Total synthesis of evelynin B and taccabulin D

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Concise total syntheses of biosynthetic retro-dihydrochalones evelynin B and taccabulin D isolated from roots and rhizomes of *Tacca chantrieri* and *T. integrifolia*, have been achieved from pyrogallol trimethylether in six steps and 1,3,5-trimethoxybenzene in three steps, respectively. A condensation between aldehyde and acetophenone was applied to form chalcone as a key step.

Keywords: total syntheses, tacca species, retro-dihydrochalcone, Claisen–Schmidt reaction

Biosynthetic retro-dihydrochalcone derivatives represent a significant class of compounds with broad and remarkable potential biological properties, such as anti-ulcer,[1] anti-histamine,[2] and anti-microbial,[3] and anti-malarial activities.[4] Therefore, it is not surprising that many synthetic methods have been developed for these types of compounds.[5-11]

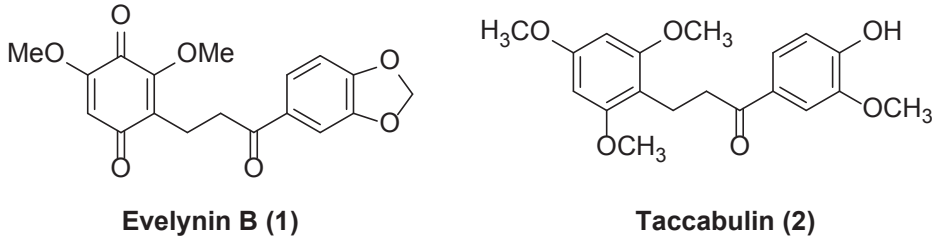
Evelynin B and taccabulin D (Fig. 1) are two novel retro-dihydrochalcone-typed compounds, isolated from fresh roots and rhizomes of *Tacca chantrieri* and *T. integrifolia* by Moberry and co-workers in 2013.[12] Compounds **1** and **2** have antiproliferative activities against three cancer cell lines: HeLa, A549 and PC-3.[12] The IC_{50} values of evelynin B (**1**) against HeLa, A549, and PC-3 cells are 8.8, 8.3 and 5.0 μM, respectively, while those of taccabulin D (**2**) are 28.9, 40.3 and more than 50 μM.

We have initiated the total synthesis of the two new compounds in order to investigate the potential bioactivity of the derivatives. We now report the concise efficient total syntheses of evelynin B (**1**) and taccabulin D (**2**) from the accessible starting material trimethoxybenzene which would provide enough compounds for further biological studies.

Results and discussion

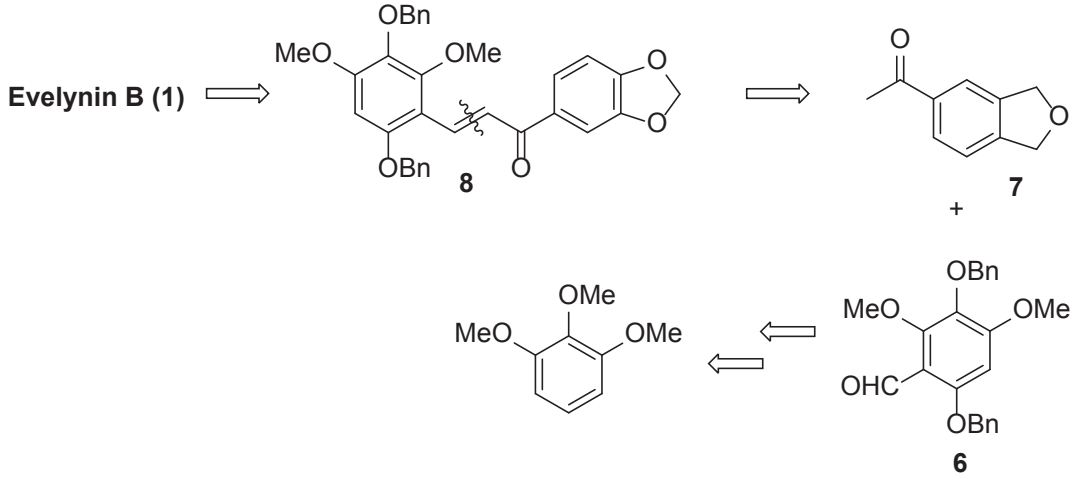
Our initial retrosynthetic analysis of **1** is outlined in Scheme 1. We envisaged that a Claisen–Schmidt reaction could be used to construct the main skeleton of evelynin B and taccabulin D. Aldehyde **6**, in turn, could be obtained from a cheap starting material 1,2,3-trimethoxybenzene.

The synthesis of evelynin B is illustrated in Scheme 2. 1,2,3-Trimethoxybenzene was oxidised with 30% HNO_3 to form 1,4-benzoquinone **3** in 80% yield.[13] Reduction of **3** with $Na_2S_2O_4$ in EtOAc for 40 min smoothly gave diphenol **4** in 84% yield.[14] Dialkylation of diphenol **4** with BnBr in refluxing acetone affords ether **5** in 86% yield.[15] Aldehyde **6** was available through Vilsmeier reaction from ether **5** in 81% yield.[14] Then, aldehyde **6** was reacted with 3,4-methylenedioxyacetophenone **7** through



Evelynin B (1) **Taccabulin (2)**

Fig 1. Structures of evelynin B and taccabulin D.



Scheme 1 Retrosynthetic analysis of evelynin B (**1**).

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a Claisen–Schmidt reaction to give the key intermediate enone **8** in 83% yield.[16] Finally, enone **8** was hydrogenated in the presence of Pd on carbon (10%) to afford diphenol **9**, which was used for next step without further purification.[17] Oxidation of **9** by PCC in DCM successfully provided natural product evelynin B (**1**) with 73% yield as a yellow solid in two steps.[18]

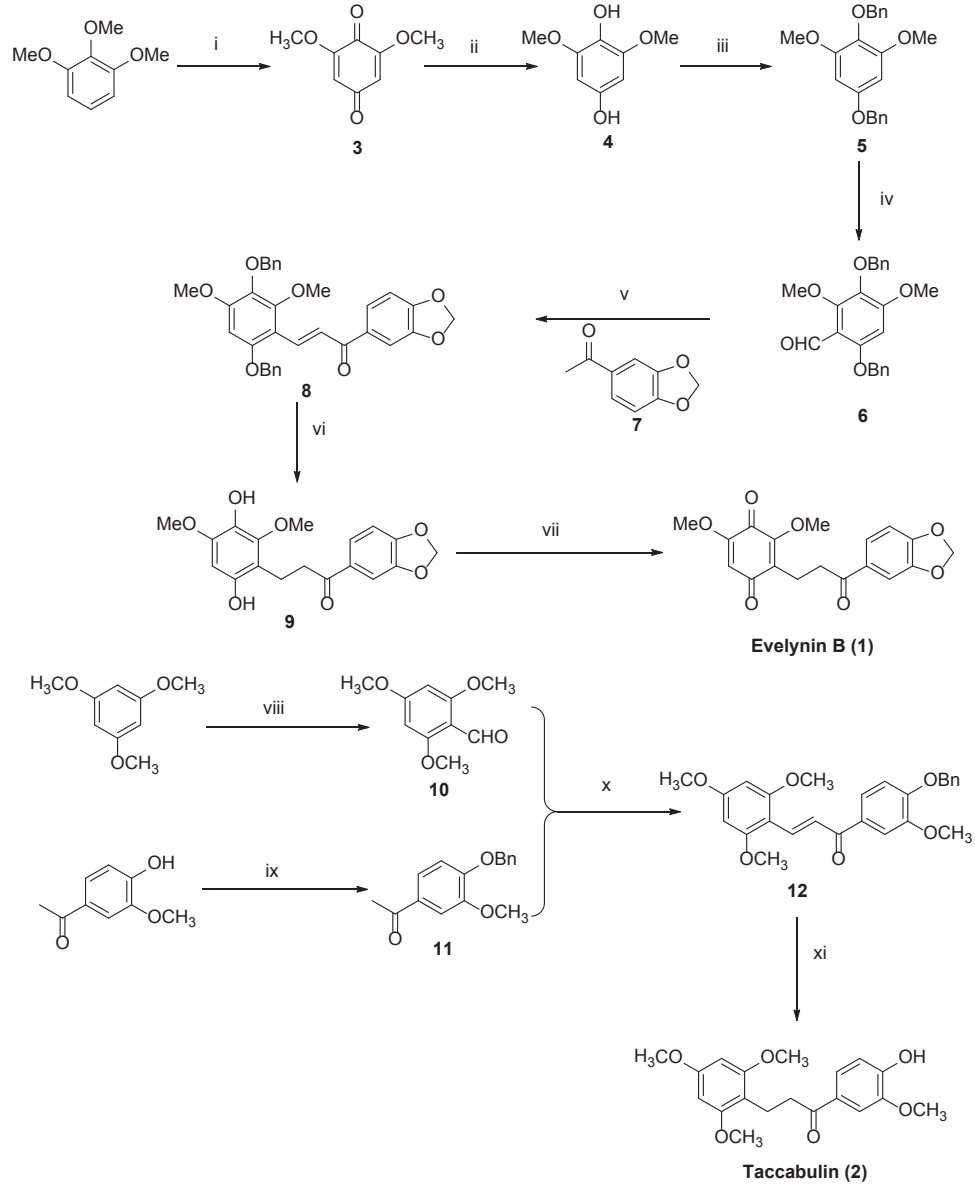
The total synthesis of taccabulin D is similar to that of evelynin B (Scheme 2). 2,4,6-Trimethoxybenzaldehyde **10** was synthesised through a Vilsmeier reaction in 92% yield.[7] 3-Methoxy-4-hydroxyacetophenone was alkylated to give ketone **11** in 98% yield.[19] Then, a Claisen–Schmidt reaction was used to afford enone **12** in 84% yield, followed by hydrogenation to give the natural product taccabulin D (**2**) in 75% yield as a colourless solid. The analytical and spectral data of **1** and **2** are consistent with those described for the natural products.

Conclusions

In summary, we have developed a concise route for the first total syntheses of evelynin B and taccabulin D starting from accessible trimethoxybenzene in 3–6 steps (overall yields: 20% for evelynin B; 56% for taccabulin D). The mild reaction conditions and operational simplicity make this method attractive for the practical synthesis of these natural products and their derivatives, which facilitates further biological experiments. Studies towards the structure modifications of these natural products for further pharmacological investigation are ongoing.

Experimental

Melting points were measured on a microscopic melting point apparatus. The IR spectra were recorded on a Bruker Tensor 27 FTIR spectrometer with a KBr disk or film. ^{1}H NMR and ^{13}C NMR spectra were taken on a Bruker AV 300 or AV 400 MHz and 75 or 100 MHz spectrometer in $CDCl_3$, chemical shifts are given in ppm relative to TMS as an internal standard. Mass spectra and high resolution mass spectra were performed on Agilent Q TOF 6520 mass spectrometer with electron spray ionisation (ESI) as the ion mode. Optical rotations were recorded using a sodium lamp with a Rudolph Autopol I Automatic Polarimeter with a 1 dm tube.



Scheme 2 Reagents and conditions: (i) 30% HNO_3, HOAc, room terature (r.t.), 1 h, 80%; (ii) 20% aq. $Na_2S_2O_4$, EtOAc, r.t., 40 min, 84%; (iii) BnBr, K_2CO_3, acetone, reflux, 24 h, 86%; (iv) $POCl_3$, DMF, r.t., 16 h, 81%; (v) 60% aq. KOH, EtOH, r.t., 2 h, 83%; (vi) H_2, 10% Pd/C (30 w/w %), EtOH, 12 h; (vii) PCC (2.2 equiv.), DCM, r.t., 2 h, 73% in two steps; (viii) POCl3, DMF, r.t., 16 h, 92%; (ix) BnBr, K_2CO_3, KI, CH_3CN, reflux, 24 h, 98%; (x) 60% aq. KOH, EtOH, r.t., 2 h, 84%; (xi) H_2, 10% Pd/C (15 w/w %), EtOH, 12 h, 75%.

2,6-Dimethoxybenzene-1,4-diol (**4**): Prepared by oxidation of 1,2,3-trimethoxybenzene with 30% HNO_3 in AcOH to give benzoquinone **3**, followed by reduction with $Na_2S_2O_4$ in EtOAc. Yield 6.5 g (67% in two steps); brown solid; m.p. 158 °C (lit.[14] 157–158 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (s, 2H, ArH), 3.83 (s, 6H, OCH_3). MS (ESI) *m/z* (%) 171 ($M+H^+$).

2,5-Dibenzyloxy-1,3-dimethoxybenzene (**5**): Prepared by alkylation of diphenol **4** with BnBr in refluxing acetone. Yield 7.8 g (86%); brown oil.[15] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.50 (m, 10H, ArH), 6.23 (s, 2H, ArH), 5.02 (s, 2H, CH_2), 4.94 (s, 2H, CH_2), 3.79 (s, 6H, OCH_3). MS (ESI) *m/z* (%) 351 ($M+H^+$).

3,6-Dibenzyloxy-2,4-dimethoxybenzaldehyde (**6**): Prepared through Vilsmeier reaction of 2,5-dibenzyloxy-1,3-dimethoxybenzene **5** with DMF in the presence of $POCl_3$. Yield 5.9 g (81%); yellow oil.[14] ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.40 (s, 1H, CHO), 7.30–7.48 (m, 10H, ArH), 6.31 (s, 1H, ArH), 5.08 (s, 2H, CH_2), 4.95 (s, 2H, CH_2), 3.95 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3). MS (ESI) *m/z* (%) 379 ($M+H^+$).

(2E)-1-(1,3-Benzodioxol-5-yl)-3-(3,6-dibenzyloxy-2,4-dimethoxyphenyl)prop-2-en-1-one (**8**):[16] 3,4-Methylenedioxyacetophenone (**7**, 0.09 g, 0.529 mmol) was dissolved in EtOH (2 mL) and cooled to 0 °C. Compound **6** (0.2 g, 0.529 mmol) was added to the solution and stirred for 10 min, 60% KOH aqueous solution (0.5 mL) was added in one portion, and the mixture was stirred for 30 min. The mixture was heated to room temperature and stirred for another 2 h. It was poured into ice cold water (20 mL) and then neutralised with 2.5N HCl (10 mL). EtOAc (30 mL) was added, and the organic phase was separated. The aqueous phase was further extracted with EtOAc (20 mL). The combined EtOAc extracts were washed successively with water (30 mL), brine (20 mL), dried, filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to give **8** (0.23 g, 83%) as a green solid; m.p. 148–150 °C; IR (KBr, cm^{-1}): ν 3033, 2941, 1648, 1583, 1439, 1245, 1114; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 15.8 Hz, 1H, CH =), 7.90 (d, *J* = 15.8 Hz, 1H, CH =), 7.28–7.50 (m, 11H, ArH), 7.22 (dd, *J* = 8.2, 1.4 Hz, 1H, ArH), 6.68 (d, *J* = 8.2 Hz, 1H, ArH), 6.38 (s, 2H, ArH), 5.99 (s, 2H, OCH_2O), 5.10 (s, 2H, OCH_2), 4.96 (s, 2H, OCH_2), 3.94 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.0, 156.0, 155.6, 155.1, 151.0, 148.0, 137.5, 136.0, 135.5, 135.1, 133.6, 128.8, 128.6, 128.4, 128.3, 128.2, 128.1, 127.9, 124.3, 122.6, 111.3, 108.3, 107.6, 101.6, 93.2, 75.4, 71.2, 61.6, 56.0; HRMS (ESI) calcd for $C_{32}H_{29}O_7$ ($M+H^+$) *m/z* 525.1908; found: 525.1923.

Evelynin B (**1**):[17,18] 0.3 g (30 w/w %) of Pd on carbon (10%) was added to a solution of compound **8** (1 g, 1.9 mmol) in 15 mL of absolute ethanol, and the mixture was stirred at room temperature under hydrogen atmosphere for 12 h. The mixture was filtered and the filtrate was evaporated under reduced pressure, yielding 0.75 g crude product, which was used for next step without further purification. The residue was dissolved in 25 mL DCM and PCC (0.93 g, 4.2 mmol) was added. The mixture was stirred at room temperature for 2 h and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to afford natural product evelynin B (**1**, 0.48 g, 73% in two steps) as a yellow solid; m.p. 110–112 °C; IR (KBr, cm^{-1}): ν 3070, 2948, 1684, 1667, 1644, 1601, 1242, 1086; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (br d, *J* = 8.4 Hz, 1H, ArH), 7.43 (br, 1H, ArH), 6.83 (d, *J* = 8.4 Hz, 1H, ArH), 6.03 (s, 2H, OCH_2O), 5.85 (s, 1H, ArH), 3.98 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.04 (t, *J* = 7.8 Hz, 2H, CH_2), 2.84 (t, *J* = 7.8 Hz, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.7, 187.1, 177.9, 157.3, 154.6, 151.7, 148.1, 132.0, 131.4, 124.3, 107.8, 107.8, 106.9, 101.8, 61.0, 56.3, 37.1, 18.9; HRMS (ESI) calcd for $C_{18}H_{17}O_7$ ($M+H^+$) *m/z* 345.0969; found: 345.0982.

2,4,6-Trimethoxybenzaldehyde (**10**): The aldehyde **11** was prepared through Vilsmeier reagents from 1,3,5-trimethoxybenzene. Yield 5.5 g (92%); colourless oil.[7] ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.35 (s, 1H, CHO), 6.67 (s, 1H, ArH), 3.88 (s, 6H, OCH_3), 3.87 (s, 3H, OCH_3). MS (ESI) *m/z* (%) 197 ($M+H^+$).

1-(4-(Benzyloxy)-3-methoxyphenyl)-ethanone (**11**): The ketone **11** was prepared by alkylation of 3-methoxy-4-hydroxyacetophenone with BnBr in refluxing CH_3CN. Yield 6.0 g (98%); white solid; m.p. 87 °C (lit.[20] 86–88 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21–7.55 (m, 7H, ArH), 6.86 (d, *J* = 8.2 Hz, 1H, ArH), 5.20 (s, 2H, CH_2), 3.91 (s, 3H, OCH_3), 2.51 (s, 3H, CH_3). MS (ESI) *m/z* (%) 257 ($M+H^+$).

(E)-1-(4-(Benzyloxy)-3-methoxyphenyl)-3-(2,4,6-trimethoxyphenyl) prop-2-en-1-one (**12**): The operating procedure was analogous to that of compound **8**. Using compound **11** (0.65 g, 2.55 mmol) and compound **7** (0.50 g, 2.55 mmol) gave **12** (0.92 g, 84%) as a green solid; m.p. 111–113 °C; IR (KBr, cm^{-1}): ν 3083, 2939, 1640, 1555, 1251, 1141; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 15.8 Hz, 1H, CH =), 7.87 (d, *J* = 15.8 Hz, 1H, CH =), 7.65 (d, *J* = 2.0 Hz, 1H, ArH), 7.58 (dd, *J* = 8.4, 2.0 Hz, 1H, ArH), 7.32–7.48 (m, 5H, ArH), 6.92 (d, *J* = 8.4 Hz, 1H, ArH), 6.14 (s, 2H, ArH), 5.25 (s, 2H, OCH_2), 3.97 (s, 3H, OCH_3), 3.90 (s, 6H, OCH_3), 3.86 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 163.0, 161.6, 151.7, 149.5, 136.6, 135.3, 132.7, 128.7, 128.0, 127.2, 122.5, 121.7, 112.2, 111.5, 106.7, 90.6, 70.8, 56.1, 55.8, 55.4; HRMS (ESI) calcd for $C_{26}H_{27}O_6$ ($M+H^+$) *m/z* 435.1802; found: 435.1816.

Taccabulin D (**2**):[17] 0.06 g (15 w/w %) of Pd on carbon (10%) was added to a solution of compound **12** (0.4 g, 0.92 mmol) in 6 mL EtOAc, and the mixture was stirred at room temperature under hydrogen atmosphere for 12 h. The mixture was filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford natural product taccabulin D (**2**, 0.24 g, 75%) as a colourless solid; m.p. 116–118 °C; IR (KBr, cm^{-1}): ν 3446, 3003, 2940, 1670, 1606, 1264, 1144; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.4, 1.5 Hz, 1H, ArH), 7.55 (d, *J* = 1.5 Hz, 1H, ArH), 6.92 (d, *J* = 8.4 Hz, 1H, ArH), 6.2 9 (br s, 1H, OH), 6.14 (s, 2H, ArH), 3.92 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.78 (s, 6H, OCH_3), 3.01–3.03 (m, 4H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5, 159.6, 158.8, 150.1, 146.5, 130.0, 123.5, 113.8, 110.1, 110.0, 90.5, 56.0, 55.6, 55.3, 38.3, 18.6; HRMS (ESI) calcd for $C_{19}H_{23}O_6$ ($M+H^+$) *m/z* 347.1489; found: 347.1500.

Electronic Supplementary Information

The ^{1}H NMR and ^{13}C NMR spectra of **8**, **12**, **1** and **2** can be found in the ESI available through stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data.

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