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

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Abstract
First total synthesis of the natural product salvianolic acid C, tournefolic acid A and tournefolal 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.\textsuperscript{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.\textsuperscript{2} Salvianolic acid C (1), one of the Salvianolic acids, is constituted of danshensu (2)\textsuperscript{3} and 2-phenyl-benzofuran neolignan tournefolic acid A (3)\textsuperscript{4} linked by ester bond. Recently, Liang et al.\textsuperscript{5} have reported that salvianolic acid C (1) displays anti-proliferative activity against HepG2 cells with IC\textsubscript{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 activity.\textsuperscript{4} However, the low contents of salvianolic acid C (1),\textsuperscript{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](image_url)

**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 °C for 2 days, followed by using iodine chloride to introduce iodine at C-2. In order to avoid over iodination, the dose of iodine chloride should not exceed 1 equiv. The other key building block 7 was prepared via four steps including benzylation from 9, iodination catalyzed by iodine and Ag$_2$SO$_4$, 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 equiv 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 °C, 2 d, 67%; (ii) ICl, Py, DCM, 0 °C–r.t., 12 h, 86%; b. (i) K$_2$CO$_3$, BnBr, DMF, r.t., 12 h, 96%; (ii) I$_2$, Ag$_2$SO$_4$, DCM / EtOH, r.t., 1 h, 95%; c. (i) Pd (PPh$_3$)$_2$Cl$_2$, CuI, TEA, r.t., 12 h, 90%; (ii) K$_2$CO$_3$, MeOH, r.t., 24
The Sonogashira coupling\(^1\) of 6 with 7 was catalyzed by Pd(Ph\(_3\))\(_2\)Cl\(_2\) (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\(_3\)SnOH as the catalyst for demethylation to afford 15 in 43% yield.\(^1\) 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). \(^1\)H (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.

\(4-\text{(Benzyloxy)-3-hydroxy-2-iodobenzaldehyde (6).} \) (1) To a stirred solution of benaldehyde 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.** 1H NMR (300 MHz, CDCl3): 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). 13C NMR (75 MHz, CDCl3): 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 C14H12IO3: 354.9831; found: 354.9835.

**3,4-Dibenzylxyiodobenzene (10).** (1) To a stirred solution of pyrocatechol 10 (5.5 g, 0.05 mol.) and K2CO3 (25 g, 0.2 mol, 4.0 equiv) in DMF (50 mL) was added BnBr (24 mL, 0.2 mol). The reaction 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 Ag2SO4 (9.3 g, 30 mmol) in EtOH / DCM (100 / 50 mL) was added I2 (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.** 1H NMR (300 MHz, CDCl3): δ 5.11 (s, 2H), 5.12 (s, 2H), 6.70 (d, J = 8.4 Hz, 1H), 7.17 (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 7.23 (d, J = 2.4 Hz, 1H), 7.29-7.45 (m, 10H). 13C NMR (75 MHz, CDCl3): 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 C20H17IO2Na: 439.0171; found: 439.0173.

**3,4-Dibenzylxyethylbenzene (7).** (1) To a stirred solution of 10 (0.98 g, 2.36 mmol), 3 mol % Pd (PPh3)2Cl2 (50 mg, 0.07 mmol), and 3 mol % Cul (9 mg, 0.047 mmol) in TEA (20 mL) were added (trimethylsilyl)acetylene (0.37 mL, 2.60 mmol). The reaction 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-dibenzylxoytrimethyl- (phenylethynyl)silane (820 mg, 90%).

(2) To a stirred solution of 3,4-Dibenzylxoytrimethyl(phenylethynyl)silane (0.82 g, 2.12 mmol) in MeOH (50 mL) was added K2CO3 (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: 1H NMR (300 MHz, CDCl3): 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). 13C NMR (75 MHz, CDCl3): 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 C22H9O2: 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 (PPh3)2Cl2 (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 % Cul (15 mg) was added. The reaction 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. 1H NMR (300 MHz, CDCl3): 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). 13C NMR (75 MHz, CDCl3): 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), 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 C36H29O5: 541.2015; found: 541.2020.

(E)-3-(7-(Benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)benzo[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 Et2O to afford a yellow solid 12 (458 mg, 85%).

Compound 12. 1H NMR (300 MHz, DMSO-d6): 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). 13C NMR (75 MHz,
DMSO-d6): 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, 143.7, 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 C38H29O6: 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 K2CO3 (550 mg, 4 mmol), and BnBr (0.25 mL, 3 mmol). The reaction mixture was degassed, charged with Ar, and heated to reflux 5 h. 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: [α]D20 +14 (c 0.05, CHCl3). 1H NMR (300 MHz, CDCl3): δ 2.61 (d, J = 6.6 Hz, 1H), 2.85 (dd, J = 14.1, 6.6 Hz, 1H), 3.02 (ddd, 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). 13C NMR (75 MHz, CDCl3): 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, 148.3, 149.1, 174.7. MS (ESI): m/z 393.3 [M+H]+. HRMS (ESI): m/z [M+H]+ Calcd for C34H25O5: 393.1702; found: 393.1698.

(R,E)-1-methoxycarbonyl-3-[4,4-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 reaction 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. [α]D20 +33 (c 0.09, CHCl3). 1H NMR (300 MHz, CDCl3): 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, 1H), 7.26-7.50 (m, 27H), 7.64 (m, 1H), 7.93 (d, J = 15.0 Hz, 1H). 13C NMR (75 MHz, CDCl3): 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 C62H52O10Na: 979.3458; found: 979.3461.
(R,E)-2-(3-(7-(Benzyloxy)-2-(3,4-bis(benzyloxy)phenyl)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 Me3SnOH (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.** [α]D²⁰ +28 (c 0.07, CHCl₃). ¹H NMR (300 MHz, CDCl₃): 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). ¹³C NMR (75 MHz, CDCl₃): 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, 2C, 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, 150.7, 166.7, 174.8. MS (ESI): m/z 943.3 [M+H]+. HRMS (ESI): m/z [M+H]+ Calcd for C₆₁H₅₁O₁₀: 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), BBr₃ (2 M in DCM, 0.53 mL, 1.06 mmol) was added at -78°C. Then the mixture was stirred at the same temperature for 2h. After completion of the reaction, 0.5 mol/L Na₂HPO₄ (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). [α]D²⁰ +8 (c 0.06, MeOH). ¹H NMR (300 MHz, CD₃OD): 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). ¹³C NMR (75 MHz, CD₃OD): 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 C₁₂₀H₁₀₀O₁₀Na: 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), BBr₃ (2 M in DCM, 1 mL, 2.0 mmol) was added at -78°C. Then the mixture was stirred at the same temperature for 2h. After completion of the reaction, 0.5 mol/L Na₂HPO₄ (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). 1H NMR of 3 (300 MHz, Me$_2$CO-$d_6$): 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). 13C NMR of 3 (75 MHz, Me$_2$CO-$d_6$): 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$_5$: 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 °C. Then the mixture was stirred at the same temperature for 2 h. After completion of the reaction, 0.5 mol/L Na$_2$HPO$_4$ (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). 1H NMR (300 MHz, Me$_2$CO-$d_6$): 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). 13C NMR (75 MHz, Me$_2$CO-$d_6$): 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.

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References

