 195.0. MS (ESI): *m/z* 355.0 $[M+H]^+$. HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{14}H_{12}IO_3$: 354.9831; found: 354.9835.

3,4-Dibenzyloxyiodobenzene (10). (1) To a stirred solution of pyrocatechol **10** (5.5 g, 0.05 mol,) and K_2CO_3 (25 g, 0.2 mol, 4.0 equiv) in DMF (50 mL) was added BnBr (24 mL, 0.2 mol). The reation mixture was degassed, charged with Ar, and stirred at r.t. overnight. After completion of the reaction, the mixture was filtered, and the solvent of the filtrate was removed under reduced pressure at 80 °C. The crude product was purified by recrystallization from MeOH to afford a white solid 1,2-dibenzyloxybenzene (14.1 g, 96%).
(2) To a stirred solution of 1,2-dibenzyloxybenzene (5.8 g, 20 mmol) and Ag_2SO_4 (9.3 g, 30 mmol) in EtOH / DCM (100 / 50 mL) was added I_2 (4.14 g, 15 mmol). The reaction was stirred at r.t. for 1 h. After completion of the reaction, the mixture was filtered, and the solvent of the filtrate was removed under reduced pressure. The crude product was purified by recrystallization from MeOH to afford a white solid **10** (7.94 g, 95%).
Compound 10. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.11 (s, 2H), 5.12 (s, 2H), 6.70 (d, *J* = 8.4 Hz, 1H), 7.17 (dd, *J* = 8.7 Hz, *J* = 2.4 Hz, 1H), 7.23 (d, *J* = 2.4 Hz, 1H), 7.29-7.45 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 71.5, 71.7, 83.5, 117.3, 124.2, 127.2(2C), 127.5, 127.6, 127.7, 127.9, 128.2, 128.3, 128.8, 128.9, 130.8, 136.9, 137.1, 149.3, 150.2. MS (ESI): *m/z* 439.3 $[M+Na]^+$. HRMS (ESI): *m/z* $[M+Na]^+$ Calcd for $C_{20}H_{17}IO_2Na$: 439.0171; found: 439.0173.

3,4-Dibenzyloxyethylbenzene (7). (1) To a stirred solution of **10** (0.98 g, 2.36 mmol), 3 mol % Pd $(PPh_3)_2Cl_2$ (50 mg, 0.07 mmol), and 3 mol % CuI (9 mg, 0.047 mmol) in TEA (20 mL) were added (trimethylsilyl)acetylene (0.37 mL, 2.60 mmol). The reation mixture was degassed, charged with Ar, and stirred at r.t. overnight. After completion of the reaction, 1 N HCl (20 mL) was added, and the aqueous layer was extracted with EtOAc (3 × 40 mL), and the combined organic layers were dried, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (PE :

EtOAc = 8 : 1) to afford a colorless oil 3,4-dibenzyloxytrimethyl- (phenylethynyl)silane (820 mg, 90%).

(2) To a stirred solution of 3,4-Dibenzyloxytrimethyl(phenylethynyl)silane (0.82 g, 2.12 mmol) in MeOH (50 mL) was added K_2CO_3 (1.465 g, 10.5 mmol). The reaction was stirred at r.t. for 24 h. After completion of the reaction, the mixture was filtered, and the solvent of filtrate was removed under reduced pressure. The crude product was purified by recrystallization from MeOH to afford a white solid **7** (0.625 g, 94%).

Compound **7**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.98 (s, 1H), 5.14 (s, 2H), 5.17 (s, 2H), 6.85 (d, *J* = 8.1 Hz, 1H), 7.085 (d, *J* = 8.1 Hz, 1H), 7.087 (s, 1H), 7.33-7.44 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 71.3, 71.6, 76.3, 84.0, 114.7, 115.2, 115.6, 118.6, 122.0, 126.4, 127.5, 127.6 128.1, 128.2, 128.7(2C), 128.8(2C), 137.1, 137.2, 148.8, 150.1. MS (ESI): *m/z* 315.3 $[M+H]^+$. HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{22}H_{19}O_2$: 315.1385; found: 315.1390.

7-(Benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)benzo-[*b*]furan-4-carbaldehyde (11). To a stirred solution of the above iodophenol **6** (177 mg, 0.5 mmol), 3 mol % Pd $(PPh_3)_2Cl_2$ (15 mg), and ethynylbenzene **7** (157 mg, 0.5 mmol) in DMF (5 mL) was added TEA (5 mL). The mixture was stirred for 15 min before 2 mol % CuI (15 mg) was added. The reation mixture was degassed, charged with Ar, and stirred at 65 °C overnight. After cooling to r.t., 1 N HCl (7 mL) was added, and the aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic layers were dried, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (PE : EtOAc = 4 : 1) to afford a yellow solid **11** (170 mg, 63%).

Compound 11. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.21 (s, 2H), 5.24 (s, 2H), 5.43 (s, 2H), 6.90 (d, *J* = 8.7 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 1H), 7.33-7.54 (m, 17H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.65 (s, 1H), 10.03 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 71.4, 71.5, 71.7, 101.1, 108.0, 112.4, 115.1, 119.6, 123.1, 123.5, 127.5(3C), 127.7(3C), 127.8, 128.2, 128.6(2C), 128.8(2C), 128.9(3C), 131.9(2C), 137.2(3C), 148.9, 149.4(2C), 150.4, 159.3, 191.1. MS (ESI): *m/z* 541.3 $[M+H]^+$. HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{36}H_{29}O_5$: 541.2015; found: 541.2020.

(*E*)-3-(7-(Benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)be-nzo[*b*]furan-4-yl)acrylic acid (12). To a stirred solution of **11** (500 mg, 0.925 mmol,) in pyridine (25 mL) was added malonic acid (288 mg, 2.78 mmol) and piperidine (0.25 mL). The reaction mixture was heated to 100 °C for 5 h. After cooling to r.t., 1 N HCl (15 mL) was added, the aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic layers were dried, filtered, and concentrated under reduced pressure. The crude product was purified by recrystallization from Et_2O to afford a yellow solid **12** (458 mg, 85%).

Compound 12. ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.18 (s, 2H), 5.24 (s, 2H), 5.39 (s, 2H), 6.50 (d, *J* = 16.2 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.23-7.56 (m, 17H), 7.71 (d, *J* = 1.5 Hz, 1H), 7.79 (s, 1H), 7.81 (d, *J* = 15.9 Hz, 1H), 12.31 (s, 1H). ^{13}C NMR (75 MHz,

DMSO-d_6): δ 70.7, 71.0, 71.0, 100.8, 109.6, 111.9, 115.1, 118.2, 118.9, 120.4, 123.2, 125.7, 128.3(4C), 128.4(3C), 128.5(2C), 128.8, 129.1, 129.3(4C), 131.0, 137.3, 137.7, 137.8, 142.1, 143.9, 145.8, 149.3, 150.0, 157.3, 168.7. MS (ESI): *m/z* 581.4 $[M–H]^-$. HRMS (ESI): *m/z* $[M–H]^-$ Calcd for $C_{38}H_{29}O_6$: 581.1964; found: 581.1969.

(*R*)-Methyl 3-(3,4-bis(benzyloxy)phenyl)-2-hydroxy-propanoate (13). (1) To a stirred solution of Sodium Danshensu **5** (220 mg, 1 mmol) in MeOH (50 mL) was added K_2CO_3 (550 mg, 4 mmol), and BnBr (0.25 mL, 3 mmol). The reaction mixture was degassed, charged with Ar, and heated to reflux 5h. After cooling to r. t., the solvent of the mixture was removed under reduced pressure. The crude product was used for the next step directly.

(2) To a stirred solution of the above crude material in MeOH (20 mL) was added *p*-TsOH (3 mg, 0.01 mmol). The reaction mixture was heated to reflux for 4 h. After cooling to r. t. , the solvent of the mixture was removed under reduced pressure. The crude product was purified by chromatography on silica gel (PE : EtOAc = 4 : 1) to afford a white solid **13** (190 mg, 51%, in two steps).

Compound **13**: $[\alpha]_D^{20}$ +14 (*c* 0.05, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.61 (d, *J* = 6.6 Hz, 1H), 2.85 (dd, *J* = 14.1, 6.6 Hz,1H), 3.02 (dd, *J* = 14.1, 4.4 Hz, 1H), 3.71 (s, 3H), 4.38 (td, *J* = 6.6, 4.4, 1H), 5.13 (s, 2H), 5.14 (s, 2H), 6.69 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.82 (d, *J* = 1.8 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 7.27-7.45 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.3, 52.6, 71.5, 71.6(2C), 115.4, 116.9, 122.7, 127.5(2C), 127.6(2C), 128.0(2C), 128.1(2C), 128.7(2C), 129.8, 137.6, 137.6, 148.3, 149.1, 174.7. MS (ESI): *m/z* 393.3 $[M+H]^+$. HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{24}H_{25}O_5$: 393.1702; found: 393.1698.

(*R*,*E*)-1-methoxycarbonyl-2-[3,4-bis(benzyloxy)phenyl]ethyl 3-[7-(benzyloxy)-2-[(3,4-bis(benzyloxy)phenyl]benzofuran-4-yl]acrylate (14). To a stirred solution of **12** (100 mg, 0.17 mmol) and **13** (80 mg, 0.21 mmol) in DMF was added EDCI (177 mg, 0.92 mmol), and DMAP (113 mg, 0.92 mmol). The reation mixture was degassed, charged with Ar, and stirred at r.t. for 2 days. After completion of the reaction, 1 N HCl (5 mL)was added, the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (PE : EtOAc = 3 : 1) to a yellow solid afford **14** (140 mg, 84%).

Compound 14. $[\alpha]_D^{20}$ +33 (*c* 0.09, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.16 (m, 2H), 3.73 (s, 3H), 5.12 (s, 4H), 5.21 (s, 2H), 5.26 (s, 2H), 5.35 (m, 1H), 5.37 (s, 2H), 6.46 (d, *J* = 15.0 Hz, 1H), 6.81 (d, *J* = 6.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 1H), 7.11 (s, 1 H), 7.26-7.50 (m, 27H), 7.64 (m, 1H), 7.93 (d, *J* = 15.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 37.3, 52.6, 71.3, 71.4, 71.5, 71.6, 71.7, 73.2, 99.5, 109.1, 112.3, 115.0, 115.2, 115.3, 116.6, 119.4, 120.2, 122.6, 123.5, 125.3, 127.5(4C), 127.7(2C), 127.9(2C), 128.1(2C), 128.5(3C), 128.6(4C), 128.8(5C), 128.9(3C), 129.5, 131.2, 136.7, 137.1, 137.3(2C), 137.5, 144.1(2C), 146.2, 148.4, 149.1, 149.3, 150.2, 157.7, 166.9, 170.7. MS (ESI): *m/z* 979.3 $[M+Na]^+$. HRMS (ESI): *m/z* $[M+Na]^+$ Calcd for $C_{62}H_{52}O_{10}Na$: 979.3458; found: 979.3461.

(*R*,*E*)-2-(3-(7-(Benzyloxy)-2-(3,4-bis(benzyloxy)phen-yl)benzofuran-4-yl)acryloyloxy)-3-(3,4-bis(benzyl-oxy)phenyl)propanoic acid (15). To a stirred solution of **14** (90 mg, 0.094 mmol) in DCE (5 mL) was added Me_3SnOH (54 mg, 0.28 mmol). The reaction mixture was heated to reflux overnight. After cooling to r.t., 1 N HCl (5 mL) was added, the aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (DCM : MeOH = 99 : 1) to afford a yellow solid **15** (38 mg, 43%).

Compound 15. $[\alpha]_D^{20}$ +28 (*c* 0.07, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.15 (m, 2H), 5.11 (s, 2H), 5.19 (s, 2H), 5.23 (s, 2H), 5.30 (s, 2H), 5.39 (s, 2H), 5.40 (m, 1H), 6.43 (d, *J* = 15.9 Hz, 1H), 6.75-6.98 (m, 7H), 7.09 (s, 1H), 7.24-7.53 (m, 26H), 7.93 (d, *J* = 15.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.8, 71.0, 71.1, 71.2, 71.3, 71.4, 72.6, 99.2, 108.7, 111.9, 114.7(2C), 114.9, 116.4, 119.1, 119.8, 122.4, 123.2, 125.1, 127.2(2C), 127.2(2C), 127.3(2C), 127.4(2C), 127.5(2C), 127.7(2C), 127.9(2C), 128.1, 128.2, 128.3(2C), 128.4(2C), 128.5(3C), 128.6(2C), 129.1, 131.0, 136.4, 136.8, 137.0, 137.1, 137.2, 143.9, 144.1(2C), 145.9, 148.1, 148.7, 149.9, 157.7, 166.7, 174.8. MS (ESI): *m/z* 943.3 $[M+H]^+$. HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{61}H_{51}O_{10}$: 943.3482; found: 943.3485.

Salvianolic acid C (1). To a stirred solution of **15** (100 mg, 0.106 mmol) in dry DCM (5 mL), BBr_3 (2 M in DCM, 0.53 mL, 1.06 mmol) was added at -78ºC. Then the mixture was stirred at the same temperature for 2h. After completion of the reaction, 0.5 mol/L Na_2HPO_4 (5 mL) was added to quench the reaction. The aqueous layer was extracted with EtOAc (3×15 mL). The combined organic layers were dried, filtered, and concentrated under reduced pressure. The crude product was purified by Sephadex LH-20 to afford a yellow solid **1** (20 mg, 40%).

Salvianolic Acid C (1). $[\alpha]_D^{20}$ +8 (*c* 0.06, MeOH). ^{1}H NMR (300 MHz, CD_3OD): δ 2.97（dd, *J* = 14.1, 9.3 Hz, 1H), 3.15 (dd, *J* = 14.1, 3.3 Hz, 1H), 5.14 (dd, *J* = 9.3, 3.3 Hz, 1H), 6.42 (d, *J* = 15.9, 1H), 6.42-6.71 (m, 3H), 6.80 (s, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 7.15 (s, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.35 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.39 (d, *J* = 1.8 Hz, 1H), 7.89 (d, *J* = 15.9 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD): δ 37.7, 76.6, 98.3, 111.4, 112.1, 113.6, 115.1, 115.5, 116.4, 117.3, 117.4, 120.6, 122.4, 125.5, 128.7, 130.1, 131.1, 143.5, 143.6, 144.1, 144.8, 145.6, 146.7, 157.6, 168.5, 176.7. MS (ESI): *m/z* 515.1 $[M+Na]^+$. HRMS (ESI): *m/z* $[M+Na]^+$ Calcd for $C_{26}H_{20}O_{10}Na$: 515.0954; found: 515.0950.

Tournefolic acid A (3). To a stirred solution of **12** (116 mg, 0.20 mmol) in dry DCM (5 mL), BBr_3 (2 M in DCM, 1 mL, 2.0 mmol) was added at -78 ºC. Then the mixture was stirred at the same temperature for 2h. After completion of the reaction, 0.5 mol/L Na_2HPO_4 (5 mL) was added to quench the reaction. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried, filtered, and concentrated under

reduced pressure. The crude product was purified by Sephadex LH-20 to afford a yellow solid **3** (27 mg, 45%).

Tournefolic acid A (3). ^{1}H NMR of **3**(300 MHz, Me_2CO-d_6): δ 6.47 (d, *J* = 16.2 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 8.1 Hz. 1H), 7.41 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.45 (s, 1H), 7.51 (d, *J* = 2.1 Hz, 1H), 7.90 (d, *J* = 16.2 Hz, 1H). ^{13}C NMR of **3**(75 MHz, Me_2CO-d_6): δ 98.8, 110.9, 112.5, 115.5, 115.9, 117.7, 118.7, 122.2, 125.4, 131.4, 143.1, 143.2, 144.7, 145.7, 146.9, 158.0, 168.5. MS (ESI): *m/z* 313.1 $[M+H]^+$. HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{17}H_{13}O_6$: 313.0712; found: 313.0708.

Tournefolal (4). To a stirred solution of **11** (180 mg, 0.33 mmol) in dry DCM (5 mL), BBr_3 (2 M in DCM, 1.65 mL, 3.3 mmol) was added at -78 ºC. Then the mixture was stirred at the same temperature for2h. After completion of the reaction, 0.5 mol/L Na_2HPO_4 (5 mL) was added to quench the reaction. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried, filtered, and concentrated under reduced pressure. The crude product was purified by Sephadex LH-20 to afford a yellow solid 4 (78 mg, 87%).

Tournefolal (4).^{1}H NMR (300 MHz, Me_2CO-d_6): δ 6.93 (d, *J* = 9.0 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 7.39 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.48 (d, *J* = 2.1 Hz, 1H), 7.6 (s, 1H), 7.66 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (75 MHz, Me_2CO-d_6): δ 99.8, 110.4, 112.5, 115.9, 117.9, 121.8, 121.9, 130.9, 132.1, 143.2, 145.8, 147.2, 148.1, 159.6, 190.6. MS (ESI): *m/z* 271.1 $[M+H]^+$. HRMS (ESI): *m/z* $[M+H]^+$ Calcd for $C_{15}H_{11}O_5$: 271.0606; found: 271.0609.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (grants 90713046, 30925040) and CAS Foundation (grant KSCX2-YW-R-179).

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