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# Studies on the oxidative cyclization of 3-hydroxyalkyl-1,2,4-trialkoxynaphthalenes and synthetic application for the biologically active natural compound rhinacanthone

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ABSTRACT

The oxidative intramolecular cyclization of 3-hydroxyalkyl-1,2,4-trimethoxynaphthalenes was investigated. A series of 1,2-naphthoquinone fused cyclic ethers were synthesized directly from 3-hydroxyalkyl-1,2,4-trimethoxynaphthalenes by exposure to diammonium cerium (IV) nitrate. To understand the reaction mechanism, the intramolecular cyclization of 3-hydroxyalkyl-naphthoquinones that were formed as reaction intermediates was also examined. The results suggested that the reaction proceeds by a stepwise oxidation–cyclization mechanism. Using this methodology, five-step synthesis of rhinacanthone was achieved with high yield.



## 1. Introduction

We previously reported that CAN (diammonium cerium (IV) nitrate) oxidation of 3-hydroxyalkyl-1,2,4-trialkoxynaphthalene derivative (**1**) regarded as the reduced 2-hydroxy-1,4-naphthoquinone (lawsone) equivalent afforded (*R*)-(−)-dehydroiso-β-lapachone (**4**) in high yield.[1] Initially, we considered that the CAN oxidation would give a mixture of **2**, **3**, **4**, and **5**. Contrary to expectation, **2** and **3** were not obtained, but (*R*)-(−)-dehydroiso-β-lapachone (**4**) was obtained with a small amount of **5** (Fig. 1).

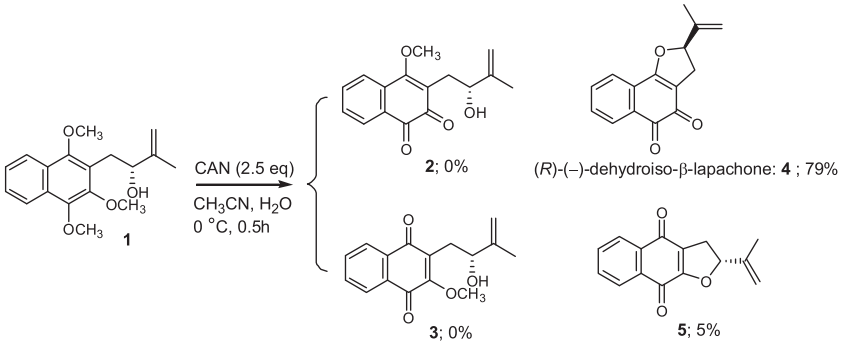


**Fig. 1.** Previous study of the synthesis of (−)-dehydroiso-β-lapachone.[1]

This interesting result prompted us to continue development of the new method to synthesize 1,2-naphthoquinones containing cyclic ether functions by CAN oxidation of the naphthalene

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derivatives having the hydroxyl group at side chains and accompanying intramolecular cyclization. In this study, four 3-hydroxyalkyl-1,2,4-trimethoxynaphthalenes (**8**, **9**, **11**, and **13**), which have a hydroxyl group at the end of each alkyl side chain, were prepared as substrates and subjected to CAN oxidation (Fig. 2). The brief consideration of the reaction mechanism of this oxidation including intramolecular cyclization is also described. We applied this method to the convenient synthesis of the biologically active natural product rhinacanthone.

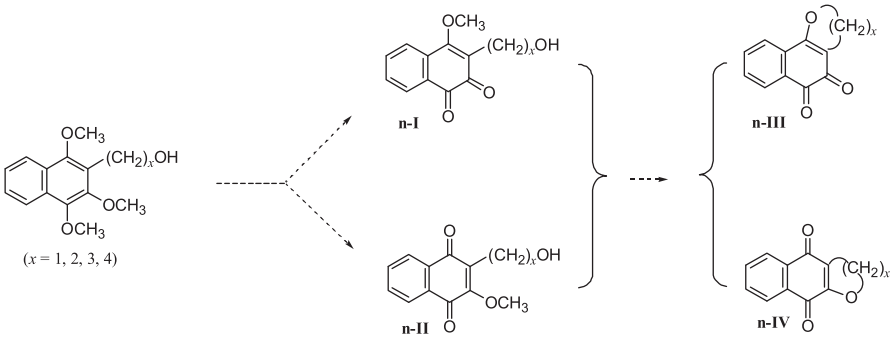


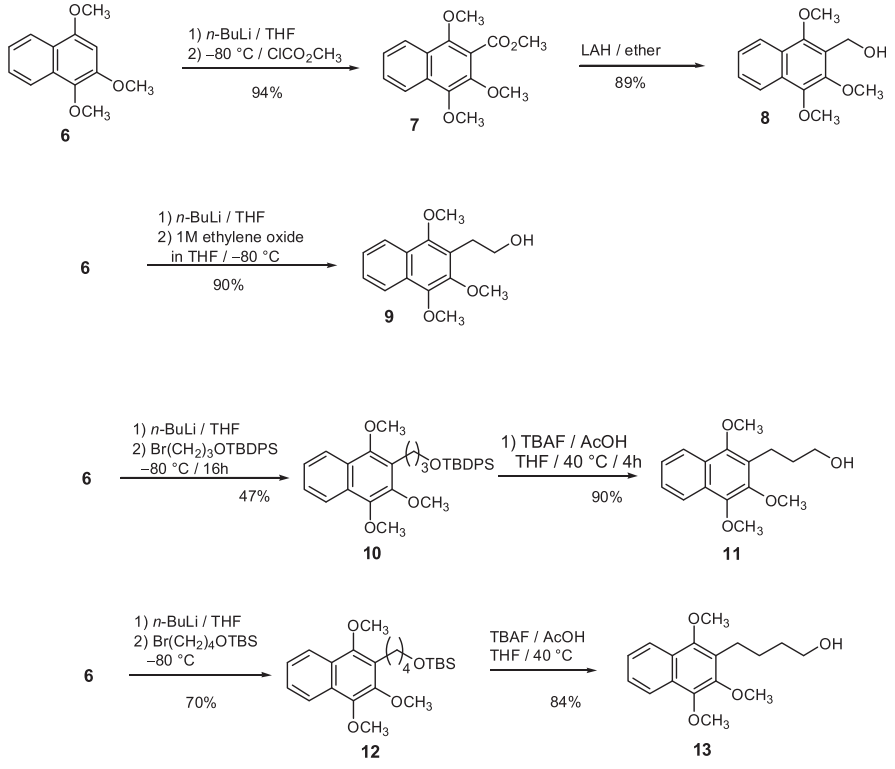

**Fig. 2.** Development of the synthesis of novel oxidative naphthoquinones linked by intramolecular ether bond formation (this study).

## 2. Results and discussion

Initial study began with the synthesis of compounds **8**, **9**, **11**, and **13** from 1,2,4-trimethoxynaphthalene (**6**). According to the known procedure, directed ortho lithiation–substitution reaction of **6** and subsequent quenching with suitable electrophiles afforded the corresponding 3-substituted-1,2,4-trimethoxynaphthalenes (**7**, **9**, **10**, and **12**).[2] Compound **9** was directly used as the starting substrate. Ester **7** was converted to **8** by lithium aluminum hydride ($LiAlH_4$) reduction. The silyl ethers **10** and **12** were treated with acidic tetrabutylammonium fluoride (TBAF) to lead to **11** and **13**, respectively. The spectroscopic data of all derived compounds (**8**, **9**, **11** and **13**) supported their chemical structures (Scheme 1) (For details, see the Experimental procedures).

We carried out CAN oxidation of naphthalenes (**8**, **9**, **11**, and **13**) according to our reported procedure.[1] Acetonitrile solution of each compound was stirred at 0 °C with aqueous CAN solution. The reaction mixture was worked up and purified to give the corresponding products in pure form. The structures of the compounds have been elucidated by spectroscopic analyses. The results summarized in Table 1 showed that we obtained two sets of isomers. One of them was a pair of naphthoquinones having hydroxyalkyl side chains, such as *n*-**I** and *n*-**II** (*n*=**14**–**17**), and the other was a pair of naphthoquinones, such as *n*-**III** and *n*-**IV**, (*n*=**14**–**17**) containing the fused cyclic ether function.

CAN oxidation of naphthalene derivative **8** afforded equal amounts of **14-I** and **14-II**, but did not afford four-membered ring compounds, such as **14-III** and **14-IV** (entry 1). Oxidation of **9** and **11** mainly afforded naphthoquinones **15-III** and **16-III** with small amounts of **15-IV** and **16-IV**, respectively (entries 2 and 3). On the other hand, from these same entries, *n*-**I** and *n*-**II** (*n*=**15** and **16**)




**Scheme 1.** Synthesis of four 3-hydroxyalkyl-1,2,4-trimethoxynaphthalenes (**8**, **9**, **11**, and **13**).