Facile and Efficient Total Synthesis of Taspine

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Abstract: The facile and efficient total synthesis of taspine was achieved in 10 steps in high yield (16.5% overall) from commercially available isovanillin. Key steps in the synthesis are preparation of a symmetrical homodimer employing a classical Ullmann coupling reaction, and introduction of an allyl substituent by the Claisen rearrangement reaction. Significantly, the facile synthetic scheme proposed in this work has the characteristics of mild reaction conditions, inexpensive reagents, higher yield, and simple operation.

Key words: taspine, natural product, total synthesis, Ullmann coupling, Claisen rearrangement

Taspine is an alkaloid isolated from *Radix et Rhizoma Leonticis*.[1] In recent years, studies on taspine have attracted increasing attention due to its various pharmaceutical properties. These include bacteriostasis,[2] wound healing,[3] cytotoxicity,[4] immunosuppression,[5] acetylcholinesterase inhibition,[6] and inhibition of the activity of tumor angiogenesis.[7]

Taspine (**1**) has a unique molecular structure, namely, a biphenyl bislactonic skeleton with one phenyl ring possessing a 2-(dimethylamino)ethyl side chain (Figure 1). This makes taspine synthesis very difficult. Kelly and Xie reported the first total synthesis of taspine in 1998,[8] but the synthetic scheme had complicated reaction conditions, expensive reagents, and lower overall yield (9.6%). We report the facile and efficient total synthesis of taspine under mild reaction conditions using inexpensive reagents to produce higher overall yield (16.5%).

Our strategy for the total synthesis of taspine (**1**) is shown in Scheme 1. The 2-(dimethylamino)ethyl side chain of taspine (**1**) was prepared from an allyl side-chain precursor **3**, which was introduced by a Claisen rearrangement of **4**. The biphenyl skeleton **5** was generated from a monocyclic precursor **6** by symmetrical Ullmann coupling.

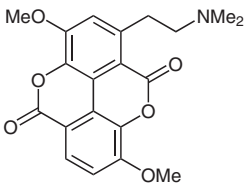
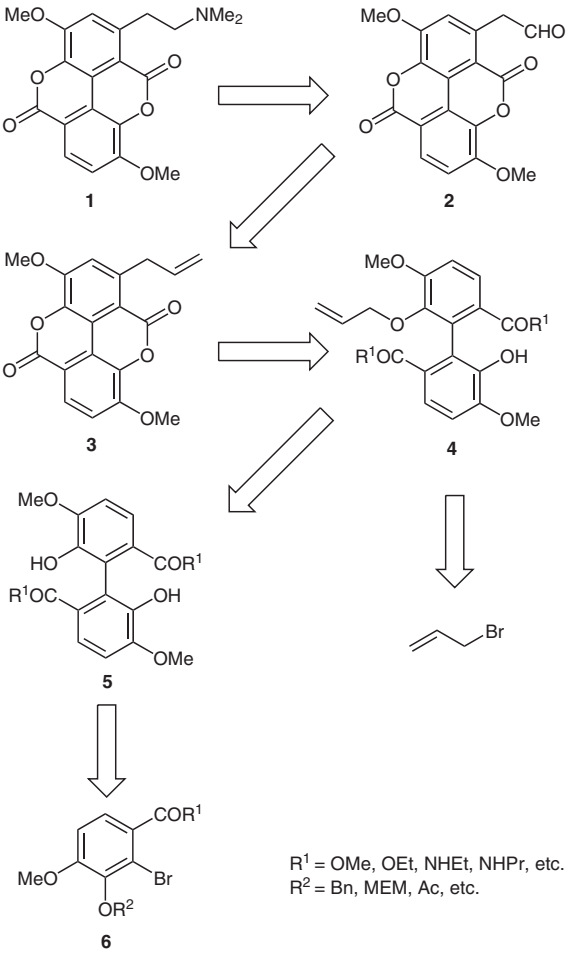


Figure 1 Structure of taspine (**1**)



Scheme 1

We used commercially available isovanillin (**7**) as the starting material (Scheme 2). The key intermediate **11** was constructed as follows. Isovanillin (**7**) was converted into 2-bromoisovanillin (**8**) by reaction with bromine in 79% yield.[9] After protection of **8** as benzyl ether,[10] the aldehyde group in **9** was oxidized to the carboxyl group to give **10**.[11] Esterification of **10** afforded the monocyclic precursor **11**[12] for the Ullmann reaction. Compared with the method reported by Kelly, our method of preparation for the monocyclic precursor for coupling **11** used the cheaper agent benzyl chloride to protect the hydroxy group and bromine as the leaving group.

Biphenyl dimethyl ester **12** was prepared by dimerization of **11** employing a classical symmetrical Ullmann reaction in high yield (85%).[13] Compound **13** could be readily ob-

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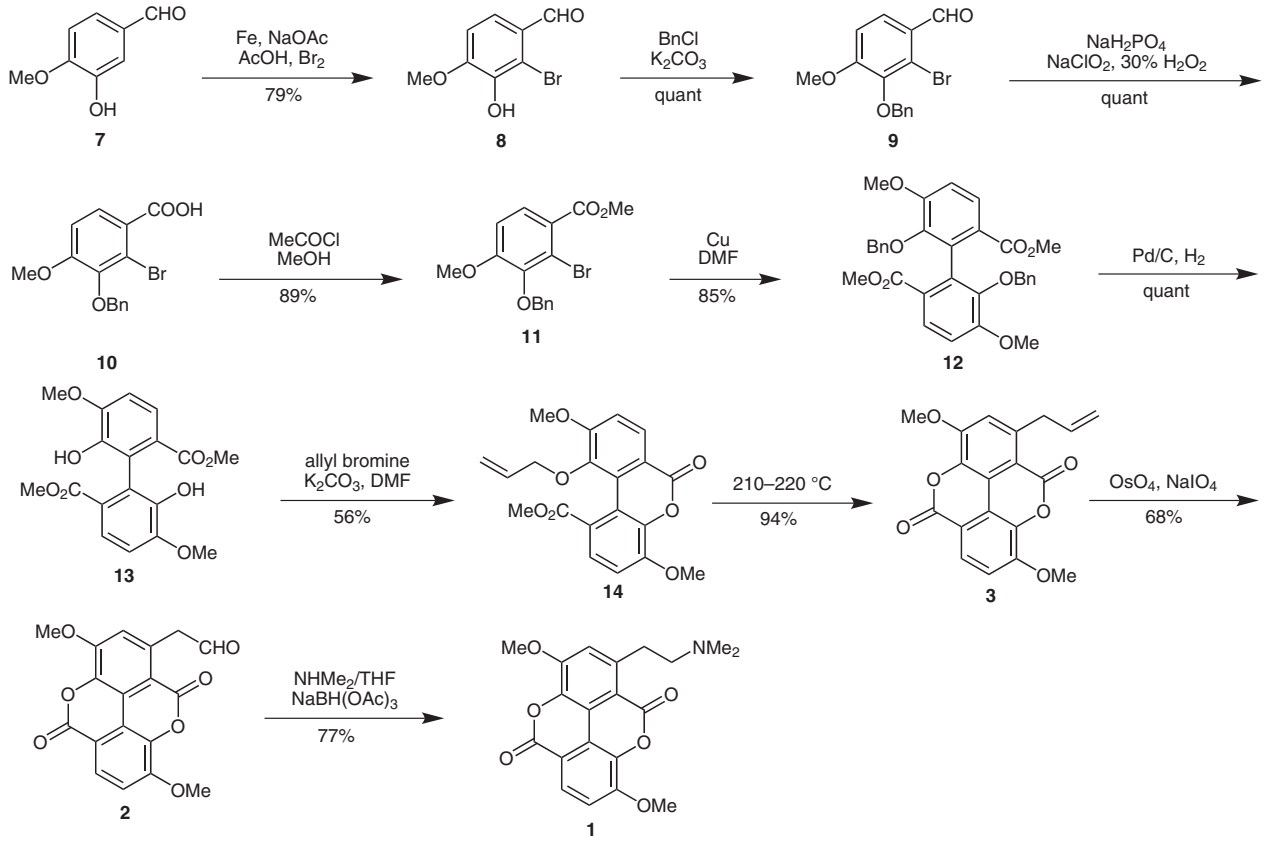

Scheme 2

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, ^{1}H NMR, ^{13}C 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 debenzylation 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 N_2. Reactions were monitored by TLC on 0.25 mm silica gel plates ($60GF_{254}$) 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. ^{1}H NMR and ^{13}C 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. Br_2 (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, $CDCl_3$): 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-Benzyloxy-2-bromo-4-methoxybenzaldehyde (9)
To a suspension of **8** (15.0 g, 0.065 mol) in dehydrated alcohol (150 mL) were added anhyd K_2CO_3 (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 H_2O (3 × 50 mL), aq 1 M NaOH (3 × 50 mL), aq 2 M HCl (3 × 50 mL), and brine (2 × 50 mL), dried (Na_2SO_4), 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, $CDCl_3$): 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-Benzyloxy-2-bromo-4-methoxybenzoic Acid (10)
To a solution of **9** (20.87 g, 0.065 mol) in THF (200 mL) was added distilled H_2O (60 mL) and NaH_2PO_4 (4.68 g, 0.039 mol). The mixture was stirred at r.t. for 10 min. $NaClO_2$ (19.40 g, 0.215 mol) and 30% H_2O_2 (14.8 mL, 0.143 mol) in distilled H_2O (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 H_2O (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, $CDCl_3$): 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-Benzyloxy-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 $CHCl_3$ (2 × 150 mL). The combined organic extracts were washed with H_2O (3 × 60 mL), aq sat. $NaHCO_3$ (3 × 60 mL), and brine (2 × 60 mL), dried (Na_2SO_4), 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, $CDCl_3$): 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 N_2, 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 $CHCl_3$ (2 × 150 mL), and the combined organic layers were washed with aq 2 M HCl (3 × 60 mL) and brine (2 × 60 mL), dried (Na_2SO_4), 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, $CDCl_3$): 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 H_2 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), CH_2Cl_2 (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).

^{13}C 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 $C_{18}H_{18}O_8$: C, 59.67; H, 5.01. Found: C, 59.53; H, 4.99.

Methyl 10-(Allyloxy)-4,9-dimethoxy-6-oxo-6*H*-benzo[*c*]chromene-1-carboxylate (14)
To a solution of **13** (1g, 2.8 mmol) in DMF (30 mL) was added anhyd K_2CO_3 (0.58 g, 4.2 mol) and allyl bromide (0.29 mL, 3.3 mol) under N_2. 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 $CHCl_3$ (2 × 25 mL), and the combined organic layers were washed with H_2O (3 × 15 mL), aq 2 M HCl (3 × 15 mL), and brine (2 × 15 mL), dried (Na_2SO_4), 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, $CDCl_3$): 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).

^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{20}H_{18}O_7$: 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** (0.57g) was stirred at 210–220 °C for 50 min under N_2. The residue was purified by column chromatography ($CHCl_3$) 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, $CDCl_3$): 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 CH_2Cl_2, H_2O, and *t*-BuOH (100 mL, 3:1:1) was added OsO_4 (9 mg, 0.035 mmol). The mixture was stirred at r.t. for 30 min in dark. $NaIO_4$ (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 CH_2Cl_2 (2 × 100 mL), and the combined organic layers were washed with H_2O (3 × 40 mL), aq 0.5% $NaHSO_3$ (2 × 30 mL) and brine (2 × 40 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography ($CHCl_3$–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, 3H).

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 CH_2Cl_2 (60 mL) was added Me_2NH (0.18 mL, 0.21 mmol) in THF under N_2 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 ($CHCl_3$–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, $CDCl_3$): 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).

^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 64.94; H, 5.21; N, 3.80.

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