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A regioselective synthesis of 7-methyl juglone and its derivatives

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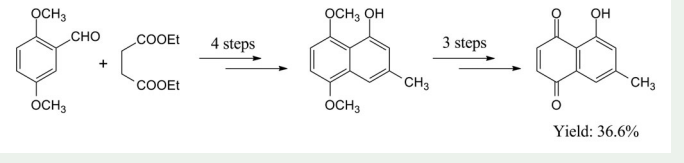
ABSTRACT

7-Methyl juglone as a naturally occurring naphthoquinone showed striking antibacterial, antifungal, antivirus and anticancer activity. Its derivatives had also been characterized as key intermediates in the preparation of natural naphthoquinones and anthraquinones. Herein, we reported a regioselective synthesis of 7-methyl juglone *via* the construction of fused polycyclic systems. The key steps of the strategy involved Stobbe condensation of 2,5-dimethoxy benzaldehyde with diethyl succinate, intramolecular cyclization, reduction, acid-facilitated debenzylation and further cerium(IV) ammonium nitrate-mediated oxidation. Compared with the reported methods employing Birch conditions in liquid ammonia or Friedel-Crafts cycloacylation with melting heat of aluminum salts, the reaction conditions in the new synthetic route were milder and suitable for large scale preparations. In addition, all of the starting materials in the synthesis were readily available. It has great implications for the design and synthesis of structurally asymmetric naphthoquinones derivatives.



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1. Introduction

7-Methyl juglone (**1**, Scheme 1), a biologically active naphthoquinone isolated from the roots of *Drosera aliciae* Raym.-Hamet, exhibited marked antibacterial and antifungal effects (Mbaveng and Kuete 2014; Rauf et al. 2016). It demonstrated potent inhibitory activity against the Gram-positive *Streptococcus mutans* and *Streptococcus sanguis* with its MIC values of 156 and 78 μg/mL, respectively (Cai et al. 2000). Towards the Gram-negative anaerobic rods *Prevotella gingivalis*, it showed much higher growth inhibitory activity with the MIC value of 39 μg/mL (Cai et al. 2000). It has been

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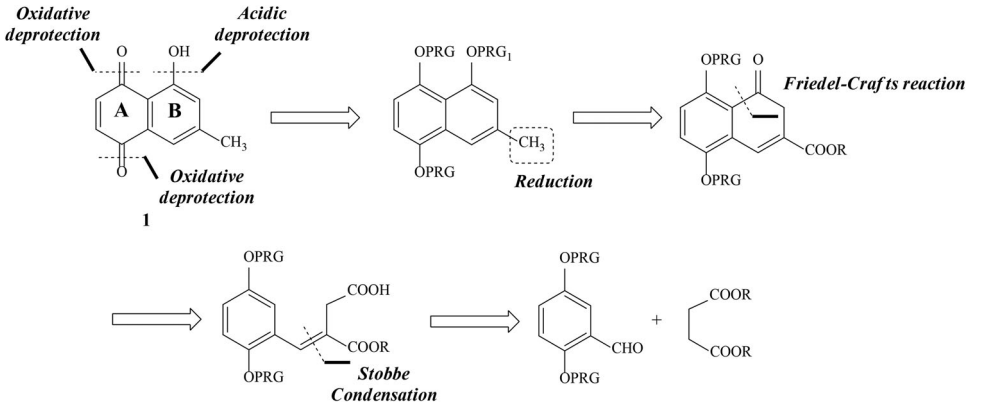


Scheme 1. Retrosynthetic analysis of 7-methyl juglone.

identified as an exceptional potent antitubercular agent with its MIC value of only 0.5 μg/mL against the *Mycobacterium tuberculosis* H37Rv (Mahapatra et al. 2007). For the drug-resistant *Mycobacterium tuberculosis* strain, 7-methyl juglone still has potential tuberculocidal efficacy through the inhibition of DNA gyrase-catalyzed supercoiling reactions (Karkare et al. 2013).

7-Methyl juglone appeared to be an effective antifungal naphthoquinone with its MIC value of 80 μg/mL against the pulmonary candidiasis *Candida albicans*, which was comparable to that of nystatin as the positive control (Sinha et al. 2009). Recently, its antivirus (Singh et al. 2001; Mahapatra et al. 2012), anticancer (Kawiak et al. 2012; Kishore et al. 2014) and anti-inflammatory (Azab et al. 2016) activity have also been reported.

Apart from its striking biological activities, 7-methyl juglone and its derivatives such as its methyl ether (**2**, Scheme 2), benzyl ether (**3**) and acetate (**4**) had also been employed as key intermediates in organic synthesis, especially for the total synthesis of many other naturally occurring quinones and their derivatives (Kuroyanagi et al. 1971; Laatsch 1980; Krohn and Broser 1984; Van der Kooy and Meyer 2006; O'Keefe et al. 2010, 2011).

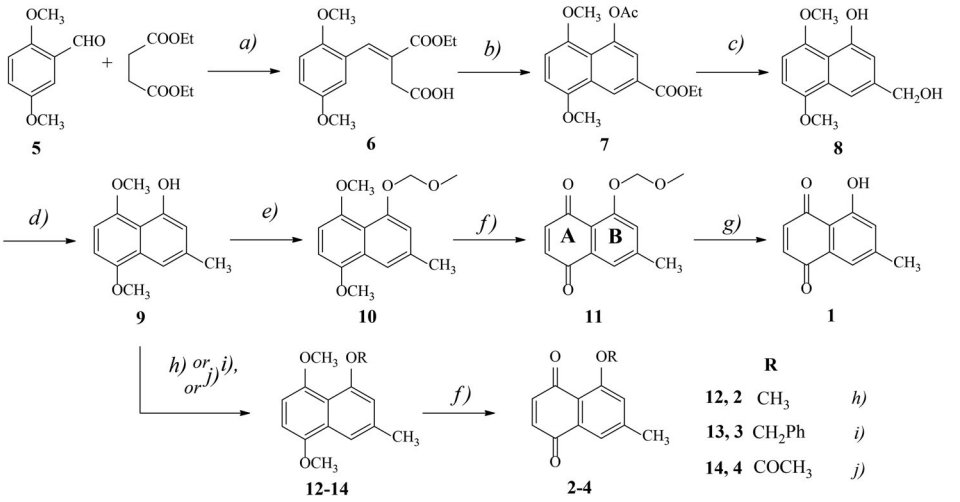
2. Results and discussion

The molecular structure of 7-methyl juglone (**1**) is quite simple apparently. However, ascribed to the active chemical reactivity of the 1,4-quinone moiety (**A**-ring) and its asymmetric structural scaffold, the concise and efficient synthesis of this natural naphthoquinone and its derivatives remains elusive. The most frequently used method for the preparation of **1** employed the Friedel-Crafts cycloacylation of 4-halo-3-methyl phenol with maleic anhydride in a melting mixture of anhydrous $AlCl_3$ and NaCl at high temperature, further acetylation and reductive dehalogenation of the corresponding halo-substituted adducts (Cooke and Dowd 1953; Laatsch 1978, 1980; Musgrave and Skoyles 2001; Mahapatra et al. 2007). Obviously, there were some serious disadvantages in this synthetic strategy such as drastic reaction conditions, troublesome purifications and very low and poorly reproducible yields. The other method rested on

the cycloaddition between 1,4-benzoquinone and silylated dienes and further acidic hydrolysis (Krohn and Broser 1984; Savard and Brassard 1984; O'Keefe et al. 2011; Jha et al. 2017). However, the synthesis of the diene intermediate was somewhat tedious and the total yield was also unsatisfactory. Parker's method rested on the annelative synthetic procedure with ethyl 3-methyl-4-cyano-4-(2,5-dimethoxyphenyl) butyrate as the starting material (Parker and Tallman 1984). However, the elimination of the nitrile group as a key step was conducted in Birch conditions using metal sodium in liquid ammonia at $-78\,^{\circ}C$ and was difficult to scale up. Thus the target compound (**1**) obtained was only at a 2 mg level (Parker and Tallman 1984). In addition, the starting material should be synthesized using the highly toxic sodium cyanide and was not readily available from general suppliers (Parker and Kallmerten 1980). Therefore, an efficient multigram synthesis of **1** with a convenient route and high overall yield was desirable for further drug development, as well as the synthesis of natural quinones and their derivatives.

The most commonly used method for the synthesis of 7-methyl juglone derivatives (**2**, **3** and **4**) were the methylation, benzylation or acetylation of the parent compound **1** in the highly reactive methyl iodide (benzyl bromide)/silver(II) oxide mixture or a heated sodium acetate/acetic anhydride system (Laatsch 1980; Maiti et al. 2005; Mahapatra et al. 2007; O'Keefe et al. 2010; Kishore et al. 2014). These strategies greatly depended on the supply of **1** as a raw material. Thus the synthesis of 7-methyl juglone analogues using intermediates in the synthetic route of **1** should be an alternative strategy.

According to the retrosynthetic analysis (Scheme 1), the construction of **B**-ring *via* Stobbe condensation and further Friedel-Crafts acylation, the conversion of an ester moiety to a methyl group, and subsequent deprotection strategies were economical and efficient synthetic methods for the preparation of the targeted compound. In our studies, 2,5-dimethoxy benzaldehyde (Scheme 2, **5**) and diethyl succinate were employed as the starting points, which were readily available from commercial suppliers. The Stobbe condensation between the benzaldehyde **5** and diethyl succinate, and further intramolecular cyclization of **6** afforded the ethyl 4-acetoxy-5,8-dimethoxy-2-naphthoate (**7**) in mild conditions. The reduction of the diester **7** by excessive amount of $LiAlH_4$ afforded 2-naphthylmethanol derivative **8** stiochiequivalently. The dehydroxylation reaction was carried out under hydrogen atmosphere with palladium hydroxide on activated charcoal ($Pd(OH)_2/C$, 20 wt. % loading) as the catalyst. The structure of the dehydroxylated product **9** was confirmed by shifting of the ^1H NMR signal belong to methylene group of the substrate at δ 4.77 ppm to upfield ($\delta = 2.45$ ppm) upon the debenzylation reaction. According to previous reports in literatures (Bruce and Thomson 1955; Wright et al. 2007; Cui et al. 2015), the chelated hydroxyl group in juglone sensitized this molecule in alkali conditions. The methoxy methyl ether (MOM), which could be easily cleaved in acidic conditions, was used as the protecting group in the synthesis. The protection of the phenolic hydroxyl group with MOM in the presence of NaH and MOMCl provided the bicyclic precursor **10**. Further cerium(IV) ammonium nitrate (CAN)-mediated oxidative demethylation reactions and acidic deprotection of MOM protecting group furnished the targeted compound in mild conditions with high yield.



Scheme 2. Synthesis of 7-methyl juglone and its derivatives. *Reagents and conditions: (a)* NaH, Toluene, 0 °C to r. t.; *(b)* NaOAc, AcOH, 120 °C, Yield: 66% for 2 steps; *(c)* $LiAlH_4$, THF, 0 °C, Yield: 98%; *(d)* $Pd(OH)_2/C$, 1 atm H_2, AcOH-MeOH (1: 200), r. t., Yield: 95%; *(e)* MOMCl, NaH, DMF, 0 °C to r. t., Yield: 96%; *(f)* CAN, DCM-ACN (2:1), 0 °C, Yield: 85% for **11**, 81% for **2**, 80% for **3** and 87% for **4**; *(g)* Diluted H_2SO_4, MeOH, 5 °C, 73%; *(h)* CH_3I, NaH, DMF, 0 °C to r. t., Yield: 97%; *(i)* BnBr, NaH, KI, DMF, 0 °C to r. t., Yield: 95%; *(j)* Ac_2O, Py, 50 °C, Yield: 89%

The heterogenouse catalyst, $Pd(OH)_2/C$, was a commonly used catalyst for the deprotection of benzyl groups under the hydrogen-rich atmospheres (Blaser et al. 2001). The reaction was conducted *via* the formation of an aryl-palladium(II) intermediate and further hydrogenation (Al Soom and Thiemann 2016). However, the debenzylation of 2-naphthylmethanol derivative **8** proceeded slowly even with the use of excessive amount of the catalyst under refluxed conditions. The acidification of the reaction mixture with catalytic amount of acetic acid greatly promoted the debenzylation reaction. As shown in Figure 1, the binding of protons with the hydroxyl group of the aryl-palladium(II)-hydrogen complex possibly contributed to the cleavage of the Pd-OH chemical bond in the complex, leading to the hydrogenation of aryl-palladium(II) intermediate.

We explored the optimum reaction conditions for the debenzylation reaction. When the proportion of the acetic acid increased from 0.1% to 0.5%, the time required for the completion of reaction decreased from more than 20 h to less than 4 h. However, further greatly increased amount of acid in the reaction system led to the generation of new spots on the baseline of the TLC plate and also a decrease in the yield. The reason should be ascribed to the possible demethylation of the substrate in acidic conditions. In the acid-facilitated debenzylation reactions, the quantity of $Pd(OH)_2/C$ (20%), was set at 80 mg per 10 mmol of the substrate, and a $2 \sim 10$ gram scale hydrogenation got completed within 4 h at room temperature under hydrogen atmosphere of 1 atm.

The debenzylation as a heterogeneous catalytic reaction was the key step for the scalable synthesis of the target compound **1**. Meanwhile, the scale-up synthesis had also been considered as one of the most important factors in heterogeneous catalysis.

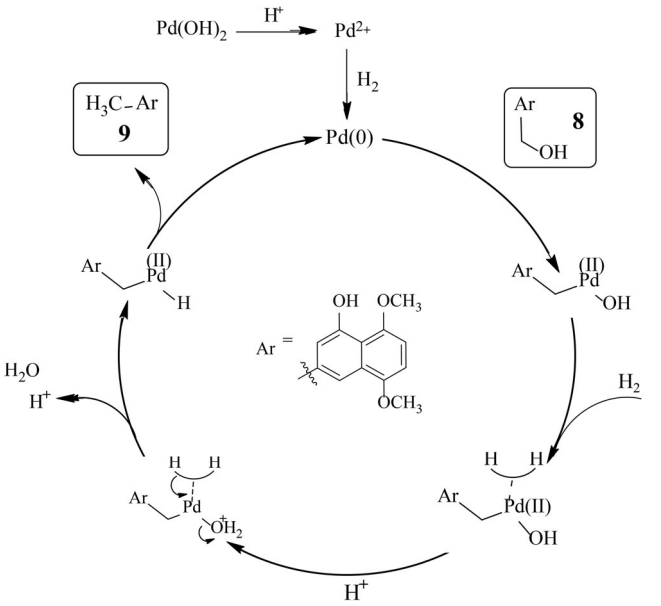


Figure 1. The plausible mechanism for acid-promoted debenzylation reaction.

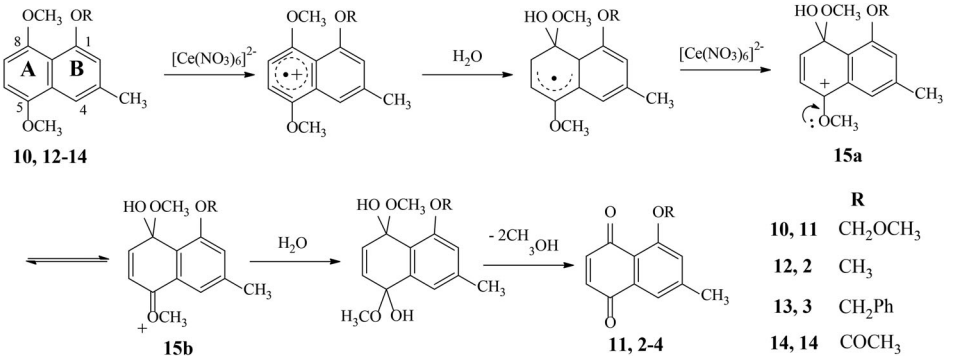


Figure 2. The plausible mechanism for CAN-mediated oxidative demethylation.

Therefore, we performed the large laboratory-scale synthesis of **9** (supplementary material). The substrate **8** (250 gram scale) could be successfully hydrogenated under hydrogen atmosphere (1 atm) within 4 h at 45 °C, with the stiochiequivalent conversion to the dehydroxylated product **9**.

In CAN-mediated oxidative demethylation, **B**-ring oxidation was not observed and the regioselective oxidative demethylation should be ascribed to the presence of the methoxy group on C(5) of **A**-ring. CAN was a single-electron oxidant and the electron-transfer oxidation proceeded *via* the formation of aryl radicals (Jacob III et al. 1976; Tanoue and Terada 1988; Nair and Deepthi 2007). The C(5) methoxy group as an electron-donating group, greatly enriched the electron density of **A**-ring, leading to an increase in chemical reactivity of the aromatic ring. Meanwhile, the lone pair electrons belonging to the oxygen atom contributed to the stabilization of the cation ions (**15a**) through a chemical equilibrium (Figure 2).

3. Experimental

Experimental section (experimental procedures, ^{1}H NMR, ^{13}C NMR and HRMS) is available in supplementary material.

4. Conclusions

Resting on Stobbe condensation of 2,5-dimethoxy benzaldehyde (**5**) with diethyl succinate, an intramolecular cyclization, reduction, acid-facilitated debenzylation and further CAN-mediated oxidation, a convenient synthesis of 7-methyl juglone was established with high overall yield (36.6%, 7 steps). Compared with the reported methods, there were several advantages in the new synthetic strategy. Firstly, the overall yield was much higher. Secondly, the reaction conditions were milder and suitable for the large scale preparations. Thirdly, the starting materials were easy to obtain. It has great implications for the design and synthesis of structurally asymmetric naphthoquinone derivatives.

Disclosure statement

No potential conflict of interest was reported by the authors.

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