Towards the Synthesis of the Skeleton of Salvianolic Acid D

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Abstract: A successful synthesis of the acid part of salvianolic acid D is described (eight steps from isovanillin, 22% overall yield). The benzaldehyde key intermediate was obtained in six steps in 52% overall yield and was converted into the trimethylated precursor molecule using the Knoevenagel procedure. Finally, the acid part of salvianolic acid D was obtained by the exhaustive deprotection of the methyl groups with boron tribromide.

Key words: natural polyphenols, antivirals, boron tribromide

Salvia is an important genus widely cultivated and used in traditional medicines. It is a rich source of polyphenols and the water-soluble extracts of *Salvia* are of great importance due to their bioactivities (antioxidant, antiplatelet, antitumor, and antiviral activities).[1] Some of them exhibit potent effects against HIV-1 enzymes.[2–4] Due to our convergent interests in the total synthesis of natural polyphenols[5–6] and the discovery of new HIV-1 integrase inhibitors,[7–8] we decided to systematically synthesize acid moieties of salvianolic acids and related compounds (Figure 1).

This work deals with the elaboration of a key intermediate in the synthesis of a series of dimers of caffeic acid and with the total synthesis of the acid part of salvianolic acid D (**1**).

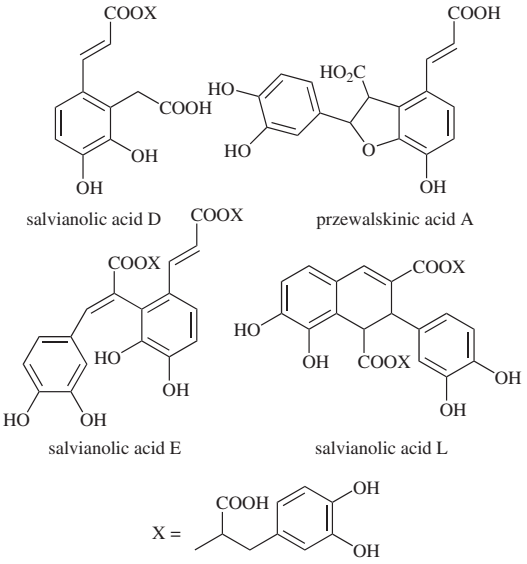

Figure 1 Structures of salvianolic acids and related compounds

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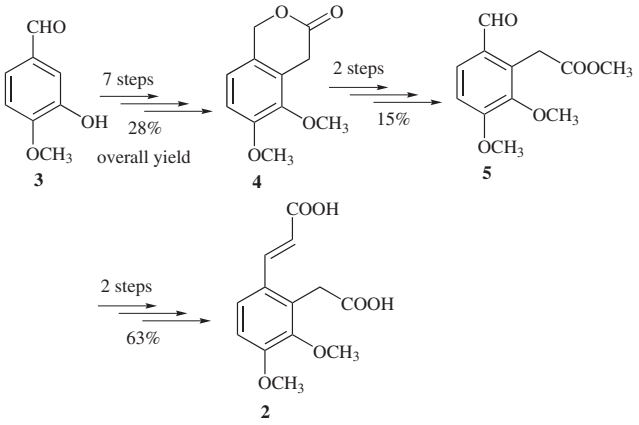
Salvianolic acid D was isolated from *Salvia miltiorrhiza* and the synthesis of the dimethylated acid part of salvianolic acid D (**2**) was described.[9] The prerequisite for the elaboration of the target polyphenol needs the building of the intermediate **5**, which can be considered a milestone in the synthesis of various natural dimers of caffeic acid. Compound **5** can be obtained either from isovanillin or 2,3-dimethoxybenzaldehyde.

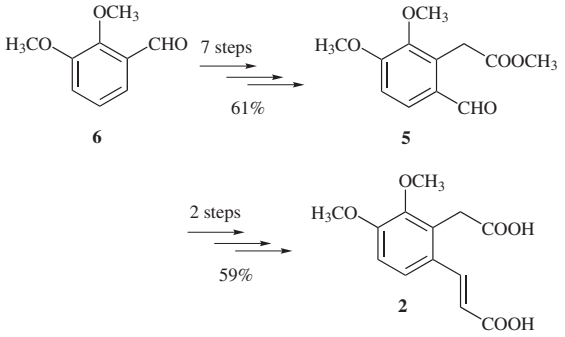
Ai and Li reported the synthesis of **5** starting from isovanillin **3** (Scheme 1). Using the same procedure, we were able to obtain compound **4** in 28% overall yield but the cleavage of the lactone previously described in 20% yield, was unsuccessful in our hands.



Scheme 1 Ai and Li procedure[9]

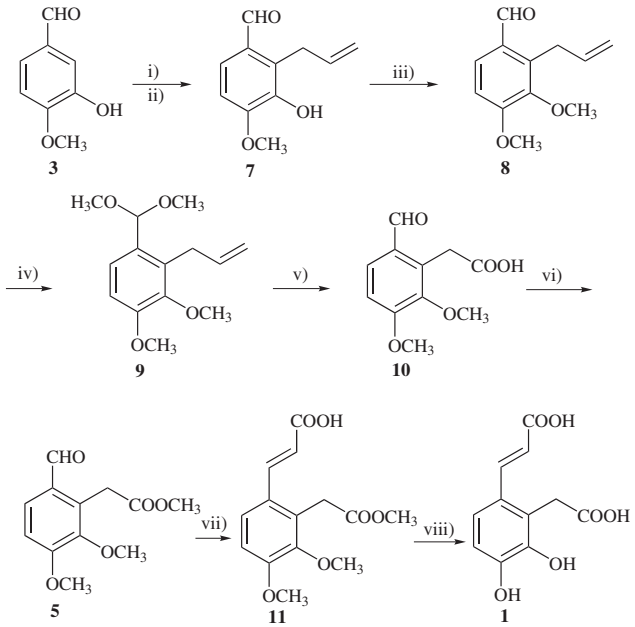
During the course of this work, **5** was also obtained in 61% yield by another method[10] using 2,3-dimethoxybenzaldehyde **6** as starting material (Scheme 2). Since the sixth step of this procedure requires purification by column chromatography of two regioisomers and we had the need for a multigram-scale synthesis of **5** in mind, we decided to explore an alternative strategy (Scheme 3).

We started, as in the Ai and Li procedure, and in a short communication dealing with the total synthesis of heptamethyl lithospermate,[11] by the O-allylation of isovanillin followed by the Claisen rearrangement of *O*-allylisovanillin in dimethylacetamide. After methylation of the phenol groups, the protection of the formyl group was required, which was perfectly achieved by its transformation into the acetal derivative **9** with trimethyl orthoformate. A Lemieux–Rudloff oxidation led to the acid **10**. The dimethylacetal was hydrolyzed during the work-up. Finally **10** was converted into its methyl ester to give **5**.



Scheme 2 Detterbeck and Hesse procedure[10]

Two steps were necessary to obtain the acid part of salvianolic acid D from **5**. First, a Knoevenagel condensation was required and the α,β-unsaturated acid side-chain was received in good yield. Secondly, treatment with boron tribromide as deprotecting reagent afforded the desired product **1** in moderate yield.



Scheme 3 *Reagents and conditions*: i) Allyl bromide, K_2CO_3, acetone, reflux, 3 h, 99%; ii) Dimethylacetamide, reflux, 10 h, 90%; iii) MeI, K_2CO_3, DMF, r.t., 10 h, 91%; iv) $HC(OMe)_3$, MeOH, NH_4Cl, reflux, 2 h, 86%; v) $KMnO_4$, $NaIO_4$, K_2CO_3, *t*-BuOH–H_2O, r.t., 4 h, 77%; vi) $SOCl_2$, MeOH, 0 °C, 1.5 h, 96%; vii) Malonic acid, py, piperidine, 60 °C, 10 h, 94%; viii) BBr_3, CH_2Cl_2, r.t., 10 h, then H_2O, 48 h, 45%.

Herein, we have described an efficient synthesis of the benzaldehyde **5** in a slightly lower overall yield (52%) than in a previous work (61%) but in a more convenient manner for a multigram scale. This key intermediate **5** is expected to allow for the total synthesis of przewalskinic acid A and the acid parts of salvianolic acid L and salvianolic acid E (Figure 1). As a first example, **5** was converted into the skeleton of salvianolic acid D (**1**) in a satisfactory 22% overall yield.

SiO_2, 200–400 mesh (Merck) was used for column chromatography. Melting points were obtained on a Reichert Thermopan melting point apparatus, equipped with a microscope. NMR spectra were obtained with 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 Thermo-Finnigan PolarisQ mass spectrometer (70 eV, Electronic Impact). Elemental analyses were performed by CNRS laboratories (Vernaison) and were within 0.4% of the theoretical values.

3-Allyloxy-4-methoxybenzaldehyde

To isovanillin (**3**) (5.00 g, 32.9 mmol) in anhyd acetone (20 mL), allyl bromide (5.00 g, 3.6 mL, 41.3 mmol) and K_2CO_3 (5.00 g, 36.2 mmol) were added. Then the mixture was refluxed for 3 h. The removal of K_2CO_3 by filtration and the evaporation of acetone gave the desired compound (6.32 g, 99%) as a yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.80 (s, 3 H, OMe), 4.55 (dt, 2 H, ^4J = 1.45 Hz, ^3J = 5.4 Hz, CH_2), 5.17 (dq, 1 H, $^2J = {}^4J$ = 1.45 Hz, $^3J_{cis}$ = 10.2 Hz), 5.29 (dq, 1 H, $^2J = {}^4J$ = 1.45 Hz, $^3J_{trans}$ = 17.9 Hz), 5.99 (m, 1 H, $^3J_{cis}$ = 10.2 Hz, $^3J_{trans}$ = 17.9 Hz, ^3J = 5.4 Hz, =CH), 6.83 (d, 1 H, ^3J = 8.3 Hz), 7.25 (d, 1 H, ^4J = 1.9 Hz), 7.31 (dd, 1 H, ^3J = 8.3 Hz, ^4J = 1.9 Hz), 9.61 (s, 1 H, CHO).

2-Allyl-3-hydroxy-4-methoxybenzaldehyde (7)

A solution of 3-allyloxy-4-methoxybenzaldehyde (6.316 g, 32.90 mmol) in dimethylacetamide (9.2 mL) was stirred at 180 °C for 10 h. The cold solution was poured into aq 2 N NaOH soln (4 × 30 mL) and washed with Et_2O (2 × 20 mL). The aq layer was acidified with conc HCl soln and was extracted with EtOAc. Evaporation gave **7** as a brown oil (5.68 g, 90%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.80 (d, 2 H, ^3J = 5.9 Hz, CH_2), 3.95 (s, 3 H, OMe), 5.00 (m, 2 H), 5.81 (br s, 1 H), 6.05 (m, 1 H, $^3J_{cis}$ = 10.5 Hz, $^3J_{trans}$ = 16.5 Hz, ^3J = 6.0 Hz, =CH), 6.83 (d, 1 H, ^3J = 8.3 Hz), 7.41 (d, 1 H, ^3J = 8.3 Hz), 10.05 (s, 1 H, CHO).

2-Allyl-3,4-dimethoxybenzaldehyde (8)

To **7** (6.00 g, 31.2 mmol) in DMF (34 mL), K_2CO_3 (8.65 g, 62.7 mmol) and MeI (6.61 g, 2.9 mL, 46.6 mmol) were added. The mixture was stirred at r.t. for 10 h, then taken up in H_2O (20 mL) and extracted with Et_2O (3 × 20 mL). Washing the organic phase with aq 2 N NaOH soln and evaporation gave **8** (5.85 g, 91%) as a brown oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.80 (s, 3 H, OMe), 3.82 (dt, 2H, ^3J = 3.5 Hz, CH_2), 3.95 (s, 3 H, OMe), 5.00 (m, 2 H), 6.05 (m, 1 H, $^3J_{cis}$ = 10.5 Hz, $^3J_{trans}$ = 16.5 Hz, ^3J = 6.0 Hz, =CH), 6.90 (d, 1 H, ^3J = 8.6 Hz), 7.61 (d, 1 H, ^3J = 8.6 Hz), 10.05 (s, 1 H, CHO).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.4 (t), 55.9 (q), 60.5 (q), 109.7 (d), 115.2 (d), 127.7 (s), 129 (d), 135.7 (s), 137 (d), 147 (s), 157.2 (s), 190.5 (d).

MS (EI, 70 eV): *m*/*z* (%) = 206 (50) [M^+], 191 (100), 190 (15), 175 (32), 115 (16), 91 (27).

Anal. Calc for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84; O, 23.27. Found: C, 69.44; H, 6.96; O, 23.39.

2-Allyl-1-(dimethoxymethyl)-3,4-dimethoxybenzene (9)

A mixture of **8** (5.85 g, 28.4 mmol), trimethyl orthoformate (6.05 g, 6.2 mL, 56.8 mmol), and a cat. amount of NH_4Cl (ca 0.1 g) in MeOH (54 mL) was refluxed for 2 h. After cooling to r.t., the mixture was poured into ice-cooled aq 2 N NaOH soln (10 mL) and extracted quickly with Et_2O (3 × 20 mL). Evaporation gave **9** (6.15 g, 86%) as a brown oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.26 (s, 6 H, OMe), 3.5 (dt, 2 H, CH_2), 3.76 (s, 3 H, OMe), 3.83 (s, 3 H, OMe), 4.95 (m, 2 H), 5.35 (s, 1 H), 5.95 (m, 1 H, =CH), 6.77 (d, 1 H, ^3J = 8.6 Hz), 7.25 (d, 1 H, ^3J = 8.6 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.4 (t), 47 (q, $2OCH_3$), 49.3 (q), 54.4 (q), 95.2 (d), 103.4 (d), 108.6 (d), 116.1 (d), 122.8 (s), 125.7 (s), 131 (d), 141 (s), 146.5 (s).

MS (EI, 70 eV): *m*/*z* (%) = 252 (6) [M^+], 221 (33) [$M^+ - OCH_3$], 206 (36), 191 (82), 189 (100), 188 (32), 175 (36), 174 (77), 149 (38).

Anal. Calc for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99; O, 25.37. Found: C, 66.45; H, 7.57; O, 25.20.

(6-Formyl-2,3-dimethoxyphenyl)acetic Acid (10)

To **9** (6.15 g, 24.4 mmol) in *t*-BuOH (40 mL) was added a solution of K_2CO_3 (10.1 g, 73.1 mmol) in H_2O (79 mL). To the resulting suspension were added $NaIO_4$ (21.6 g, 101 mmol) and $KMnO_4$ (3.15 g, 19.5 mmol). The mixture started to warm and was stirred for 4 h at r.t. The mixture was washed with EtOAc (10 mL) and this organic layer discarded. The aq layer was acidified with concd HCl soln and again exhaustively extracted with EtOAc. Evaporation yielded **10** (4.2 g, 77%) as a brown oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.75 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 4.12 (s, 2 H, CH_2), 6.85 (d, 1 H, ^3J = 8.3 Hz), 7.5 (d, 1 H, ^3J = 8.3 Hz), 9.8 (s, 1 H, CHO).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.3 (t), 56.1 (q), 61.1 (q), 110.7 (d), 128.3 (s), 129.3 (s), 132.9 (d), 148.3 (s), 157.6 (s), 177 (s), 192.2 (d).

MS (EI, 70 eV): *m*/*z* (%) = 194 (38) [$M^+ - CH_2O$], 180 (20), 179 (100), 91 (15).

Anal. Calc for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39; O, 35.68. Found: C, 58.67; H, 5.25; O, 35.90.

Methyl (6-Formyl-2,3-dimethoxyphenyl)acetate (5)

To an ice-cooled solution of **10** (4.20 g, 18.8 mmol) in MeOH (31 mL), $SOCl_2$ (3.72 g, 2.3 mL, 31.3 mmol) was slowly added dropwise. After 1.5 h stirring, evaporation yielded **5** (4.28 g, 96%) as a brown oil.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.67 (s, 3 H, CO_2Me), 3.8 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 4.18 (s, 2 H, CH_2), 7.00 (d, 1 H, ^3J = 8.6 Hz), 7.58 (d, 1 H, ^3J = 8.6 Hz), 9.90 (s, 1 H, CHO).

3-[3,4-Dimethoxy-2-(2-methoxy-2-oxoethyl)phenyl]acrylic Acid (11)

To a solution of **5** (1.10 g, 4.62 mmol) in pyridine (136 mL) were added malonic acid (979 mg, 9.41 mmol) and two drops of piperidine. The mixture was refluxed for 10 h and then poured into an excess of concd HCl soln. Extraction with EtOAc and evaporation gave **11** (1.216 g, 94%) as a brown solid.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.7 (s, 3 H), 3.82 (s, 3 H), 3.88 (s, 2 H), 3.91 (s, 3 H), 6.29 (d, 1 H, ^3J = 15.6 Hz), 6.9 (d, 1 H, ^3J = 8.9 Hz), 7.42 (d, 1 H, ^3J = 8.9 Hz), 7.92 (d, 1 H, ^3J = 15.6 Hz).

Acid Part of Salvianolic Acid D (1)

To a solution of **11** (4.88 g, 17.4 mmol) in CH_2Cl_2 (20 mL), a 1 M BBr_3 soln in CH_2Cl_2 (69.5 mL) was added dropwise at 20 °C. After 24 h of stirring, the reaction was carefully quenched with H_2O (40 mL). A brown solid precipitated rapidly and filtration of this gave **1** (1.87 g, 45%) as a brown solid.

^{1}H NMR (200 MHz, CD_3COCD_3): δ = 4.09 (s, 2 H), 6.29 (d, 1 H, ^3J = 16.13 Hz), 6.96 (d, 1 H, ^3J = 8.51 Hz), 7.38 (d, 1 H, ^3J = 8.51 Hz), 7.58 (d, 1 H, ^3J = 16.0 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 32.9 (t), 116.4 (d), 117.9 (d), 121.5 (s), 124.7 (d), 125.7 (s), 140.9 (d), 141.4 (s), 142.9 (s), 167.6 (s), 173.9 (s).

MS (EI, 70 eV): *m*/*z* (%) = 220 (46) [$M - H_2O]^+$, 176 (100) [$M - H_2O - CO_2]^+$, 148 (45), 147 (50), 146 (20), 119 (31), 91 (46).

Anal. Calc for $C_{11}H_{10}O_6$: C, 55.47; H, 4.23; O, 40.30. Found: C, 55.87; H, 4.61; O, 40.57.

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