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Asymmetric synthesis of 3(*S*),17-dihydroxytanshinone

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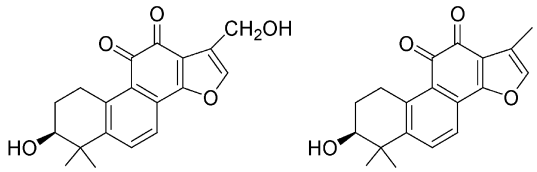
Abstract—The first synthesis of 3(*S*),17-dihydroxytanshinone was achieved by ultrasound promoted Diels–Alder reaction of the protected 3-hydroxymethyl-4,5-benzofurandione with a vinylcyclohexene derivative. Bioassay showed that the synthetic 3(*S*),17-dihydroxytanshinone was active in vitro against HL-60 tumor cell line by MTT method.

1. Introduction

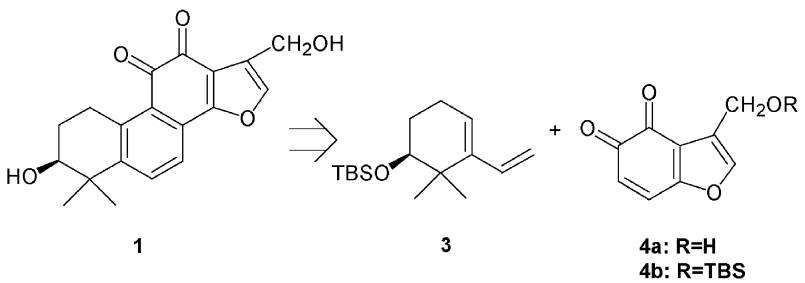
Danshen diterpene quinones exhibit significant cytotoxicity against various tumor cell lines.[1] It is notable that the extract of Dan Shen showed higher activities than the pure natural products.[2] This has led to more intensive search for minor active metabolites.[3] 3,17-Dihydroxytanshinone **1** was isolated from the roots of *Salvia bians* Royle ex Benth. (Labiatae), a native of the Kumaon Himalayan glaciers.[4] It is one of the three known tanshinone diterpene natural products bearing 17-hydroxyl group. However, the authors did not report its absolute configuration and biological activities. Lee and co-workers reported that the absolute stereochemistry of 3-hydroxytanshinone **2**, another natural product isolated from the same plant as **1**, was *S*.[5] According to biosynthesis, 3(*S*),17-dihydroxytanshinone is likely to be the natural one. Its unusual structure and potential biological properties combined to make the compound a challenging synthetic target.



In this paper, we described an asymmetric synthesis of compound **1**.

2. Result and discussion

The retro-synthesis of compound **1** was shown in Scheme 1. The Diels–Alder approach to tanshinone diterpenes was widely employed. Indeed, Lee and co-workers[5] reported the



Scheme 1.

Keywords: Natural product; Antitumor; Tanshinone diterpene; Dihydroxytashinone; Diels–Alder cycloaddition; Ultrasound; Total synthesis.
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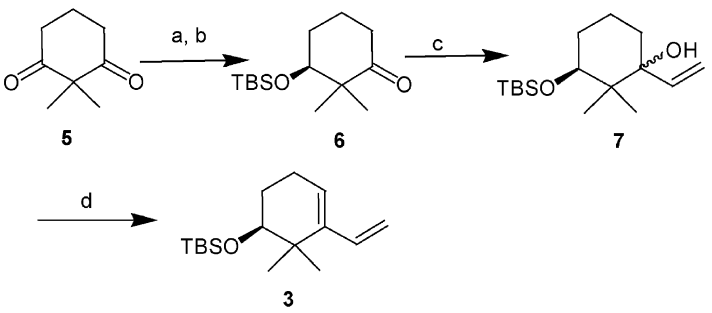


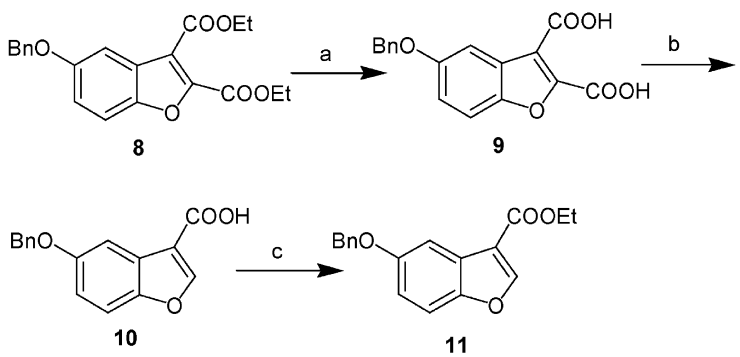
Scheme 2. *Conditions*: (a) Baker's yeast, 25 °C, 18 h, 70%; (b) 1.2 equiv. TBSCl, 1.5 equiv. imidazole, DMF, 25 °C, overnight, 91%; (c) 5 equiv. vinylmagnesium bromide, THF, 0 °C, 2 h; (d) 0.01 equiv. *p*-toluenesulfonic acid, 10 equiv. $MgSO_4$, toluene, reflux, 30 min, 42% two steps.

syntheses of some tanshinone diterpene natural products by ultrasound-promoted Diels–Alder cycloaddition. However, there were few reports on the synthesis of tanshinone diterpenes bearing 17-hydroxyl group.[6]

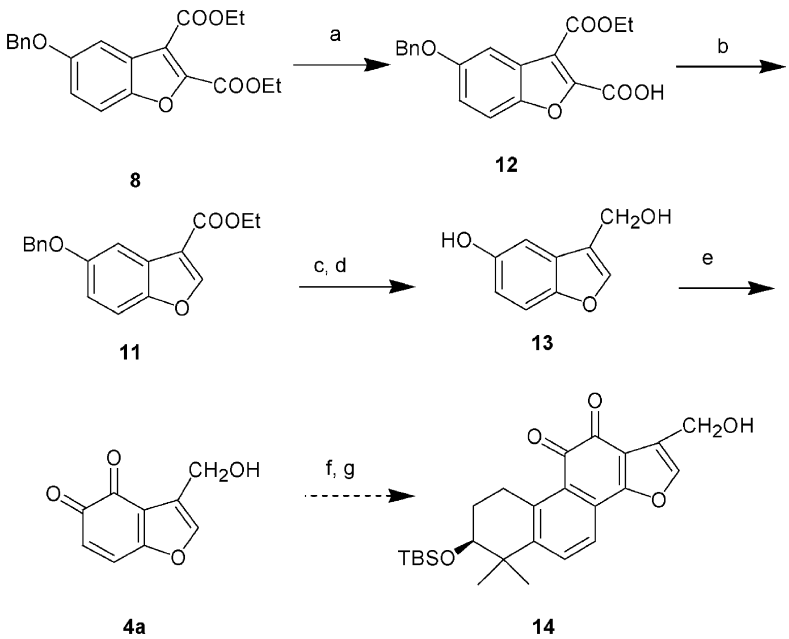
The diene **3** was synthesized from 2,2-dimethyl-1, 3-dicyclohexanone **5**. The starting material **5** was reduced by baker's yeast (70% yield, and >95% ee). Then the hydroxyl group was protected with *t*-butyldimethylsilyl (TBS) according to the conventional procedure to give ketone **6**, the analytical data (including optical rotation) of **6** was identical with that of product in literature.[7] The stereochemistry at C3 of ketone **6** was then assigned to be 'S' as reported in literature. To avoid harsh conditions in synthesis of diene **3** reported by Lee and co-workers in which LDA-mediated triflation, palladium-catalyzed coupling and use of highly toxic tri-*n*-butylstannane were involved, we resorted to a tertiary alcohol dehydration approach. Ketone **6** was treated with vinylmagnesium bromide to give tertiary alcohol **7** in 70% yield. Elimination of the hydroxyl group to form diene was problematic due to acid-sensitive TBS group. After failure with reagents such as $MsCl-Et_3N$, pyridine–$SOCl_2$, and *p*-toluenesulfonic acid, diene **3** was prepared by refluxing **7** with excessive dry magnesium sulfate in the presence of catalytic amount of *p*-toluenesulfonic acid (Scheme 2). The analytical data including optical rotation of diene **3** were identical with that of product in literature.[5] So, the diene **3** possessed S configuration as reported in literature.

With the diene **3** at hand, the next step is to synthesize *o*-quinone **4**, of which compound **11** is the key intermediate, with a synthetic route (Scheme 3) reported by Robins et al. [8] Robin's synthesis of **11** was completed in three steps: first, hydrolysis of benzofuran-2,3-dicarboxylate **8** to give benzofuran-2,3-dicarboxylic acid **9**, and then selective decarboxylation of 2-carboxyl group to benzofuran 3-carboxylic acid **10** and finally esterification of carboxylic acid **10** to afford **11** (Scheme 3).

Although the author reported a moderate yield in monodecarboxylation step, we found that the monodecarboxylation was affected by several factors such as reaction temperature, the quantity of copper, the activation of copper, particle size of copper, and stirring condition, etc. the reaction often encountered either sluggish monodecarboxylation or rapid decarboxylation of two carboxyl groups. We managed to prepare monocarboxylate **11** in a more efficient way (Scheme 4). The 2-carboxylate group of dicarboxylate **8** was selectively hydrolyzed to carboxylic acid **12** when **8** upon reaction with 1 equiv. of sodium hydroxide in ethanol. Then, the 2-carboxyl group of **12** underwent decarboxylation in the presence of copper powder in quinoline at 200 °C to give monocarboxylate **11** in 70% overall yield.[9] 3-Hydroxylmethyl-5-hydroxybenzofuran **13** was then prepared from 3-carboxylate **11** by debenzylation with Pd-catalyzed hydrogenation, and subsequent reduction with $LiAlH_4$ according to our previous work.[6] Cycloaddition of freshly prepared *o*-quinone **4a** from **13** with Fremy's salt with diene **3** was attempted with ultrasonic irradiation to achieve **14**, no cycloaddition product was formed and *o*-quinone **4a** was decomposed. This result was in accordance with our previous findings that *o*-quinone **4a** was very sensitive to temperature, acidic, and



Scheme 3. *Conditions*: (a) NaOH, EtOH, reflux; (b) Cu powder quinoline, 2 h, 200 °C; (c) $SOCl_2$, EtOH.



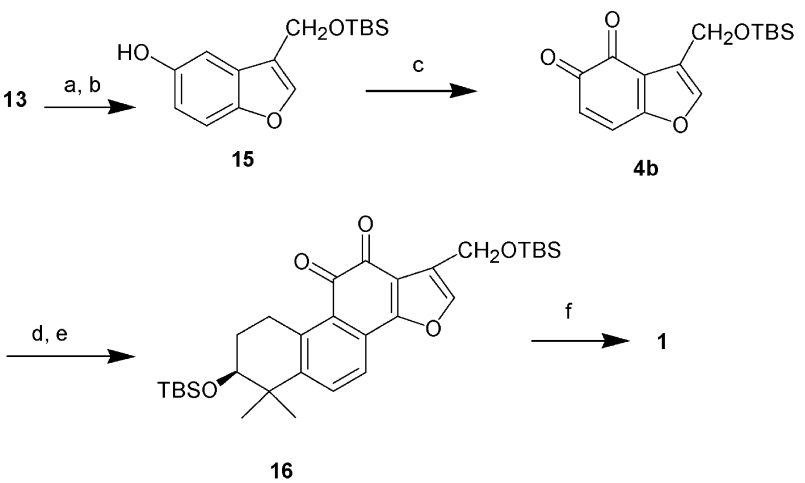
Scheme 4. *Conditions*:(a) 1 equiv. NaOH, EtOH, 2 h, rt; (b) Cu powder, quinoline, 2 h, 200 °C, 70% in two steps; (c) H_2/10% Pd–C, EtOH, 16 h, rt; (d) 5 equiv. $LiAlH_4$, THF, 10 h, 25 °C; (e) Fremy's salt, KH_2PO_4 buffer; (f) 3 equiv. **3**, ultrasonic, 6 h, 5 °C; (g) 1.5 equiv. DDQ, benzene, 10 h, reflux.

basic condition. It is unstable after standing in room temperature for several hours. The instability of *o*-quinone **4a** in fact caused a low overall yield in synthesis of Przewaquinone A.[6] Alternatively, the hydroxyl groups of **13** was protected as its TBS ether.(Scheme 5). The phenolic silyl ether was then selectively cleaved to give **15** upon reflux with potassium carbonate in ethanol (80% yield in two steps).[10] Oxidation of **15** to *o*-quinone **4b** with Fremy's salt was also troublesome. There was no reaction in aqueous methanol and aqueous acetone as the solvents. Finally, the oxidation of **15** to **4b** was achieved with modified phase transfer reaction pioneered by Kende.[11] Compound **16**, the precursor of **1**, was obtained after **3** and **4b** were subjected to ultrasonic irradiation at 5 °C for 6 h followed by aromatization with DDQ. Since the stereochemistry of **3** determined the stereochemistry of **16**, the absolute configuration of **16** was 'S' as in compound **3**. Finally, removal of the TBS protective groups with 15% hydrogen fluoride in acetonitrile[12] gave the target molecule, 3(*S*),17-dihydroxytanshinone, $[\alpha]_D^{20}$ −10° (acetone, *c*=0.4). The data of ^{1}H NMR, IR, MS, and melting point are identical with that of the natural product.[4]

In vitro cytotoxic activity of compound **1** on tumor lines was evaluated by MTT and SRB method, the synthetic 3(*S*),17-dihydroxytanshinone was active against HL60 cell line, the inhibition rate is 62% at 3 μM.

3. Conclusions

We successfully used ultrasound-promoted Diels–Alder cycloaddition to develop a first, concise total synthesis of optically active 3(*S*),17-dihydroxytanshinone (**1**). Chemical



Scheme 5. *Condition*: (a) 3 equiv. TBSCl, 5 equiv. Imidazole, DMF, 16 h, 25 °C; (b) 1.5 equiv. K_2CO_3, 5 equiv. H_2O, EtOH, reflux, 80% in two steps; (c) 5 equiv. Fremy's salt, 10 equiv. TBABr, CH_2Cl_2, KH_2PO_4 buffer, 18 h, 0 °C; (d) 3 equiv. **3**, ultrasonic, 6 h, 5 °C; (e) 1.5 equiv. DDQ, benzene, 10 h, reflux, 28% in three steps; (f) 15% HF, CH_3CN, 3 h, 25 °C, 85%.

synthesis and biological investigations of the analogues of this natural product are in progress.

4. Experimental

4.1. General

All moisture sensitive reactions were carried out under nitrogen atmosphere All reagents were purchased from Shanghai Chemical Reagent Company and Acros, and were used without further purification unless otherwise stated. Melting points were uncorrected. Infrared spectra were recorded on a Nicolet Magna 750 spectrometer and only characteristic absorptions were reported. The ^{1}H NMR spectra were measured with a Bruker AM-400 (400 MHz) spectrometer. ^{13}C NMR spectra were measured with an AM-400 (100 MHz) spectrometer. Coupling constants (J values) were reported in Hertz. Chemical shifts were expressed in ppm, using residual solvent as an internal standard. Mass spectra (medium and high resolution) were run on Varian MAT-711 and MAT-95 spectrometers. All solvents were purified and dried prior to use according to standard procedures.[13] 'Petroleum ether' referred to petroleum ether bp, 60–90 °C.

4.2. Synthesis

4.2.1. (−)-(*S*)-3-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-1-vinylcyclohexene (3). A solution of **6** (2.00 g, 7.8 mmol) in anhydrous THF (50 mL) was cooled to 0 °C, vinylmagnesium bromide (1.0 M in THF, 39 mL, 39 mmol) was then added dropwise, and the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with saturated NH_4Cl (50 mL), and the aqueous layer was extracted with ether (3×30 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution (50 mL) and brine (50 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 40:1) to give **7** (1.60 g), as a mixture of diastereomers. Then **7** was dissolved in dry toluene (80 mL). $MgSO_4$ (10 g, 83 mmol) and *p*-toluenesulfonic acid (9 mg, 0.4 mmol) were added. Then the mixture was refluxed for 30 min, and cooled to room temperature. $MgSO_4$ was then filtered off, the filtrate was washed with saturated $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel eluting with petroleum ether to afford **3** as a colorless oil (0.873 g, 42% from **6**): $[\alpha]_D^{20}$ −14.6° (lit.[5] −15.0°); IR (KBr): 2956, 2856, 1471, 1362, 1256, 1092, 1007, 879, 737, 773 cm^{-1}; ^{1}H NMR ($CDCl_3$, J=400 Hz, TMS): δ 0.05 (s, 3H), 0.06 (s, 3H), 0.9 (s, 9H), 0.98 (s, 3H), 1.01 (s, 3H), 1.64–1.68 (m, 2H), 2.01–2.20 (m, 2H), 3.53 (dd, 1H, J=6.3, 6.3 Hz), 4.93 (dd, 1H, J=10.7, 1.9 Hz), 5.27 (dd, 1H, J=17.0, 1.9 Hz), 5.69 (dd, 1H, J=3.6, 3.6 Hz), 6.29 (dd, 1H, J=17.0, 10.7 Hz) ppm. EIMS (m/z): 266 (M^+). HRMS 266.2060, calcd for $C_{16}H_{30}SiO$, 266.2066.

4.2.2. 5-Benzyloxy-benzofuran-2,3-dicarboxylic acid 3-ethyl ester (12). Compound **8** (1.00 g, 2.7 mmol) was dissolved in ethanol (50 mL) at room temperature, and NaOH (0.108 g, 2.7 mmol) in ethanol (14 mL) was added dropwise. After stirring for 2 h, the solution was acidified with HCl (2 M) to pH=4. Ethanol (40 mL) was removed under reduced pressure. The resultant residue was added with water (10 mL), the precipitate formed was collected by filtration, and washed with cold ethanol to give **12** (0.83 g, 2.4 mmol, 90% yield) as a white solid: mp 132–134 °C; IR (KBr): 2984, 1749 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 Hz, TMS): δ 1.52 (t, 3H, J=7.1 Hz), 4.61 (q, 2H, J=7.1 Hz), 5.16 (s, 2H), 7.24 (dd, 1H, J=9.3, 2.6 Hz), 7.35–7.48 (m, 5H), 7.49 (d, 1H, J=2.6 Hz), 7.59 (d, 1H, J=9.3 Hz) ppm. EIMS (m/z): 340 (M^+). HRMS 340.0963, calcd for $C_{19}H_{16}O_6$, 340.0947.

4.2.3. 5-Benzyloxy-benzofuran-3-carboxylic acid ethyl ester (11). Compound **12** (1.00 g, 2.94 mmol), copper powder (30 mg, 0.47 mmol) and quinoline (5 mL) were added to a flask. After stirring at 200 °C for 1 h, the mixture was cooled to room temperature. The solution was acidified with conc. HCl (16 mL), and extracted with ether (3×30 mL). The combined extract was washed, respectively, with water (3×30 mL), saturated $NaHCO_3$ solution (30 mL) and brine (30 mL), and dried over Na_2SO_4. After evaporation of the solvent in vacuo, the residue was purified by flash chromatography on silica gel eluting with petroleum ether/ethyl acetate (10:1) to give **11** (0.694 g, 2.36 mmol, 80% yield) as a white crystal: mp 64–66 °C; IR (KBr): 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ 1.39 (t, 3H, J=7.1 Hz), 4.38 (q, 3H, J=7.1 Hz), 5.12 (s, 2H), 7.02 (dd, 1H, J=9.2, 2.7 Hz), 7.35–7.50 (m, 6H), 7.59 (d, 1H, J=2.7 Hz), 8.20 (s, 1H) ppm. EIMS (m/z): 296 (M^+). Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96%; H, 5.44%. Found: C, 73.20%; H, 5.47%.

4.2.4. 3-Hydroxymethyl-benzofuran-5-ol (13). A mixture of **11** (1.20 g, 4.05 mmol) and 10% palladium on carbon (0.2 g) in ethanol (100 mL) was hydrogenated at room temperature under hydrogen (1 atm) for 16 h. Then, the catalyst was filtered-off, and the solvent was removed in vacuo. The residue was dissolved in anhydrous THF (40 mL) under N_2, and added dropwise to a mixture of $LiAlH_4$ (0.77 g, 20.1 mmol) in THF (40 mL) at room temperature. After stirred for 10 h, ethyl acetate (20 mL) was added to consume the residual $LiAlH_4$, then HCl (2 M, 40 mL) was added to the reaction mixture. The aqueous layer was then separated and extracted with ether (3×30 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution (40 mL) and brine (40 mL), dried over Na_2SO_4 and filtered. The solvent was evaporated to dryness, and the residue was purified by flash chromatography on silica gel eluting with petroleum ether/acetone (1:1) to give **13** (0.553 g, 3.36 mmol, 83% yield) as a white crystal: mp 135–136 °C; IR (KBr) 3409, 3201 cm^{-1}; ^{1}H NMR (400 Hz, DMCO-d_6, TMS): δ 4.70 (s, 2H), 6.84 (dd, 1H, J=8.8, 2.6 Hz), 7.11 (dd, 1H, J=2.6 Hz), 7.30 (d, 1H, J=8.8 Hz), 7.67 (s, 1H) ppm. EIMS (m/z): 164 (M^+). Anal. calcd for $C_9H_8O_3$: C, 65.85%; H, 4.91. Found: C, 66.01%; H, 4.91%.

4.2.5. 3-(*tert*-Butyldimethylsilyloxymethyl)-benzofuran-5-ol (15). To a solution of **13** (0.630 g, 3.84 mmol), and imidazole (1.30 g, 19.4 mmol) in anhydrous DMF (10 mL) was added a solution of TBSCl (1.74 g, 11.5 mmol) in

anhydrous DMF (8 mL). The resulting solution was stirred at room temperature for 24 h. $NaHCO_3$ solution (5%, 50 mL) and ether (60 mL) was added, and the aqueous layer was separated and extracted with additional ether (3×30 mL). The combined ether layer was washed with brine (30 mL), dried with Na_2SO_4, and filtered. The solvent was removed in vacuo, the residue was purified by flash chromatograph on silica gel eluting with petroleum ether/ethyl acetate (80:1) to afford a colorless oil. This oil was dissolved in ethanol (32 mL), to which water (0.33 mL, 18 mmol) and K_2CO_3 (0.560 g, 4.06 mmol) were added. The resultant mixture was heated to reflux for 12 h. Then the reaction mixture was cooled to room temperature, and filtered. The filtrate was evaporated to dryness. The residue was purified by flash chromatograph on silica gel eluting with petroleum ether/ethyl acetate (20:1) to give **15** (0.854 g, 3.07 mmol, 80% yield) as a white crystal: mp 72–74 °C; IR (KBr) 3244, 2955, 2854, 1462, 1217, 1070, 924, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS): δ 0.1 (s, 6H), 0.9 (s, 9H), 4.8 (s, 2H), 6.79 (dd, 1H, J=8.8, 2.6 Hz), 6.89 (1H, d, J=2.6 Hz), 7.30 (1H, d, J=8.8 Hz), 7.49 (1H, s) ppm. EIMS (*m*/*z*): 278 (M^+); HRMS 278.1344, calcd for $C_{15}H_{22}SiO_3$, 278.1338.

4.2.6. Oxidize 15 to 3-(*tert*-butyldimethylsilyloxy methyl)-benzofuran-4,5-dione and cycloaddition 3 with 4b to (+)-3(*S*),17-dihydroxytanshinone di-*tert*-butyldimethylsilyl ether (16). A solution of **15** (50 mg, 0.18 mmol) and TBABr (579 mg, 1.8 mmol) in CH_2Cl_2 (20 mL) were cooled to 0 °C in an ice bath, and an ice-cooled aqueous solution of Fremy's salt (300 mg dissolved in 20 mL of 0.1 M KH_2PO_4 buffer adjusted to pH 7) was added dropwise. After the addition, the solution was stirred at 0 °C for 18 h. The aqueous layer was separated and extracted with CH_2Cl_2 (3×20 mL). The combined organic phase was washed with water (2×20 mL) and brine (3×20 mL), over Na_2SO_4. The solvent was removed under reduced pressure to afford crude **4b** as a red oil, which was unstable at room temperature. Crude **4b** was quickly used in next step without purification. A mixture of crude **4b** and **3** (144 mg, 0.54 mmol) in anhydrous methanol (0.2 mL) was subjected to ultrasonic irradiation at 5 °C for 6 h. Methanol was then removed in vacuo, and the residue was passed through a silica gel plug, eluting initially with petroleum ether to recover unreacted **3** (101 mg, 70% recovery), and then with CH_2Cl_2 to give a mixture of aromatized and dihydro-adducts. This mixture was fully aromatized by refluxing in benzene (5 mL) with DDQ (62 mg, 0.27 mmol) for 10 h. Then the solution was purified by flash chromatography on silica gel eluting with petroleum ether/ethyl acetate (8:1) to give **16** as a red crystal (34 mg, 0.06 mmol, 30% yield): mp 184–186 °C; $[\alpha]_D^{20}$ +10 (*c* 0.4, $CHCl_3$); IR (KBr) 2955, 2856, 1697, 1677, 1471, 1387, 1082, 849 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS): δ 0.06 (s, 3H), 0.10 (s, 3H), 0.12 (s, 6H), 0.88 (s, 9H), 0.94 (s, 9H), 1.26 (s, 3H), 1.29 (s, 3H), 1.80–1.85 (m, 1H), 1.86–2.00 (m, 1H), 3.18–3.24 (m, 1H), 3.31–3.40 (m, 1H), 3.70 (dd, 1H, J=8.8, 2.9 Hz), 4.87 (d, 1H, J=1.5 Hz), 7.41 (t, 1H, J=1.5 Hz), 7.59 (d, 1H, J=8.2 Hz), 7.64 (d, 1H, J=8.2 Hz) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ −5.3, −4.8, −4.0, 18.2, 18.4, 25.9, 25.96, 25.98, 26.8, 26.9, 29.3, 40.6, 57.5, 74.8, 117.2, 120.7, 126.0, 127.3, 127.6, 133.8, 141.8, 143.6, 150.0, 162.1, 175.1, 183.3 ppm. EIMS (*m*/*z*): 554 (M^+). HRMS 554.2892, calcd for $C_{31}H_{46}Si_2O_5$, 554.2884.

4.2.7. (−)-3(*S*),17-Dihydroxytanshinone 1. Silyl ether **16** (30 mg, 0.054 mmol) was dissolved in a solution of 40% aqueous HF/CH_3CN (20 mL, 1:4, v/v) and stirred at room temperature for 3 h. Water (20 mL) was then added, and the mixture was extracted with ethyl acetate (3×20 mL). The combined organic layer was washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel eluting with CH_2Cl_2/CH_3OH (20:1) to give **1** (15 mg, 0.46 mmol, 85% yield) as red crystals: mp 208–210 °C (lit. 209–210 °C);[4] $[\alpha]_D^{20}$ −10 (*c* 0.4, acetone); IR (KBr): 3553, 3045, 1673, 1658, 1383, 1365, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, TMS): δ 1.32 (s, 3H), 1.35 (s, 3H), 2.15–2.29 (m, 2H), 3.32–3.45 (m, 2H), 3.96 (dd, 1H, J=8.6, 2.8 Hz), 4.70 (s, 2H), 7.33 (s, 1H), 7.50 (d, 1H, J=8.3 Hz), 7.63 (d, 1H, J=8.3 Hz); ^1H NMR (DMSO-d_6, 400 MHz, TMS): δ 1.19 (s, 3H), 1.22 (s, 3H), 1.64–1.78 (m, 1H), 1.82–1.88 (m, 1H), 2.98–3.07 (m, 1H), 3.18–3.26 (m, 1H), 3.52 (dd, 1H, J=8.8, 2.6 Hz), 4.55 (s, 1H), 7.56 (d, 1H, J=8.1 Hz), 7.73 (s, 1H), 7.76 (d, 1H, J=8.1 Hz) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 25.3, 26.2, 26.5, 29.1, 54.6, 72.1, 118.3, 120.4, 126.0, 126.8, 126.9, 134.0, 142.4, 142.5, 149.7, 161.0, 174.7, 182.5 ppm. EIMS (*m*/*z*): 326 (M^+). HRMS 326.1155, calcd for $C_{19}H_{18}O_5$, 326.1154.

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