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TETRAHEDRON

The Total Synthesis Of Salvianolic Acid F

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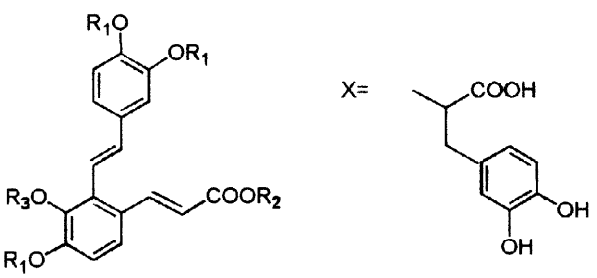
Abstract : An expeditious synthesis of salvianolic acid F **2** is described in 10% overall yield. Tetramethyl salvianolic acid F **3** was obtained in six steps in 39% overall yield and was converted into the target molecule using boron tribromide in 26% yield.

INTRODUCTION

During the last 15 years, several water-soluble phenolic acids have been isolated from the genus *Salvia*[1-8]. The first of them, named salvianolic acid A **1** (scheme 1), has been widely studied and numerous biological properties have been found (antitumoral[9], antiinflammatory[10] activities, gastric H^+, K^+-ATPase[11] inhibition, peroxidative damage to biomembranes[12] inhibition and antioxidant properties[13-14]). As a part of our programme devoted to the total synthesis of salvianolic acid A **1** and to the identification of its biologically active pharmacophore, the preparation of salvianolic acid F **2**, appeared to us to be an evident intermediate goal.



1: $R_1=R_3=H$, $R_2=X$; **2**: $R_1=R_2=R_3=H$;
3: $R_1=R_3=CH_3$, $R_2=H$; **4**: $R_1=R_2=H$, $R_3=CH_3$

Scheme 1

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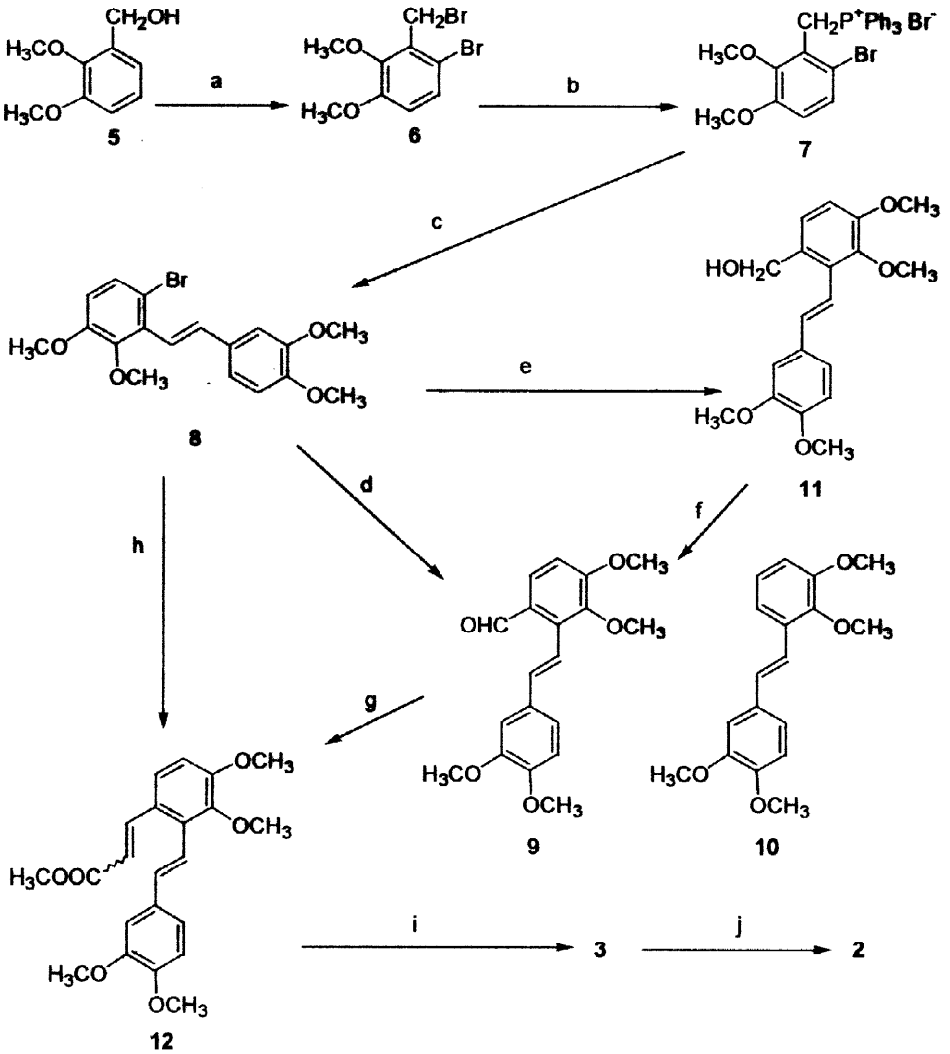
Attempts at synthesizing **2** led to the already described tetramethyl salvianolic acid F **3**[15]. Since the demethylation of **3** with boron tribromide gave **2** only in low yield[16] and the reported synthesis of **3** was long, fastidious and low yielding, we embarked in an expeditious high yielding synthesis of **3**. The conversion of **3** into **2** has also been reexamined.

RESULTS AND DISCUSSION

The route described here involves two stages (scheme 2): (i) access to the 1,2,3,4-substitution pattern of the «central» aromatic ring; (ii) conversion to the desired *E,E*-2-styrylcinnamic acid ring system. Our entry into the required 1,2,3,4-substitution pattern was found in the synthesis of 6-bromo-2,3-dimethoxybenzyltriphenylphosphonium bromide **7**. To this end, 2,3-dimethoxybenzylalcohol **5** was converted to **6**[17] in one step upon the action of bromine in chloroform involving the successive bromination of the aromatic ring and the methyl group. **6** reacted with triphenylphosphine to give **7** in 95% yield. **7** was obtained in 85% overall yield from 2,3-dimethoxybenzylalcohol.

With a satisfactory large scale synthesis of **7** in hand, we turned to the transformation of **7** into the tetramethyl salvianolic acid F **3**. Wittig reaction of **7** with 3,4-dimethoxybenzaldehyde yielded (*E*)-6-bromo-2,3,3',4'-tetramethoxystilbene **8** (80% yield). The bromine/lithium interconversion was accomplished in almost quantitative yield by treatment of **8** with butyllithium at -78°C. Unfortunately, quenching with dimethylformamide at –78°C led to only 36% of the desired aldehyde **9** with 58% of 2,3,3',4'-tetramethoxystilbene **10** as main product. The use of other agent such as *N*-formylpiperidine[18] or *N*-formylmorpholine[19] gave the same deceptive results. A large excess of BuLi or the use of hindered base such as sec-BuLi or tert-BuLi did not increased the yield in **9**. Since the halogen-metal exchange was almost quantitative, the low yield in **9** should be improved by performing the reaction at elevated temperature. As expected, best results were obtain when DMF was added at –20°C (85% yield in **9** with only 9% yield in **10**). At higher temperatures, the yield in **9** (and **10**) decreased dramatically probably due to a rapid decomposition of the aryllithium derivative (35% and 11% yields in **9** at 0°C and 20°C respectively). Alternatively **9** may be obtained in 71% yield in a two-steps procedure involving, the hydroxymethylation reaction of the organolithium derivative which gave 6-hydroxymethyl-2,3,3',4'-tetramethoxystilbene **11** in 75% yield followed by the oxidation of the benzylic alcohol with manganese dioxide in 95% yield. Transformation of **9** into **3** could be realized *via* two related methods. Perkin condensation of **9** with malonic acid and catalytic amounts of piperidine[20] in pyridine afforded **3** in modest yield (20%). The Wittig reaction of **9** with methyloxycarbonylmethyltriphenylphosphonium iodide (obtained from methyl iodoacetate and triphenylphosphine quantitatively) in the presence of sodium methylate in methanol proved to be more efficient and led to **12** as a mixture of *E* and *Z* isomers in 70% yield. This isomeric mixture was treated with KOH to give pure **3** (only in the E stereoisomer) in 95% yield. A more expeditive strategy involving the Heck reaction has been envisaged. The poor yield in styrylcinnamic acid obtained by Heck using $Pd(OAc)_2$ and triphenylphosphine[21] prompted us to use an acetate-bridged palladacycle (a more stable catalyst developed by Herrmann *et al*[22]). Prior to the conversion of **8** into **12**, 1-bromo-3,4-dimethoxybenzene was treated with this catalyst and methyl acrylate according to [22]. As expected, methyl 3,4-dimethoxycinnamate was obtained in 65% yield. Unfortunately, attempts to convert **8** into **12** using the same catalyst gave only 5% of **12** as a mixture of *E* and *Z* isomers. This poor yield was probably due to steric hindrance. Nevertheless, the use of other catalyst for the Heck reaction might lead to a substantial improvement

in terms of yield and number of step. In spite of this last deceptive results, 3 was obtained in 39% yield from 2,3-dimethoxybenzylalcohol.



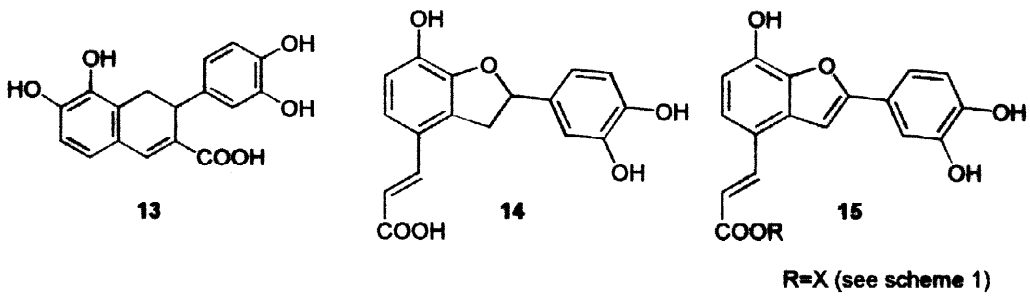
a. Br_2, $CHCl_3$, rt, 1h, 90% ; b. $P(C_6H_5)_3$, toluene, reflux, 4h, 95% ; c. MeOH, MeONa, then 3,4-dimethoxybenzaldehyde, reflux, 5h, 80% ; d. THF, BuLi, -78°C, 0.5h, then DMF, -20°C, 0.5h, 85% ; e. THF, BuLi, -78°C, then gazeous CH_2O, 75% ; f. MnO_2, CH_2Cl_2, rt, 16h, 95% ; g. MeOH, MeONa, then $MeOOCCH_2P^+(C_6H_5)_3$ I^-, reflux, 3h, 70% ; h. Acetate-bridged palladacycle obtained from $Pd(OAc)_2$ and tri(*o*-tolyl)phosphorane, methyl acrylate, diethyleneglycol di-*n*-butyl ether, 140°C, 24h, 5%; i. EtOH, KOH, reflux, 4h, then HCl 3M, 95% ; j. $CH_2(COOH)_2$, pyridine, cat. piperidine, 20% ; k. BBr_3, CH_2Cl_2, 20°C, 1h, 26%.

Scheme 2

The conversion of **3** into the target molecule, salvianolic acid F **2**, was previously reported[16]. **2** was

obtained in only 10% yield with the monomethylated salvianolic acid F **4** as the main product (30% yield). Unfortunately, **2** was rapidly converted into a mixture of **13** and **14** (Scheme 3) when stored in solution.

Since the chromatographic purification of polyhydroxylated cinnamic acids needed protic acids such as formic acid, we felt that the instability of **2** could be due to acid traces. Moreover, it has been observed[2] that salvianolic acid A **1** was converted into salvianolic acid C **15** (Scheme 3) on TLC plate impregnated with 2% of formic acid solution. Therefore, we decided to modify the work-up of the deprotection reaction. In order to avoid the possible conversion of **2** into **13** during the work-up, the reaction medium was poured into a saturated solution of K_2HPO_4. As expected, **2** was obtained in 26% yield with **13** (39%) and **14** (30%). Alternatively, **13** may be obtain almost quantitatively when **3** was treated with boron tribromide at 20°C and water slowly added to the reaction mixture.



Scheme 3

As a conclusion, the synthesis of tetramethyl salvianolic acid F **3** has been substantially improved (39% in six steps versus 0.2% in eleven steps[15]). The sensibility of **2** to protic acids, the difficulties to accomplish the total demethylation and the reactivity of the cinnamic ester function to BBr_3[23-24] lead us to modify our strategy for the total synthesis of salvianolic acid A **1**, *i.e.*, change the methyl groups by other more labile protective groups (benzyl or allyl) or carry out the demethylation at a previous stage in the present synthetic strategy. Nevertheless, **2** was successfully obtained in 10% overall yield from 2,3-dimethoxybenzylalcohol in a seven-step sequence. In spite of the fact that the discovery of substances in Nature after their synthesis in the laboratory is not common, it would not be unexpected that natural depsides with similar structure of **13** will be isolated in future.

EXPERIMENTAL

TLC analyses were performed on a 3×10 cm plastic sheet precoated with silica gel 60F254 (Merck) (Solvent system: ethyl acetate/cyclohexane 1:1). SiO_2, 200-400 mesh (Merck) was used for column chromatography. Melting points were obtained on a Reichert Thermopan melting points apparatus, equipped with a microscope and are uncorrected. NMR spectra were obtained on a AC 200 Bruker spectrometer in the appropriate solvent with TMS as internal reference. *J* values are given in Hz. Mass spectra were recorded on a Ribermag R 10-10 spectrometer (Electron Impact, 60eV) or on a Finigan MAT vision 2000 spectrometer (for the MALDI (mass assisted laser desorption ionization). Elemental analysis were performed by CNRS laboratories (Vernaison) and were within 0.4% of the theorical value.

4-Bromo-3-bromomethylveratrole 6

3,4-Dimethoxybenzylalcohol **5** (1.68g, 10mmol) was dissolved in chloroform (100mL), and bromine (1.60g, 10mmol) was added at 0°C. The mixture was then allowed to come to room temperature. The solvent was evaporated to give 2.79g (90%) of pure **6** as yellow crystals: mp=74°C (lit.,[17] 74°C); δ_H(200 MHz, $CDCl_3$; Me_4Si): 3.83 (3H, s, OMe), 3.95 (3H, s, OMe), 4.67 (2H, s, CH_2), 6.75 (1H, d, ^3J=8.8Hz, 5-H), 7.25 (1H, d, ^3J=8.8Hz, 6-H).

4-Bromo-3-triphenylphosphoniomethylveratrole bromide 7

6 (1.55g, 5mmol) was dissolved in toluene (50mL), triphenylphosphine (1.31g, 5mmol) was added and the mixture was heated under reflux for 4h and then allowed to cool to room temperature. The precipitate was filtered to give 2.71g (95%) of pure **7** as white powder: mp=169°C; δ_H(200 MHz, $CDCl_3$; Me_4Si): 3.72 (3H, s, OMe), 3.77 (3H, s, OMe), 5.13 (2H, d, ^2J=14.0Hz, CH_2), 6.72 (1H, d, ^3J=8.8Hz, 5-H), 7.02 (1H, d, ^3J=8.8Hz, 6-H), 7.55-7.80 (15H, m, 3 Phenyl); Elemental analysis calcd for $C_{27}H_{25}Br_2O_2P$: C, 56.67; H, 4.40; Br, 27.93; O, 5.59; P, 5.41; found: C, 56.62; H, 4.25; Br, 27.38; O, 5.34; P, 5.14.

(E)-6-Bromo-2,3,3',4'-tetramethoxystilbene 8

To a solution of sodium (0.23g, 10mmol) in dry methanol (30mL) was added **7** (5.72g, 10mmol) dissolved in dry methanol (30mL). The solution was vigorously stirred for 0.5h and 3,4-dimethoxybenzaldehyde (1.66g, 10mmol) dissolved in dry methanol (30mL) was added. The mixture was heated under reflux for 5h. The solvent was evaporated and the residue was crystallized from methanol to give 3.03g (80%) of pure **8** as yellow crystals : mp=80°C; δ_H(200 MHz, $CDCl_3$; Me_4Si): 3.75 (3H, s, OMe), 3.85 (3H, s, OMe), 3.90 (3H, s, OMe), 3.95 (3H, s, OMe), 6.68 (1H, d, ^3J=8.8Hz, 4-H), 6.87 (1H, d, ^3J=8.8Hz, 5'-H), 7.03 (1H, d, ^3J=16.4Hz, C*H*=), 7.05-7.11 (2H, m, 2'-H and 6'-H), 7.30 (1H, d, ^3J=8.8Hz, 5-H), 7.35 (1H, d, ^3J=16.4Hz, C*H*=); δ_C(50 MHz, $CDCl_3$; Me_4Si): 55.5 (q), 55.6 (q), 56.0 (q), 59.8 (q), 109.5 (d), 111.9 (d), 112.9 (d), 114.0 (d), 119.7 (d), 121.4 (d), 128.1 (d), 130.0 (s), 130.7 (s), 135.0 (s), 147.7 (s), 149.0 (s), 149.1 (s), 152.6 (s); *m/z* : 380 ($M^{+\circ}$(^{80}Br), 62%), 378 ($M^{+\circ}$(^{79}Br), 65), 284 (67), 268 (100), 151 (88); Elemental analysis calcd for $C_{18}H_{19}BrO_4$: C, 57.00; H, 5.05; Br, 21.07; O, 16.88; found: C, 56.87; H, 4.84; Br, 21.26; O, 17.00.

(E)-6-Formyl-2,3,3',4'-tetramethoxystilbene 9 and (E)-2,3,3',4'-tetramethoxystilbene 10 (from 8)

To a solution of **8** (1.89g, 5mmol.) in dry THF (20mL) was added dropwise a solution of butyllithium in hexane (6.25mL, 1.6M, 10mmol.) at -78°C. The mixture was stirred for 0.5h and the temperature was raised to -20°C. DMF (3.86mL, 50mmol.) in THF (10mL) was added and the mixture was stirred for 0.5h. HCl was added until pH=1 and the solution was extracted with ether (4×20mL). The organic layers were dried over Na_2SO_4. The solvents were evaporated and the oily residue was purified by column chromatography (cyclohexane/Ethyl acetate : 1 :1) to give 1.01g (85%) of pure **9** and 0.135g (9%) of pure **10**.

(E)-6-Formyl-2,3,3',4'-tetramethoxystilbene 9

δ_H(200 MHz, $CDCl_3$; Me_4Si): 3.80 (3H, s, OMe), 3.91 (3H, s, OMe), 3.95 (3H, s, OMe), 3.96 (3H, s, OMe), 6.75 (1H, d, ^3J=16.4Hz, C*H*=), 6.85 (1H, d, ^3J=8.8Hz, 4-H), 6.95 (1H, d, ^3J=8.8Hz, 5'-H), 7.10-7.11 (2H, m, 2'-H and 6'-H), 7.40 (1H, d, ^3J=16.4Hz, C*H*=), 7.75 (1H, d, ^3J=8.8Hz, 5-H), 10.10 (1H, s, C*H*O) ; δ_C(50 MHz, $CDCl_3$; Me_4Si): 54.7 (q), 55.3 (q), 55.5 (q), 60.3 (q), 105.4 (d), 110.5 (d), 111.3 (d), 114.2 (d), 118.8 (d), 119.3

(d), 120.1 (d), 133.2 (s), 133.5 (s), 136.4 (s), 147.3 (s), 149.1 (s), 149.2 (s), 152.8 (s), 186.2 (d); *m/z* : 328 ($M^{+\circ}$, 9%), 300 (25), 85 (75), 57 (100), 43 (94); Elemental analysis calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14; O, 24.36; found: C, 69.23; H, 6.42; O, 24.59.

(E)-2,3,3',4'-tetramethoxystilbene 10

δ_H(200 MHz, $CDCl_3$; Me_4Si): 3.84 (3H, s, OMe), 3.87 (3H, s, OMe), 3.89 (3H, s, OMe), 3.94 (3H, s, OMe), 6.81 (1H, dd, ^3J=8.2Hz, ^4J=1.3Hz, 4-H), 6.86 (1H, d, ^3J=8.8Hz, 5'-H), 7.04 (1H , d, ^3J=16.4Hz, C*H*=), 7.09-7.11 (3H, m, 2'-H, 5-H and 6'-H), 7.21 (1H, dd, ^3J=8.1Hz, ^4J=1.3Hz, 6-H), 7.30 (1H, d, ^3J=16.4Hz, C*H*=); δ_C(50 MHz, $CDCl_3$; Me_4Si): 55.7 (q), 55.87 (q), 55.88 (q), 60.9 (q), 109.1 (d), 111.0 (d), 111.2 (d), 117.7 (d), 119.9 (d), 124.0 (d), 124.0 (d), 129.7 (d), 130.8 (s), 131.7 (s), 146.7 (s), 148.9 (s), 149.1 (s), 153.0 (s); *m/z* : 300 ($M^{+\circ}$, 97%), 207 (51), 151 (100); Elemental analysis calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71; O, 21.31; found: C, 72.05; H, 6.95; O, 21.48.

(E)-6-Hydroxymethyl-2,3,3',4'-tetramethoxystilbene 11

To a solution of 7 (1.895g, 5mmol.) in dry THF (20mL) was added dropwise a solution of butyllithium in hexane (6.25mL, 1.6M, 10mmol.) at -78°C. The mixture was stirred for 0.5h and gazeous formaldehyde was added. HCl was immediately added until pH=1 and the solution was extracted with ether (3×20mL). The organic layers were dried over Na_2SO_4. The solvents were evaporated and the oily residue was purified by column chromatography (Hexane/Petroleum ether : 3 :2). **11** was obtained as yellow oil (2.47g, 75%) : δ_H(200 MHz, $CDCl_3$; Me_4Si):1.65 (1H, br s, OH), 3.75 (3H, s, OMe), 3.87 (3H, s, OMe), 3.89 (3H, s, OMe), 3.93 (3H, s, OMe), 4.69 (2H, s, CH_2OH), 6.79 (1H, d, ^3J=8.8Hz, 4-H), 6.85 (1H, d, ^3J=8.8Hz, 5'-H), 7.03 (1H, d, ^3J=16.4Hz, C*H*=), 7.06-7.08 (2H, m, 2'-H and 6'-H), 7.11 (1H, d, ^3J=8.8Hz, 5-H), 7.25 (1H, d, ^3J=16.4Hz, C*H*=); δ_C(50 MHz, $CDCl_3$; Me_4Si): 55.8 (q), 55.92 (q), 55.95 (q), 60.3 (q), 63.7 (t), 109.1 (d), 110.7 (d), 111.2 (d), 114.5 (d), 119.8 (d), 119.9 (d), 125.0 (d), 131.1 (s), 131.4 (s), 131.5 (s), 147.3 (s), 149.0 (s), 149.1 (s), 152.6 (s); *m/z* : 330 ($M^{+\circ}$, 9%), 312 (25), 161 (75), 151 (100); Elemental analysis calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.72; O, 24.21; found: C, 69.43; H, 6.82; O, 24.36.

(E)-6-Formyl-2,3,3',4'-tetramethoxystilbene 9 (from 11)

11 (1.65g, 5mmol.) was dissolved in CH_2Cl_2 (5mL), MnO_2 (8.69g, 100mmol.) was added and the solution was allowed to cool to room temperature for 16h. The solution was filtered and the solvent was evaporated to give **9** (3.12g, 95%) as brown oil.

Tetramethyl salvianolic acid F 3 (from 9 via 12)

To a solution of sodium (0.127g, 5.5mmol) in dry methanol (10mL) was added methyl triphenylphosphonioacetate (2.54g, 5.5mmol.) dissolved in dry methanol (10mL). The solution was vigorously stirred for 0.5h. **9** (1.64g, 5mmol) dissolved in dry methanol (10mL) was then added and the mixture was heated under reflux for 3h. The solvent was evaporated and the residue was treated with ethyl acetate. The solution was filtered, the solvent evaporated and the residual oil was purified by column chromatography (Petroleum ether/ Ethyl acetate : 3 :1) to give 1.34g (70%) of **12** as a mixture of E and Z isomers. **12** was dissolved in ethanol (10mL) and KOH (0.112g, 2mmol) was added. The solution was heated under reflux for 4h. The solvent was evaporated and the residue treated with HCl (5mL, 3M). The solid was filtered off, washed with iced water and

dried to give 1.23g (95%) of pure **3**: mp=200°C ; δ_H(200 MHz, DMSO-6d; Me_4Si): 3.78 (3H, s, OMe), 3.90 (3H, s, OMe), 3.92 (3H, s, OMe), 3.94 (3H, s, OMe), 6.30 (1H, d, ^3J=15.9Hz, CH=C*H*-COOH), 6.65 (1H, d, ^3J=16.9Hz, C*H*=), 6.85 (1H, d, ^3J=8.8Hz, 5-H), 6.88 (1H, d, ^3J=8.8Hz, 5'-H), 7.04-7.09 (2H, m, 2'-H and 6'-H), 7.17 (1H, d, ^3J=16.9Hz, C*H*=), 7.40 (1H, d, ^3J=8.8Hz, 6-H), 8.08 (1H, d, ^3J=15.9Hz, C*H*=CH-COOH), 11.90 (1H, br s, COO*H*); δ_C(50 MHz, DMSO-6d; Me_4Si): 55.55 (q), 55.57 (q), 55.8 (q), 59.9 (q), 109.6 (d), 111.9 (d), 117.9 (d), 119.7 (d), 119.9 (d), 123.7 (d), 125.6 (d), 125.7 (d), 129.9 (d), 132.9 (s), 136.4 (s), 142.6 (s), 146.3 (s), 149.0 (s), 149.2 (s), 153.5 (s), 167.7 (s); *m/z* : 370 ($M^{+\bullet}$, 12%), 151(100); Elemental analysis calcd for $C_{21}H_{22}O_6$: C, 68.10; H, 5.99; O, 25.91; found: C, 68.52; H, 6.02; O, 25.75.

Heck reaction of 1-bromo-3,4-dimethoxybenzene or 8

The bromoarene was treated with methyl acrylate according to the published procedure [23]. 1-Bromo-3,4-dimethoxybenzene gave methyl 3,4-dimethoxycinnamate in 65% yield as a mixture of E and Z isomers (3/1). **8** gave **12** in 5% yield as a mixture of E and Z isomers (4/1).

Tetramethyl salvianolic acid F 3(from 9)

Malonic acid (0.208g, 2mmol.) and **9** (0.328g, 1mmol.) were dissolved in dry pyridine (40mL). Some drops of piperidine were added and the solution was heated at 80°C for 1.5h, and at reflux for 3h. The solution was allowed to cool to room temperature. HCl (12M) was slowly added until pH=1 and the solution was extracted with ether (4×20mL). The organic layer was dried over Na_2SO_4. The solvents were evaporated and the oily residue was crystallized from ethyl acetate to give 0.148g (20%) of pure **3**.

Reaction of tetramethyl salvianolic acid F with boron tribromide

BBr_3 (1M in CH_2Cl_2, 10mL) was added dropwise to a solution of **3** (370mg, 1mmol) in CH_2Cl_2 (25mL) at 20°C. The mixture was stirred for 1h, then poured at once into a saturated solution of K_2HPO_4. The aqueous layer was separated and extracted with ether (3×20mL). The ethereal solution was dried over Mg_2SO_4 and evaporated. The crude product was dissolved in acetone (5mL) and purified by column chromatography (methanol/chloroform/formic acid: 84/15/1) to give 82mg (26%) of pure **2**, 122.5mg (39%) of pure **13** and 94.2mg (30%) of pure **14**.

Salvianolic acid F 2

δ_H(200 MHz, CD_3COCD_3; Me_4Si): 6.23 (1H, d, ^3J=15.75Hz, CH=C*H*-COOH), 6.69 (1H, d, ^3J=16.5Hz, C*H*=), 6.79 (1H, d, ^3J=8.1Hz, 5'-H), 6.81 (1H, d, ^3J=8.35Hz, 5-H), 6.87 (1H, dd, ^3J=8.1Hz, ^4J=2.0Hz, 6'-H), 7.08 (1H, d, ^4J=2.0Hz, 2'-H), 7.13 (1H, d, ^3J=8.35Hz, 6-H), 7.14 (1H, d, ^3J=16.5Hz, C*H*=), 7.98 (1H, d, ^3J=15.75Hz, C*H*=CH-COOH); *m/z* (MALDI$^+$) : 314 (M^+), 327 ($M+Na^+$), 353 ($M+K^+$).

3,4-Dihydro-5,6-dihydroxy-3-(3,4-dihydroxyphenyl)-2-naphthoic acid 13

δ_H(200 MHz, CD_3COCD_3; Me_4Si): 2.99(1H, dd, ^2J=16.8Hz,^3J=8.2Hz, 4-H), 3.41(1H, dd, ^2J=16.8Hz,^3J=1.5Hz, 4-H), 4.08(1H, dd, ^3J=8.2Hz,^3J=1.5Hz, 3-H), 6.50 (1H, dd, ^3J=8.0Hz, ^4J=2.0Hz, 6'-H), 6.59 (1H, d, ^3J=8.0Hz, 7-H), 6.62 (1H, d, ^4J=2.0Hz, 2'-H), 6.73 (1H, d, ^3J=8.0Hz, 5'-H), 6.81 (1H, d, ^3J=8.0Hz, 8-H), 7.66 (1H, s, 1-H) ; *m/z* (MALDI$^+$) : 314 (M^+), 327 ($M+Na^+$), 353 ($M+K^+$).

3-[-4-(2,3-Dihydro-2-(3,4-dihydroxyphenyl)-7-hydroxybenzofurannyl)]propenoic acid 14

δ_H(200 MHz, CD_3COCD_3; Me_4Si): 3.32(1H, dd, ^2J=16.2Hz,^3J=7.95Hz, 3-H), 3.81(1H, dd, ^2J=16.2Hz,^3J=9.2Hz, 3-H), 5.75(1H, dd, ^3J=9.2Hz,^3J=7.95Hz, 2-H), 6.25 (1H, d, ^3J=16.0Hz, CH=C*H*-COOH), 6.75-6.85 (4H, m, 2'-H, 5'-H, 6'-H and 5-H), 7.11 (1H, d, ^3J=8.2Hz, 6-H), 7.61 (1H, d, ^3J=16.0Hz, C*H*=CH-COOH) ; *m/z* (MALDI$^+$) : 314 (M^+), 327 ($M+Na^+$), 353 ($M+K^+$).

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