An efficient multigram synthesis of juglone methyl ether

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Based on the regioselective oxidation of 1,4,5-trimethoxynaphthalene by cerium (IV) ammonium nitrate, an efficient synthesis of juglone methyl ether has been achieved with high overall yield (74%) and good purity (98.6%). Compared with the reported methods, the reaction conditions are milder and the work-up of each step is much simpler. Moreover, the new strategy considerably reduces the cost in the synthesis of juglone methyl ether and is suitable for large-scale preparations.

Keywords: juglone methyl ether, ceric ammonium nitrate oxidation, juglone derivatives

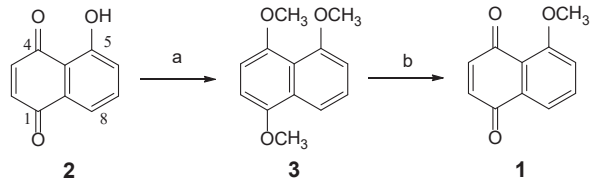
Juglone methyl ether (**1**), a naturally occurring naphthoquinone in *Juglans mandshurica* Maxim. Cortex,[1] exhibits a wide variety of biological activities and attracted considerable interests from scientists. It showed much more potent antitumour effects against a series of cancer cell lines than its parent compound, juglone (**2**).[2] The strong antiviral, antibacterial and antifungal activity of **1** was also reported.[3,4] In the synthesis of pharmacologically active naphthoquinones[5-10] and anthraquinones,[11,12] it served as a key intermediate. Recently, the irreversible inactivation of the fatal botulinum neurotoxin serotype A by this natural naphthoquinone was also disclosed.[13]

For the preparation of **1**, the methylation of **2** might be the simplest method. However, because the strongly chelated hydroxyl group in juglone sensitised the molecule towards alkali reagents, several attempts to methylate juglone employing nucleophilic substitutions under alkaline conditions failed.[14] At present, the only reported method for this purpose was confined to the use in an excess of silver(I) oxide and methyl iodide.[7-9,15] This is not an attractive procedure for large-scale preparations since silver-containing chemicals are expensive. The oxidation of 4-hydroxy-8-methoxy-1-naphthaldehyde by the Fremy's radical[16] and the hypervalent iodine oxidation of 4,8-dimethoxynaphthalen-1-ol[17] could afford the desired compound but the two naphthols used in the oxidation were not easy to obtain. Miller's synthetic strategy[18] rested on the Diels–Alder cycloaddition between benzoquinone and 1,4-dimethoxy-1,3-butadiene and a further oxidation–elimination reaction. But the yield of the strategy was unsatisfactory and the synthesis of the diene intermediate was somewhat tedious. The anodic oxidation of 1,4,5-trimethoxynaphthalene[19] and the chemical oxidation of this compound using Jones reagent[20] or silver-catalysed ammonium peroxodisulfate[21] would provide the desired product, but none of these processes has been extensively employed for large-scale preparations. Thus it was necessary to design a favourable method for the multigram synthesis of **1** with an efficient route and inexpensive starting materials.

Results and discussion

Rested on the regioselective oxidation of 1,4,5-trimethoxynaphthalene (**3**), an efficient synthesis of **1** was established (Scheme 1). The synthetic study started from juglone, which was prepared by the oxidation of 1,5-naphthalenediol using the Fremy's radical.[22, 23] Due to the instability of juglone under alkaline conditions, the reported method[24] for the preparation of **3** employed the methylation of the chelated phenolic hydroxyl group of **2** and further reduction-methylation of the quinone ring. In our synthetic route, the quinone ring of **2** was firstly reduced to a hydroquinone moiety and the resulting polyhydroxyl-naphthalene was successfully converted into the methylated product **3** in the presence of dimethyl sulfate and sodium hydroxide with high yield. The 1,4,5-trimethoxynaphthalene was quickly oxidised by cerium(IV) ammonium nitrate (CAN) to the title compound in mild conditions.

According to the mechanism of CAN-mediated oxidation[25,26], the reaction proceeded *via* the formation of aryl radicals (**4** and **5**, Fig. 1). The methoxyl group at position 1 as an electron-



Scheme 1 (a) $Na_2S_2O_4$, $Bu_4N^+Br^-$, THF/H_2O; then $(CH_3)_2SO_4$, NaOH; 89%. (b) CAN, CH_3CN/DCM; 83%.

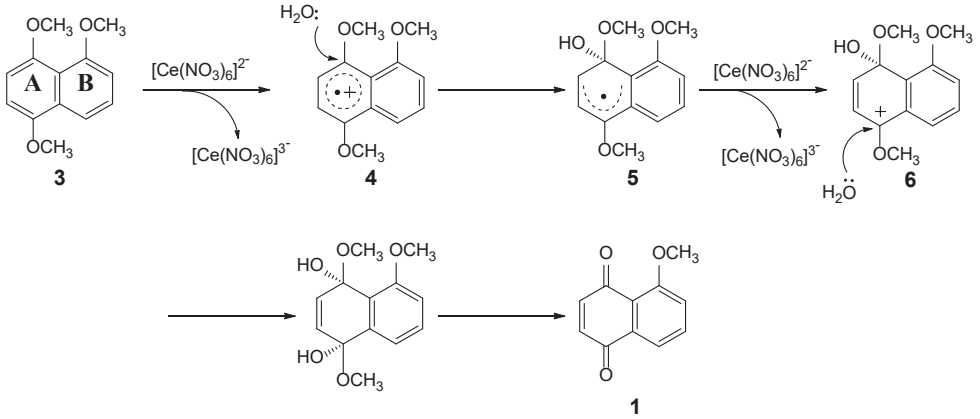


Fig. 1 The plausible mechanism for the oxidative demethylation of **3**.

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donating group could increase the electron density of A-ring of **3** and help in the formation and stabilisation of these aryl radicals. The radical **5** underwent an oxidation to form cation (**6**) that then afforded the desired compound. The presence of the 1-methoxyl group was the reason that the oxidative demethylation occurred regioselectively at the A-ring and that no B-ring oxidation was observed. In the oxidation, the best ratio of **3** to CAN (1: 2.2) and the optimum reaction temperature (5 °C) were established by analysis of a series of experimental conditions. When the reaction temperature was much higher than 5 °C, the amount of by-products increased. However, at much lower temperatures, the reaction proceeded more slowly. After the oxidation, compound **1** with high purity was obtained by simple extraction and further crystallisation from a mixture of petroleum-ether and ethyl acetate.

Conclusion

Based on the regioselective oxidative demethylation of 1,4,5-trimethoxynaphthalene (**3**) by CAN, an efficient synthesis of juglone methyl ether (**1**) has been achieved with high overall yield (74%) and good purity (98.6%). Compared with the reported methods,[7-9, 15-21] our synthetic strategy have several advantages. First, the reaction conditions are milder and the work-up of each step is much simpler. Second, the starting materials are cheaper and readily available. Thirdly, all the reactions in the strategy are suitable for large-scale preparations.

Experimental

CAUTION: Dimethyl sulfate is highly toxic and should only be used when suitable safety precautions have been taken.

Reagents and solvents were obtained from commercial suppliers and purified using standard techniques.[27] Column chromatography was conducted on silica gel (100–200 mesh) from the Qingdao Ocean Chemical Factory. Juglone (**2**) was prepared by the reported method.[22, 23] Melting points were determined on a SGW X-4 micromelting point apparatus. ^{1}H NMR Spectra were measured on a Bruker Avance 400 spectrometer (400 MHz) and chemical shifts were recorded with tetramethylsilane as the internal standard.

Purity was evaluated by HPLC on an Agilent 1260 system using a SUPELCO Discovery® C18 column (150×4.6 mm, 5 μm) at room temperature with a gradient elution using the mobile phase (**A**) water and (**B**) methanol (30% of **B** at 0–20 min, 30% to 80% of **B** at 20–35 min, 80% of **B** at 35–70 min), with a flow rate of 0.8 mL min^{-1}. The injection volume was 10 μL and the detection wavelength was set at 254 nm.

1,4,5-Trimethoxynaphthalene (**3**): Juglone (**2**, 3.48 g, 20 mmol) was dissolved in THF (60 mL) and a solution of sodium dithionite (17.41 g, 100 mmol) and tetrabutyl ammonium bromide (TBAB, 4.84 g, 15 mmol) in water (50 mL) was added. The mixture was stirred at room temperature under a nitrogen atmosphere until the colour of the organic layer turned from orange to light-yellow. Then dimethyl sulfate (10.09 g, 80 mmol) and a solution of sodium hydroxide (10.0 M, 20 mL) was dropwise added to the light-yellow solution under water-ice cooling. After the addition, the mixture was allowed to warm to room temperature and was stirred for another 4 h. After completion of the reaction, the mixture was diluted with water and extracted with ethyl acetate (30 mL×5). The combined organic layer was washed with a solution of sodium hydroxide (1.0 M, 60 mL), water (100 mL) and brine (100 mL) in sequence and then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure at 35 °C and the residue was subjected to flash column chromatography (petroleum-ether:ethyl acetate, 10:0.5, V/V) to give **3** as white solid. Yield 3.88 g (89%). Recrystallisation of the solid from *n*-hexane gave **3** as colourless plates; m.p. 117–118 °C (lit.[24] 117–118 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.4 Hz, 1H), 7.38 (dd, *J* = 8.4, 7.7 Hz, 1H, H-7), 6.91 (d, *J* = 7.7 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.73 (d, *J* = 8.5 Hz, 1H), 3.97 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3).

5-Methoxy-1,4-naphthoquinone (**1**): A solution of CAN (14.47 g, 26.4 mmol) in water (25 mL) was dropwise added to a solution of **3** (2.62 g, 12 mmol) in a mixture of acetonitrile-dichloromethane (1:3, V/V, 40 mL) under water-ice cooling. After the addition, the yellow-orange solution was stirred for another 15 min until all the starting material was consumed. Then the solution was diluted with water (100 mL) and extracted with ethyl acetate (40 mL×4), washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated to about one-tenth volume at 35 °C under reduced pressure. Petroleum-ether (1.2 L) was added and the mixture was cooled in a refrigerator at 0 °C for 6 h. The title compound as short yellow-orange needles was then obtained by simple filtration and washed with petroleum-ether (30 mL). Yield 1.88 g (83%). m.p. 184–186 °C (lit.[7] 184–189 °C). The crystal contained 98.6% of pure **1** according to the HPLC analysis (area normalisation method, t_R=11.13 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (dd, *J* = 7.6, 1.2 Hz, 1H, H-8), 7.69 (dd, *J* = 7.6, 8.2 Hz, 1H, H-7), 7.32 (dd, *J* = 8.2, 1.2 Hz, 1H, H-6), 6.87 (s, 2H, H-2, H-3), 4.02 (s, 3H, OCH_3).

The research is supported by China Postdoctoral Science Foundation (grant no. 2014M561479). We are grateful to the Instrumental Analysis Center of Shanghai Jiaotong University for recording the ^{1}H NMR spectra.

Received 14 June 2015; accepted 21 August 2015
Paper 1503420 doi: 10.3184/174751915X14405203456709
Published online: 1 September 2015

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