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A concise and efficient synthesis of salvinal from isoeugenol via a phenoxenium ion intermediate

Eng-Chi Wang,[a] Yung-Shung Wein[b] and Yueh-Hsiung Kuo[b,c,d,*]

[a]*Faculty of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 807, Taiwan*
[b]*Department of Chemistry, National Taiwan University, Taipei 106, Taiwan*
[c]*Agricultural Biotechnology Research Center, Academia Sinica, Taipei 115, Taiwan*
[d]*College of Pharmacy, China Medical University, Taichung 404, Taiwan*

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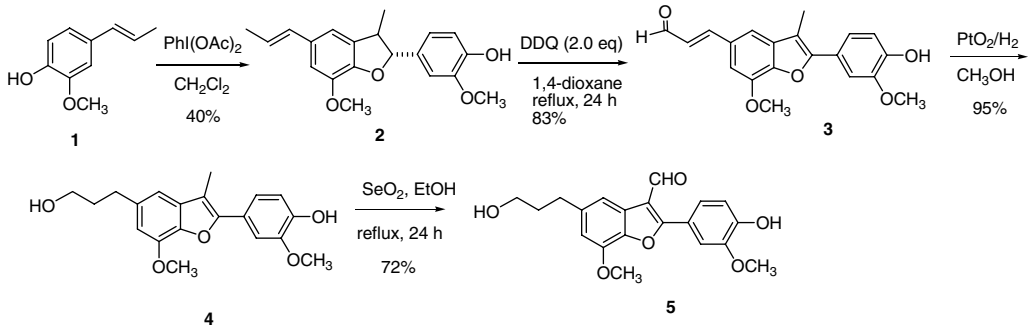
Abstract—In this letter, we describe how salvinal can be efficiently synthesized from isoeugenol via a phenoxenium ion intermediate by four steps in 23% over all total yield.

Salvinal, a naturally occurring neolignan, was firstly isolated from *Salvia mitorrhiza* Burge (Danshen), a Chinese medicinal plant, and was found as a novel adenosine A_1 receptor ligand.[1] The aqueous extract of this plant has been popularly used as folk medicine for treatment of angina pectoris, acute myocardial infarction, etc. in China.[2] In addition, chloroform extract of this plant exhibits cytotoxic activities against various cell lines derived from human carcinomas.[3] Recently, the detailed molecular action mechanism of salvinal has been clarified as a microtubule inhibitor, similar to the effect of colchicines.[4] For further animal studies and other biological interesting purposes, a larger amount of salvinal is required. Thus, there is an urgent need to develop a concise and efficient synthetic method for producing salvinal is urgent. After carefully examining the published methods for the synthesis of salvinal reported by Yang et al.,[1a] Hutchison et al.,[5] Kao and Chern,[6] and our previous study,[7] we found that some common drawbacks still exist including multiple synthetic steps, low over all total yield and tedious reaction conditions. We herein report an improved strategy for the synthesis of salvinal starting from isoeugenol in four steps with good over all total yield (Scheme 1).

Oxidation coupling of isoeugenol was carried out by the hypervalent iodine reagent, iodobenzene diaceate (IDA) reported by Juhasz et al.,[8] to give 2,3-dihydrobenzofuran



Scheme 1. The synthesis of salvinal from isoeugenol.

Keywords: Isoeugenol; Iodobenzene diacetate; Oxidative coupling; Salvinal.
* Corresponding author. E-mail: yhkuo@ntu.edu.tw

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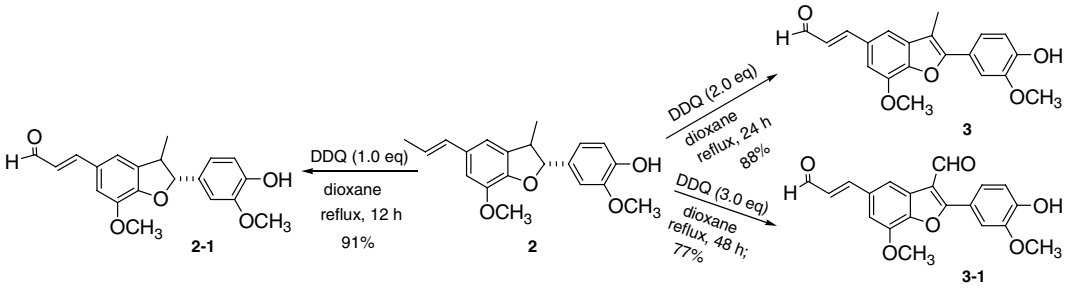

Scheme 2. Compound **2** was oxidized by 1–3 equiv of DDQ.

(**2**) in 40% yield. When **2** was reacted with 2 equiv of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in refluxing 1,4-dioxane, benzofuran (**3**)[9] was produced through dehydrogenation and allylic oxidation in one-pot within 24 h, giving a yield of 83%. At the same reaction condition, when **2** was treated with 1 equiv DDQ, it gave compound **2–1**[10] in a yield of 91% through allylic oxidation and no product from dehydrogenation reaction was isolated. Furthermore when 3 equiv of DDQ was used instead to carry out the reaction, compound **3–1**[11] was obtained in 77% yield. These reactions described above can be summarized as follows (Scheme 2).

From this result, we have successfully improved the previous study reported by Iliefski et al.[12] They reported that the allylic oxidation of arylpropene with DDQ can only be worked slowly at the condition of appropriate amount of water at room temperature. We also found that the arylpropene functionality was more easily oxidized to arylpropenal than that of oxidation of aryldihydrofuran to arylfuran in compound **2**. The other oxidant and dehydrogenating reagent, selenium oxide was limited for lower yield in this reaction due to the poor solubility in dioxane compared to DDQ which can be soluble and reacted efficiently. The reduction of α,β-unsaturated aldehyde moiety in benzofuran (**3**) was smoothly achieved by Adam's catalyst (PtO_2/H_2) to afford compound **4** in a yield of 95%.[13] Finally, the methyl group at 3-position of alcoholic benzofuran (**4**) was successfully oxidized by selenium oxide in refluxing ethanol to give the title compound, salvinal (**5**) in 72% yield.[14]

In conclusion, in our process compound **2** was oxidized and dehydrogenated by DDQ in refluxing 1,4-dioxane in one-pot to give compound **3** in high yield and in a short reaction time which is an advantage. In addition, effective oxidation of allylic methyl carbon, at 3-position of benzofuran (**4**) by inexpensive selenium oxide is also an advantage. Thus, we have successfully established a concise and efficient synthesis for salvinal in four steps and in 23% over all total yield.

Acknowledgement

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9. Synthesis of **3**: To a stirred solution of **2** (2.12 g, 6.43 mmol) in 1,4-dioxane (50 mL) was added DDQ (3.24 g, 14.27 mmol) and heated to the reflux for 24 h. After usual work-up process and column chromatographic purification process (EtOAc/*n*-hexane = 1/8), pure **3** (1.81 g, 83%) was obtained as colorless crystal, mp 221–222 °C. IR (KBr) cm^{-1}, ν_{max}: 2949, 2811, 2727, 1674, 1616, 1513, 1214, 1128, 972. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.40 (3H, s, CH_3–C-3), 3.95 (3H, s, OCH_3–C-3′), 4.03 (3H, s, OCH_3–C-7), 5.85 (1H, br s, OH), 6.70 (1H, dd, $J = 15.9$, 7.6 Hz, H-2″), 6.97 (1H, s, H-2′), 6.99 (1H, d, $J = 8.0$ Hz, H-5′), 7.26–7.30 (3H, m, H-4, H-6, H-6′), 7.55 (1H, d, $J = 15.9$ Hz, H-1″), 9.68 (1H, d, $J = 7.6$ Hz, H-3″). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 9.5, 56.1, 105.6, 109.4, 110.1, 113.8, 114.6, 120.8, 123.0, 127.4, 129.6, 133.5, 144.6, 145.4, 146.2, 146.7, 153.9, 193.6. EI-MS *m*/*z* (%) (70 eV): 338 (M^+, 100), 326 (21), 310 (100), 295 (14), 267 (15), 151 (13), 137 (14), 69 (17), 57 (19). HRMS (EI, *m*/*z*): Calcd for $C_{20}H_{18}O_5$: 338.1154. Found: 338.1141.
10. Compound **2-1** was obtained as colorless crystal, mp 177–178 °C. IR (KBr) cm^{-1}, ν_{max}: 3486, 2821, 2734, 1684, 1620, 1133, 821. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.40 (3H, d, $J = 6.8$ Hz, CH_3–C-3), 3.50 (1H, m, H-3), 5.18 (1H, d, $J = 7.9$ Hz, H-2), 5.66 (1H, s, OH), 6.60 (1H, dd, $J = 15.8$, 7.6 Hz, H-2″), 6.87 (1H, d, $J = 8.1$ Hz, H-5′), 6.89 (1H, s, H-2′), 6.93 (1H, d, $J = 8.1$ Hz, H-6′), 6.99 (1H, s, H-6), 7.02 (1H, s, H-4), 7.41 (1H, d, $J = 15.8$ Hz, H-1″), 9.64 (1H, d, $J = 7.6$ Hz, H-3″). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.7, 45.1, 55.9, 56.0, 94.5, 108.9, 111.8, 114.3, 117.3, 119.9, 126.3, 128.1, 131.2, 134.0, 144.6, 146.0, 146.7, 150.6, 153.2, 193.6. EI-MS *m*/*z* (%) (70 eV): 340 (100), 325 (7), 203 (7), 151 (8), 137 (15), 97 (15), 83 (16), 71 (18), 57 (30). HRMS (EI, *m*/*z*): Calcd for $C_{20}H_{20}O_5$: 340.1311. Found: 340.1300.

11. Compound **3-1** was obtained as colorless crystal, mp 234–235 °C, IR (KBr) cm^{-1}, ν_{max}: 3488, 2854, 2734, 1680, 1619, 1513, 1279, 1027. ^1H NMR ($CDCl_3$, 300 MHz): δ 4.01 (3H, s, OCH_3), 4.06 (3H, s, OCH_3), 6.02 (1H, s, OH), 6.75 (1H, dd, $J = 15.9$, 7.7 Hz, H-2″), 7.07 (1H, d, $J = 8.0$ Hz, H-5′), 7.09 (1H, $J = 1.8$ Hz, H-2′), 7.37 (1H, d, $J = 1.9$ Hz, H-6), 7.41 (1H, dd, $J = 8.0$, 1.8 H, H-6′), 7.58 (1H, d, $J = 15.9$ Hz, H-1″), 8.05 (1H, d, $J = 1.9$ Hz, H-4), 9.72 (1H, d, $J = 7.7$ Hz, –C*H*O-3″), 10.30 (1H, s, C*H*O-3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 55.9, 56.2, 107.0, 112.4, 115.3, 116.0, 116.2, 118.5, 123.1, 127.4, 128.4, 132.3, 143.7, 145.0. 148.2, 150.4, 153.8, 165.7, 186.6, 194.3. EI-MS *m*/*z* (%) (70 eV): 352 (M^+, 100), 323 (40), 296 (15), 281 (20), 253 (33), 181 (18), 152 (23). HRMS (EI, *m*/*z*): Calcd for $C_{20}H_{16}O_6$: 352.0947. Found: 352.0939.

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13. Reduction of **3** to prepare **4**: To a stirred solution of **3** (1.33 g, 3.93 mmol) in MeOH (20 mL) was added 10% PtO_2/H_2O (96.3 mg) and bubbled H_2 at room temperature for 6 h. The reaction was monitored by TLC until the starting material was completely consumed. After usual work-up and column chromatographic purification process (EtOAc/*n*-hexane = 2/5), pure **4** (1.28 g, 95%) was obtained as colorless crystal, mp 165–166 °C. IR (KBr) cm^{-1}, ν_{max}: 3431, 2851, 1602, 1516, 1455, 1386, 1222, 1052, 793. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.95 (2H, m, H-2″), 2.38 (3H, s, CH_3–C-3), 2.79 (2H, t, $J = 7.9$ Hz, H-1″), 3.71 (2H, t, $J = 6.5$ Hz, H-3″), 3.96 (3H, s, OCH_3–C-3′), 4.01 (3H, s, OCH_3–C-7), 5.73 (1H, br, OH–C-4′), 6.63 (1H, d, $J = 2.0$ Hz, H-6), 6.91 (1H, d, $J = 2.0$ Hz, H-2′), 6.98 (1H, d, $J = 8.2$ Hz, H-5′), 7.26 (1H, dd, $J = 8.2$, 2.0 Hz, H-6′), 7.30 (1H, d, $J = 2.0$ Hz, H-4). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 9.6, 32.6, 34.8, 56.1, 62.4, 107.4, 109.5, 110.8, 114.5, 120.6, 123.8, 133.0, 136.9, 144.7, 145.7, 146.6, 151.4. EI-MS *m*/*z* (%) (70 eV): 342 (M^+, 5), 340 (100), 324 (37), 312 (26), 297 (19), 284 (20), 148 (13), 97 (16), 91 (18), 69 (23), 57 (28); HRMS (EI, *m*/*z*): Calcd for $C_{20}H_{22}O_5$: 342.1467. Found: 342.1481.

14. Synthesis of **5**: To a stirred solution of **4** (0.64 g, 1.87 mmol) in EtOH (20 mL) was added SeO_2 (0.42 g, 3.74 mmol) and heated to reflux for 12 h. Then, the reaction mixture was cooled to room temperature and was filtered through Celite 545^R. After concentration in vacuo, the resulting residue was subjected to silica gel chromatographic column (EtOAc/*n*-hexane = 1/5). Pure **5** (0.48 g, 72%) was obtained as colorless crystal, mp 173–174 °C. The spectral data of ^1H NMR, ^{13}C NMR, EI-MS are all coincident to the reported salvinal.