



Scheme 2

tained by deprotection of benzyl ethers of **12** under catalysis with palladium-on-carbon.¹⁴ Compound **13** had poor solubility, but had some solubility in DMF.

Our scheme highlights the utility of the Claisen rearrangement to introduce an allyl side chain. The method involves skillful design and uses inexpensive reagents than the method reported by Kelly. One of the hydroxy groups in **13** was etherified with allyl bromide in anhydrous DMF in the presence of potassium carbonate,¹⁵ and the other hydroxy group in **13** was transesterified simultaneously in one-pot.¹⁶ The yield of **14** was improved by controlling the molar ratio of reagents (**13**/allyl bromide/potassium carbonate = 1:1.2:1.5) and the reaction temperature (60 °C). Compound **3** was obtained by the Claisen rearrangement of **14**.¹⁷ The other intramolecular transesterification reaction was processed in one-pot at high temperature as we expected. The starting material of the Claisen rearrangement did not transform completely, and there were many by-products if the reaction temperature was <200 °C. A solvent-free Claisen rearrangement at 210–220 °C was achieved using an oil bath in 94% yield. Compound **3** was oxidized by osmium tetroxide and sodium metaperiodate to generate aldehyde **2** in 68% yield.¹⁸ Reductive amination of **2** with dimethylamine and sodium triacetoxyborohydride gave taspine (**1**) in 77% yield.⁸ Synthetic **1** was identical to taspine isolated from plant in all aspects: TLC, ¹H NMR, ¹³C NMR, MS, IR, and melting point.

In summary we have reported here a facile and efficient total synthesis of taspine (**1**) from commercially available isovanillin (**7**) in ten steps in high yield (16.5% overall yield). The key intermediate, methyl 3-benzyloxy-2-bromo-4-methoxybenzoate (**11**), was obtained through bromination, benzyl protection, oxidation, and esterification, respectively. The biphenyl dimethyl ester **12** was then prepared by a symmetrical Ullmann coupling. One of the hydroxy groups was allylated after debenzoylation with palladium-on-carbon. Taspine (**1**) was then obtained by Claisen rearrangement, allyl oxidation, and reductive amination. The method has the advantages of mild reaction conditions, easy manipulation, low cost, and higher yield than the synthesis described by Kelly.

Solvents were purified before use by previously reported methods. Petroleum ether (PE) used refers to the fraction boiling in the range 60–90 °C. All reactions except those in aqueous media were carried out by standard techniques for moisture exclusion. Anhydrous reactions were carried out over dried glassware under N₂. Reactions were monitored by TLC on 0.25 mm silica gel plates (60GF₂₅₄) and visualized with ultraviolet light. Melting points were obtained on electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8100 spectrophotometer. ¹H NMR and ¹³C NMR spectra were measured with a Bruker Avance 300 MHz or Varian Inova 400 MHz spectrometer. Quoted chemical shifts (δ) are relative to TMS. Coupling constants are given in hertz. Mass spectra were obtained on a Shimadzu GC-MS-QP2010 instrument. Elemental analyses were done on an Elementar Vario EL III instrument.

2-Bromo-3-hydroxy-4-methoxybenzaldehyde (8)

To a mixture of **7** (25.0 g, 0.164 mol), NaOAc (26.94 g, 0.325 mol), and Fe powder (0.75 g, 0.015 mol) was added glacial AcOH (150 mL). The mixture was stirred at r.t. for 30 min. Br₂ (9 mL, 0.18 mol) in glacial AcOH (40 mL) was added dropwise into the above mixture at 23–25 °C. The mixture was stirred at the same temperature for 3 h. Ice water (325 mL) was added to the mixture and stirred for another 1 h and filtered. The solid obtained was dried and recrystallized from EtOH to give **8** (30.0 g, 79%) as a gray solid; mp 206–207 °C.

IR (KBr): 3235, 2890, 1669, 1593 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 10.26 (s, 1 H), 7.58 (d, *J* = 8.5 Hz, 1 H, ArH), 6.93 (d, *J* = 8.5 Hz, 1 H, ArH), 6.07 (s, 1 H), 4.01 (s, 3 H).

MS (EI, 70 eV): *m/z* = 230.9 (100%, [M + H]⁺).

3-Benzoyloxy-2-bromo-4-methoxybenzaldehyde (9)

To a suspension of **8** (15.0 g, 0.065 mol) in dehydrated alcohol (150 mL) were added anhyd K₂CO₃ (27 g, 0.196 mol) and benzyl chloride (11.3 mL, 0.098 mol). The mixture was refluxed for 4 h. Filtration and evaporation of alcohol was done in a vacuum. The residue was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with H₂O (3 × 50 mL), aq 1 M NaOH (3 × 50 mL), aq 2 M HCl (3 × 50 mL), and brine (2 × 50 mL), dried (Na₂SO₄), and concentrated to give **9** (23.05 g, quant) as a yellow solid; mp 79–81 °C.

IR (KBr): 2940, 2839, 1713, 1593 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 10.27 (s, 1 H), 7.76 (d, *J* = 8.4 Hz, 1 H, ArH), 7.54–7.35 (m, 5 H, ArH), 6.98 (d, *J* = 9.2 Hz, 1 H, ArH), 5.03 (s, 2 H), 3.96 (s, 3 H).

MS (EI, 70 eV): *m/z* (%) = 91.1 (100), 320.9 (15, [M + H]⁺).

3-Benzoyloxy-2-bromo-4-methoxybenzoic Acid (10)

To a solution of **9** (20.87 g, 0.065 mol) in THF (200 mL) was added distilled H₂O (60 mL) and NaH₂PO₄ (4.68 g, 0.039 mol). The mixture was stirred at r.t. for 10 min. NaClO₂ (19.40 g, 0.215 mol) and 30% H₂O₂ (14.8 mL, 0.143 mol) in distilled H₂O (60 mL) were added into the above mixture. The mixture was stirred at the same temperature for 3 h. THF was evaporated under vacuum and the residue was extracted with EtOAc (2 × 150 mL). The combined organic layers were washed with H₂O (3 × 50 mL) and the product was extracted with aq 2 M NaOH (5 × 50 mL). The aqueous phase was acidified with concd HCl and the solid obtained was collected by filtration and dried to give **10** (21.94 g, quant) as a white solid; mp 159–161 °C.

IR (KBr): 2940, 2639, 1695 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.87 (d, *J* = 9.1 Hz, 1 H, ArH), 7.56–7.37 (m, 5 H, ArH), 6.93 (d, *J* = 9.2 Hz, 1 H, ArH), 5.03 (s, 2 H), 3.94 (s, 3 H).

MS (EI, 70 eV): *m/z* (%) = 91.1 (100), 336.9 (9, [M + H]⁺).

Methyl 3-Benzoyloxy-2-bromo-4-methoxybenzoate (11)

AcCl (10.5 mL, 0.147 mol) was added to MeOH (300 mL) at 0 °C. The mixture was stirred at r.t. for 30 min. Compound **10** (24.75 g, 0.074 mol) was added to the above mixture and refluxed for 4 h. MeOH was evaporated under vacuum and the residue was extracted with CHCl₃ (2 × 150 mL). The combined organic extracts were washed with H₂O (3 × 60 mL), aq sat. NaHCO₃ (3 × 60 mL), and brine (2 × 60 mL), dried (Na₂SO₄), and concentrated. The residue was chromatographed on silica gel (PE–EtOAc, 5:1) to give **11** (22.97 g, 89%) as an oil.

¹H NMR (300 MHz, CDCl₃): δ = 7.64 (d, *J* = 8.6 Hz, 1 H, ArH), 7.57–7.36 (m, 5 H, ArH), 6.89 (d, *J* = 8.5 Hz, 1 H, ArH), 5.01 (s, 2 H), 3.91 (s, 6 H).

MS (EI, 70 eV): *m/z* (%) = 91.0 (100), 351.0 (20, [M + H]⁺).

Dimethyl 6,6'-Dibenzyloxy-5,5'-dimethoxybiphenyl-2,2'-dicarboxylate (12)

To a solution of **11** (22.32 g, 0.064 mol) in anhyd DMF (150 mL) was added freshly activated Cu (40.81 g, 0.64 mol) under N₂, and the mixture refluxed for 4 h at 150–160 °C. The mixture was filtered and DMF evaporated under vacuum. The residue was extracted with CHCl₃ (2 × 150 mL), and the combined organic layers were washed with aq 2 M HCl (3 × 60 mL) and brine (2 × 60 mL), dried (Na₂SO₄), and concentrated. The residue was chromatographed on silica gel (PE–EtOAc, 5:1) to give **12** (14.6 g, 85%) as a white solid; mp 124.5–125 °C.

IR (KBr): 3023, 2947, 2841, 1711, 1592 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 7.88 (d, *J* = 8.6 Hz, 2 H, ArH), 7.16–6.93 (m, 12 H, ArH), 4.85 (d, *J* = 11.1 Hz, 2 H), 4.71 (d, *J* = 11.1 Hz, 2 H), 3.92 (s, 6 H), 3.58 (s, 6 H).

MS (EI, 70 eV): *m/z* (%) = 91 (100), 542.1 (10, [M]⁺).

Dimethyl 6,6'-Dihydroxy-5,5'-dimethoxybiphenyl-2,2'-dicarboxylate (13)

To a solution of **12** (10.53 g) in THF (200 mL) was added 10% Pd/C (3.16 g) under H₂ atmosphere. The mixture was stirred at r.t. until no starting material could be observed by TLC. Pd/C was filtered and washed with EtOH (100 mL), CH₂Cl₂ (100 mL), EtOAc (100 mL), and DMF (100 mL). The combined filtrates were evaporated under vacuum to give **13** (7.13 g, quant) as a gray solid; mp 165–202 °C (dec.).

IR (KBr): 3374, 2944, 1710, 1607 cm⁻¹.

¹H NMR (300 MHz, DMSO-*d*₆): δ = 7.43 (d, *J* = 8.5 Hz, 2 H, ArH), 6.96 (d, *J* = 8.6 Hz, 2 H, ArH), 3.87 (s, 6 H), 3.46 (s, 6 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 165.705, 149.772, 142.765, 126.199, 121.960, 120.871, 108.386, 55.238, 55.165, 50.634, 50.561.

MS (EI, 70 eV): *m/z* (%) = 298 (100), 362.1 (16, [M]⁺).

Anal. Calcd for C₁₈H₁₈O₈: C, 59.67; H, 5.01. Found: C, 59.53; H, 4.99.

Methyl 10-(Allyloxy)-4,9-dimethoxy-6-oxo-6H-benzo[c]chromene-1-carboxylate (14)

To a solution of **13** (1 g, 2.8 mmol) in DMF (30 mL) was added anhyd K₂CO₃ (0.58 g, 4.2 mol) and allyl bromide (0.29 mL, 3.3 mol) under N₂. The mixture was stirred at 60 °C in a water bath for 4 h. The mixture was filtered and DMF was evaporated under vacuum. The residue was extracted with CHCl₃ (2 × 25 mL), and the combined organic layers were washed with H₂O (3 × 15 mL), aq 2 M HCl (3 × 15 mL), and brine (2 × 15 mL), dried (Na₂SO₄), and concentrated. The residue was chromatographed on silica gel (PE–EtOAc, 5:1) to give **14** (0.57 g, 56%) as a white solid; mp 161–162 °C.

IR (KBr): 2946, 2844, 1729, 1597 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 8.19 (d, *J* = 8.7 Hz, 1 H, ArH), 7.63 (d, *J* = 8.5 Hz, 1 H, ArH), 7.20 (m, 1 H, ArH), 7.03 (d, *J* = 8.6 Hz, 1 H, ArH), 5.81 (m, 1 H), 5.03 (m, 2 H), 4.23 (d, *J* = 6.2 Hz, 2 H), 4.01 (s, 3 H), 4.00 (s, 3 H), 3.75 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 168.489, 160.106, 157.793, 149.674, 143.968, 141.095, 132.994, 128.855, 127.339, 125.955, 124.461, 118.992, 115.869, 115.573, 113.446, 110.464, 75.001, 56.241, 51.979.

MS (EI, 70 eV): m/z (%) = 313.0 (100), 370.1 (24, [M]⁺).

Anal. Calcd for C₂₀H₁₈O₇: C, 64.86; H, 4.90. Found: C, 64.86; H, 4.79.

3,8-Dimethoxy-1-(prop-2-enyl)[1]benzopyrano[5,4,3-cde][1]benzopyran-5,10-dione (3)

Compound **14** (0.57 g) was stirred at 210–220 °C for 50 min under N₂. The residue was purified by column chromatography (CHCl₃) to give **3** (0.49 g, 94%) as a white solid; mp 275–290 °C (dec.).

IR (KBr): 1748, 1603 cm⁻¹.

¹H NMR (300 MHz, CDCl₃): δ = 8.21 (d, J = 8.7 Hz, 1 H, ArH), 7.31 (d, J = 8.8 Hz, 1 H, ArH), 7.14 (s, 1 H, ArH), 6.06 (m, 1 H), 5.13 (m, 2 H), 4.12 (m, 2 H, partially hidden underneath aromatic MeO peaks), 4.11 (s, 3 H), 4.10 (s, 3 H).

MS (EI, 70 eV): m/z (%) = 323 (100), 338.1 (40, [M]⁺).

3,8-Dimethoxy-1-(2-oxoethyl)[1]benzopyrano[5,4,3-cde][1]benzopyran-5,10-dione (2)

To a suspension of **3** (240 mg, 0.7 mmol) in a mixture of CH₂Cl₂, H₂O, and *t*-BuOH (100 mL, 3:1:1) was added OsO₄ (9 mg, 0.035 mmol). The mixture was stirred at r.t. for 30 min in dark. NaIO₄ (600 mg, 2.8 mmol) was added to the above mixture and stirred at r.t. away from light for another 20 h. The residue was extracted with CH₂Cl₂ (2 × 100 mL), and the combined organic layers were washed with H₂O (3 × 40 mL), aq 0.5% NaHSO₃ (2 × 30 mL) and brine (2 × 40 mL), dried (Na₂SO₄), and concentrated. The residue was purified by column chromatography (CHCl₃–MeOH, 50:1) to give **2** (164 mg, 68%) as a white solid; mp the white solid turned yellow at 220 °C and decomposed at 278 °C.

IR (KBr): 2917, 1738, 1601 cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.69 (s, 1 H), 8.05 (d, J = 8.8 Hz, 1 H, ArH), 7.56 (d, J = 9.2 Hz, 1 H, ArH), 7.32 (s, 1 H), 4.27 (s, 2 H), 4.04 (s, 3 H), 4.03 (s, 3 H).

MS (ESI): m/z = 340.9 (100%, [M + H]⁺).

1-[2-(Dimethylamino)ethyl]-3,8-dimethoxy[1]benzopyrano[5,4,3-cde][1]benzopyran-5,10-dione (1, Taspine)

To a suspension of **2** (60 mg, 0.18 mmol) in CH₂Cl₂ (60 mL) was added Me₂NH (0.18 mL, 0.21 mmol) in THF under N₂ and stirred at r.t. for 20 min. NaBH(OAc)₃ (47 mg, 0.21 mmol) was added in three batches to the mixture, and the mixture stirred at r.t. for 4 h. The solvent was evaporated under vacuum, and the residue separated by column chromatography (CHCl₃–MeOH, 10:1) to give **1** (50.2 mg, 77%) as a white solid; mp 365 °C (dec).

IR (KBr): 2950, 1742, 1601 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.19 (d, J = 8.8 Hz, 1 H, ArH), 7.30 (d, J = 8.8 Hz, 1 H, ArH), 7.19 (s, 1 H, ArH), 4.11 (s, 6 H), 3.51 (t, J = 8.0 Hz, 2 H), 2.68 (t, J = 7.6 Hz, 2 H), 2.41 (s, 6 H).

¹³C NMR (100 MHz, CDCl₃): δ = 158.585, 157.560, 151.108, 150.812, 144.287, 137.675, 136.569, 126.843, 118.924, 118.209, 116.465, 113.569, 111.338, 109.002, 60.152, 56.541, 56.446, 45.180, 32.927.

MS (ESI): m/z = 370.1 (100%, [M + H]⁺).

Anal. Calcd for C₂₀H₁₈NO₆: C, 65.03; H, 5.18; N, 3.79. Found: C, 64.94; H, 5.21; N, 3.80.

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