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# Unusual, chemoselective etherification of 2-hydroxy-1,4-naphthoquinone derivatives utilizing alkoxymethyl chlorides: scope, mechanism and application to the synthesis of biologically active natural product (±)-lantalucratin C

Tokutaro Ogata *, †, Tomoyo Yoshida, Maki Shimizu, Manami Tanaka, Chie Fukuhara, Junko Ishii, Arisa Nishiuchi, Kiyofumi Inamoto, Tetsutaro Kimachi *

*School of Pharmacy and Pharmaceutical Sciences, Mukogawa Women's University, 11-68 Koshien Kyu-bancho, Nishinomiya, 663-8179, Hyogo, Japan*

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ABSTRACT

A novel etherification of 2-hydroxy-1,4-naphthoquinone derivatives with alkoxyalkyl chlorides and hydride bases is described. Precise study of the conditions and substrate scope suggested that the reaction occurs specifically in the molecule having a 2-hydroxy-1,4-benzoquinone skeleton. A chemoselective O-methylation reaction was achieved to afford a synthetically important intermediate, which offered easy access to a natural product possessing *anti*-tumor activity.



## 1. Introduction

A large number of biologically active compounds containing the 1,4-naphthoquinone skeleton have been found over the past century.[1] Among the 1,4-naphthoquinone derivatives, 2-hydroxy-1,4-naphthoquinone (**1a**: lawsone) has been used as a dye for coloring hair and skin since ancient times. Today, **1a** and its analogs are recognized as synthetically valuable building blocks for synthesizing dyes,[2] agrochemicals[3] and drugs.[4] From the viewpoint of drug discovery, **1a** is an interesting pharmacophore due to its redox potential at the quinone moiety.

Over the past few years, our research interest has been directed toward the synthesis of naturally occurring naphthoquinones possessing biological activities such as *anti*-tumor activity.[5] These compounds are accessible from 2-hydroxy-1,4-naphthoquinones as a common synthon (Fig. 1). Recently, we found that the reaction of **1a** with chloromethyl methyl ether (MOMCl) and NaH leads an unusual etherification reaction giving methyl ether **3a** (Scheme 1).[6]

**1a** was treated with excess of MOMCl and NaH to give methyl ether **3a** in 59% yield along with methoxymethyl ether **2a** (34%). Although MOMCl is frequently used to protect alcohol groups in synthetic organic chemistry, to the best of our knowledge, there is no example of its use for the production of *O*-methyl ether using the MOMCl/NaH reagent system. This extraordinary phenomenon prompted us to continue our study of it. Here we describe a full detail of the study in the reaction scope, limitations, mechanism and application of this phenomenon to the synthesis of biologically active natural product (±)-lantalucratin C.

## 2. Results and discussion

Our study began with a thorough investigation of the reaction conditions as summarized in Table 1. First, **1a** was treated with excess amounts of NaH and MOMCl in DMF at rt, which is a common OH protection method. The unusual O-methylation proceeded, and methyl ether **3a** was obtained in moderate yield (Table 1, entry 1). However, reproducibility was poor. Therefore, we tried the reaction under various conditions and found that the water

* Corresponding authors. E-mail addresses: t-ogata@hokuriku-u.ac.jp (T. Ogata), tkimachi@mukogawa-u.ac.jp (T. Kimachi).
† Present address: Faculty of Pharmaceutical Sciences, Hokuriku University, Kanagawa-machi, Kanazawa, 920-1181, Ishikawa, Japan.

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0040-4020/

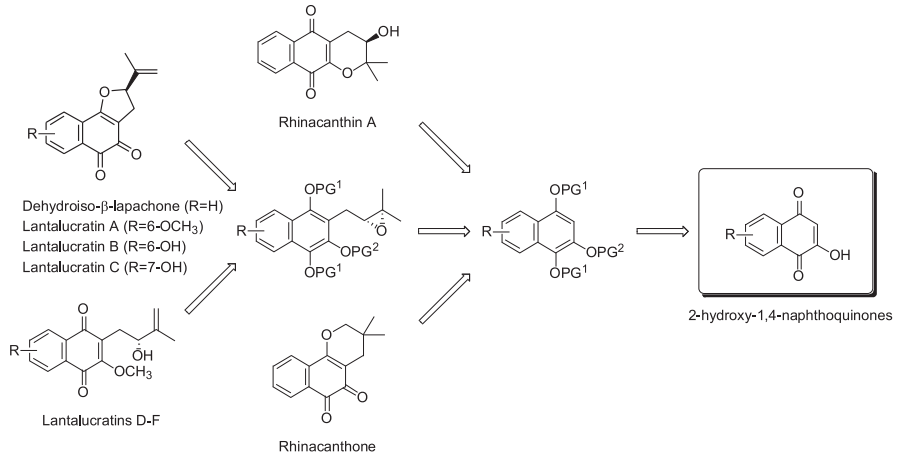
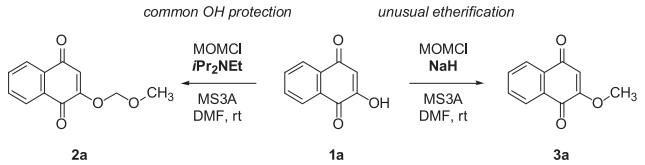



**Fig. 1.** 2-Hydroxy-1,4-naphthoquinones as useful synthetic building blocks toward various biologically active natural products.




**Scheme 1.** Unusual O-alkylation of 2-hydroxy-1,4-naphthoquinone with MOMCl and NaH.

content of the reaction mixture strongly affects the product yield. Without moisture control, the yield of **3a** decreased (Table 1, entry 1 vs 2). In addition, the formation of **3a** markedly decreased when the reaction was performed with a small volume of water (Table 1, entry 1 vs 3).

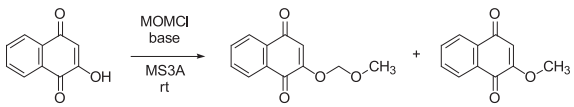
Finally, we found that using activated molecular sieves 3A gave reproducible results (Table 1, entry 4). Thus, further examinations were carried out with moisture control. Extended reaction time resulted in improvement of the yield of **3a** although excess reaction time caused a slight decrease (Table 1, entries 4 vs 5, 10 vs 12). Controlling the amount of reagent and concentration of the reaction solution was also effective for improving results. The product ratio of **3a** increased with use of a larger amount of base and MOMCl although excess use of these reagents caused a decrease (Table 1, entries 6–9). The selectivity could be completely regulated by using 1 or 3 equiv of the reagent against **1a** (Table 1, entries 6, 8 and 9). These results indirectly indicated that the rate of formation of **2a** was faster than that of **3a**, and the formation of **3a** went through the production of **2a**. Good selectivity of **3a** was observed at higher solution concentrations (Table 1, entries 10 and 11).

Various kinds of organic and inorganic bases were tested, and the results indicated that a base of appropriate basicity and molecular size is needed to obtain the methyl ether **3a** (Table 1, entries 13–19). Using a weaker base afforded **2a** in good to excellent yield with complete selectivity. This result implied that there is a deprotonation sequence during the transformation of **2a** into **3a** (see Scheme 2).

The choice of solvent also affected the ratio of the product. On examining polar aprotic solvents, we found that a solvent including an amide function was crucial for efficient production of **3a** (Table 1, entries 20–26). The absence of significant impurities such as methanol in MOMCl was confirmed by $^1$H NMR analysis.

In order to elucidate the route of the generation of methyl ether **3a**, the isolated compound **2a** or **3a** was treated using the NaH/MOMCl reagent system (Table 2). As expected, we found that **3a** was generated from **2a**, and this molecular conversion requires both NaH and MOMCl (Table 2, entries 1–4). Interestingly, the transformation of **3a** into **2a** did not proceed under anhydrous condition but did occur under wet condition, indicating that the water in the reaction may promote degradation by hydrolysis of **3a** (Table 2, entries7 and 8). On the other hand, the alkoxide is

**Table 1**
Scope of the reaction conditions[a]




| Entry | Base (equiv) | MOMCl (equiv) | Solvent (mol/L) | Time (h) | Product | |
|---|---|---|---|---|---|---|
| | | | | | **2a** (%) | **3a** (%) |
| 1[b] | NaH (2.0) | 3.0 | DMF (0.2) | 0.25 | 34 | 59 |
| 2[c] | NaH (2.0) | 3.0 | DMF (0.2) | 0.25 | 69 | 23 |
| 3[d] | NaH (2.0) | 3.0 | DMF (0.2) | 0.25 | 76 | 10 |
| 4 | NaH (2.0) | 3.0 | DMF (0.2) | 0.25 | 43 | 44 |
| 5 | NaH (2.0) | 3.0 | DMF (0.2) | 1 | 29 | 61 |
| 6 | NaH (1.0) | 1.0 | DMF (0.2) | 1 | 85 | 0 |
| 7 | NaH (2.0) | 2.0 | DMF (0.2) | 1 | 14 | 83 |
| 8 | NaH (3.0) | 3.0 | DMF (0.2) | 1 | 0 | 47 |
| 9 | NaH (3.0) | 2.0 | DMF (0.2) | 1 | 0 | 31 |
| 10 | NaH (2.0) | 2.0 | DMF (1.0) | 1 | 5 | 73 |
| 11 | NaH (2.0) | 2.0 | DMF (0.05) | 1 | 13 | 69 |
| 12 | NaH (2.0) | 2.0 | DMF (1.0) | 5 | Trace | 63 |
| 13 | LiH (2.0) | 2.0 | DMF (1.0) | 1 | 82 | 0 |
| 14 | KH (2.0) | 2.0 | DMF (1.0) | 1 | 20 | 40 |
| 15 | $K_2CO_3$ (2.0) | 2.0 | DMF (1.0) | 1 | 75 | 0 |
| 16 | $i$Pr$_2$NEt (2.0) | 2.0 | DMF (1.0) | 1 | 90 | 0 |
| 17 | KO$t$Bu (2.0) | 2.0 | DMF (1.0) | 1 | 50 | 10 |
| 18 | NaOMe (2.0) | 2.0 | DMF (1.0) | 2 | 64 | 0 |
| 19[e] | NaOH (2.0) | 2.0 | DMF (1.0) | 1 | Trace | 0 |
| 20 | NaH (2.0) | 2.0 | THF (1.0) | 1 | 24 | 0 |
| 21 | NaH (2.0) | 2.0 | MeCN (1.0) | 1 | 44 | 5 |
| 22 | NaH (2.0) | 2.0 | DMSO (1.0) | 1 | 53 | 13 |
| 23 | NaH (2.0) | 2.0 | NMP[f] (1.0) | 1 | 11 | 74 |
| 24 | NaH (2.0) | 2.0 | DMA[g] (1.0) | 1 | 2 | 80 |
| 25 | NaH (2.0) | 2.0 | TMU[h] (1.0) | 1 | 45 | 52 |
| 26 | NaH (2.0) | 2.0 | Pyridine (1.0) | 1 | Complex mixture | |

[a] The reaction was carried out using a flame-dried round bottom flask filled with argon gas. **1a** (2 mmol) and activated MS3A (500 mg) were stirred at rt.
[b] The reaction was conducted without MS3A.
[c] The reaction was carried out without moisture control.
[d] The reaction was carried out with addition of water (1 drop).
[e] Most of the **1a** was recovered.
[f] *N*-methyl pyrrolidone.
[g] *N*,*N*-dimethylacetamide.
[h] Tetramethylurea.

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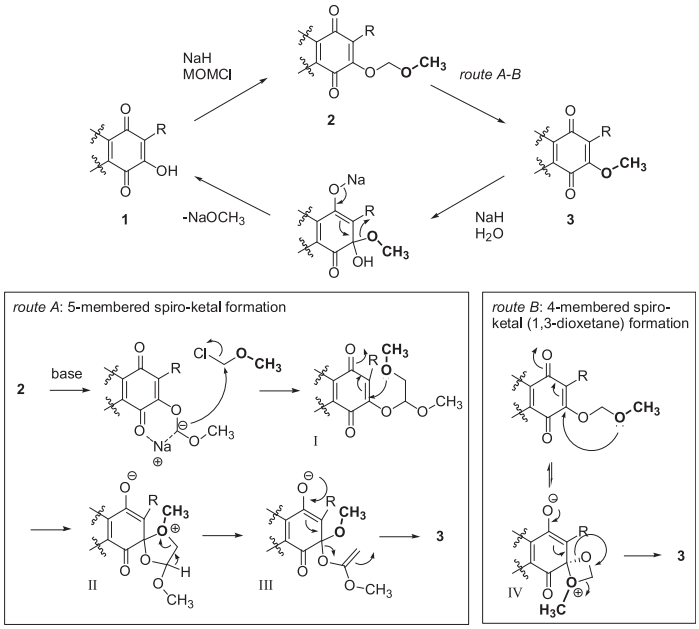



**Scheme 2.** Postulated reaction pathway for formation of **2** and **3**.

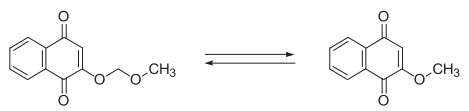
considered to be one of the degradation fragments at the MOM group and is thought to act as an *O*-nucleophile to yield **3a**. However, only a small amount of methyl ether **3a** was obtained using sodium methoxide as a base, and most of the **2a** was recovered (Table 2, entry 9). The radical reduction and/or radical chain reaction pathway is unlikely as the major route because the O-methylation was not inhibited in the presence of dibutylhydroxytoluene (BHT) as a free radical scavenger (Table 2, entry 6).

Instead of MOMCl, other alkoxyalkyl halides were used for the reaction of **1a** (Table 3). The reaction using benzyloxymethyl or ethoxymethyl chloride with NaH proceeded smoothly, and the corresponding alkyl ether **3b**–**c** was obtained together with alkoxymethyl ether **2b**–**c** (Table 3, entries 1 and 3). In both cases, **3a** was not obtained, strongly suggesting that the methyl group of **3a** did not originate from the methylene moiety of **2a** but from the terminal methyl moiety in the reaction of **1a** with NaH and MOMCl. On the other hand, extending one carbon at the methylene position caused no reaction even when the reaction was conducted at higher temperature over a longer period of time (Table 3, entry 4). Bromide also acted similarly to chloride, giving the corresponding ethers at different yields (Table 3, entry 5).

Some of the 2-hydroxy-1,4-naphthoquinones and related compounds were prepared and examined for the O-alkylation reactions to evaluate the substrate scope and limitations (Table 4). Methyl ethers (**3e**,**f**) were obtained from 2-hydroxy-1,4-naphthoquinones (**1e**,**f**), respectively, which contained substituent groups at the 3-position (Table 4, entries 1 and 2). These findings clearly showed that deprotonation at the 3-position by strong base and subsequent migration did not occur during the alkyl ether (**3**) formation. The O-alkylation reaction was also applicable for anthraquinone derivatives (Table 4, entry 3). Normal O-methoxymethylation occurred when cyclic or acyclic 1,3-diketone was used as a substrate, the alkyl ether was not obtained at all (Table 4, entries 4 and 5). As expected, only the normal O-methoxymethylation occurred in the case of 1-naphthol (Table 4, entry 6). The reaction of 2-amino-1,4-naphthoquinone with NaH and MOMCl afforded tertiary amine as the sole product (Table 4, entry 7). Interestingly, the reaction conducted using weaker LiH to repress the formation of tertiary amine led to accumulation of the secondary amine (Table 4, entry 8). The reaction of monocyclic compound **1m** with NaH and MOMCl provided the *O*-methylated product (Table 4, entry 9). These results indicated that the substrate involving the 2-hydroxy-1,4-benzoquinone skeleton is thought to be essential for the unusual O-alkylation reaction.[7] In other words, this reaction system can specifically and sensitively recognize the 2-hydroxy-1,4-benzoquinone structure. We hope that it can be used for the development of novel chemical sensors in the future.

Based on experimental results, the proposed reaction pathway is illustrated in Scheme 2. The transformation of compound **2**, which was obtained by simple $S_N2$ reaction from compound **1**, can be explained by two pathways. In route A, deprotonation at the methylene carbon by strong base such as NaH generates a six-membered chelate complex,[6] and this reacts with MOMCl to give intermediate I. The intramolecular *oxa*-Michael addition provides

**Table 2**
Molecular conversion between **2a** and **3a** in the presence of NaH and MOMCl[a]

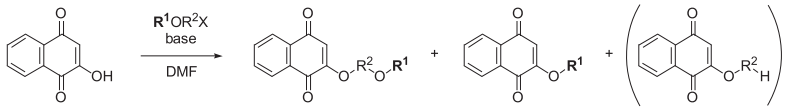


**2a** **3a**

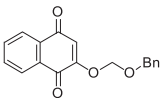
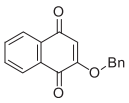
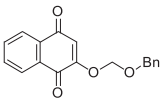
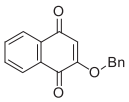
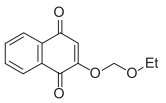
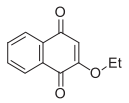
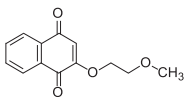
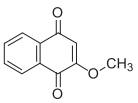
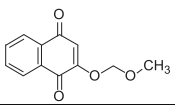
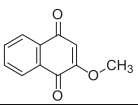
| Entry | Substrate | Base (equiv) | MOMCl (equiv) | Time (h) | Product (recovered) | |
|---|---|---|---|---|---|---|
| | | | | | **2a** (%) | **3a** (%) |
| 1 | **2a** | NaH (1.0) | 1.0 | 1 | 39 | 21 |
| 2 | **2a** | None | 1.0 | 1 | 91 | 0 |
| 3 | **2a** | NaH (1.0) | None | 1 | <26[b] | 0 |
| 4 | **2a** | None | None | 24 | Quant | 0 |
| 5[c] | **2a** | NaH (1.0) | 1.0 | 1 | 69 | 11 |
| 6[d] | **2a** | NaH (1.0) | 1.0 | 1 | 61 | 36 |
| 7 | **3a** | NaH (1.0) | 1.0 | 1 | 0 | 88 |
| 8[c] | **3a** | NaH (1.0) | 1.0 | 1 | 36 | 33 |
| 9 | **2a** | NaOMe (1.0) | 1.0 | 2 | 90 | 4 |

[a] The reaction was carried out using a flame-dried round bottom flask filled with argon gas. In this flask, 0.5 mmol of substrate (**2a** or **3a**), anhydrous DMF (0.5 mL) and activated MS3A (125 mg) were placed with stirring at rt.
[b] Unidentified compounds were also obtained.
[c] A drop of water was added to the reaction mixture.
[d] 0.6 mmol of BHT (dibutylhydroxytoluene) was added.

**Table 3**
Reaction of 1a with various alkoxyalkyl halides[a]




1a b: $R^1$=Bn, $R^2$=$CH_2$ c: $R^1$=Et, $R^2$=$CH_2$ d: $R^1$=$CH_3$, $R^2$=$CH_2CH_2$ 2b-d 3b-d 3a, 4d 0 %

| Entry | Base (equiv) | $R^1OR^2X$ (equiv) | Product **2b–d** | Yield (%) | Product **3b–d** | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | NaH (2.0) | $BnOCH_2Cl$ (2.0) |  | 44 |  | 53 |
| 2 | $K_2CO_3$ (1.5) | $BnOCH_2Cl$ (3.0) |  | Quant |  | 0 |
| 3 | NaH (2.0) | $EtOCH_2Cl$ (2.0) |  | 32 |  | 51 |
| 4[b] | NaH (2.0) | $CH_3OCH_2CH_2Cl$ (2.0) |  | 0[c] |  | 0 |
| 5 | NaH (2.0) | MOMBr (2.0) |  | 27 |  | 48 |

[a] The reaction was carried out using a flame-dried round bottom flask and filled with argon gas. **1a** (2 mmol), anhydrous DMF (2 mL) and activated MS3A (500 mg) were stirred at rt for 1 h.
[b] The reaction was carried out at 100 °C for 24 h.
[c] **1a** was recovered quantitatively.

a five-membered spiro-ketal II, and finally compound **3** is obtained by release of the methyl acetate from intermediate III. On the other hand, in route B, 1,3-dioxetane intermediate IV[8] is generated directly by *oxa*-Michael addition of **2**, and subsequent removal of formaldehyde gives **3**. From the results presented in Table 2, the transformation of **2** into **3** seems to require both NaH and MOMCl, which supports route A because those reagents are not included in the transformation in route B. The reverse reaction from **3** into **2** is considered to occur by the following processes. A Michael addition between sodium hydroxide, which is generated from NaH and water, and **3** occurs first, and subsequent elimination yields **1**. The formation of **2** occurs in the same way as explained above.

As part of our study on the application of the unusual O-alkylation reaction, we designed 2,7-dihydroxy-1,4-naphthoquinone (**1n**) in an attempt to realize a chemoselective O-methylation reaction (Table 5). As expected, the reaction of **1n** with NaH and MOMCl gave the desired product **6** but the selectivity and yield were not satisfactory. The reaction was accelerated when a large excess of the reagents was used to afford **6**, with some unidentified products (Table 5, entry 2). The concentration of the reaction solution strongly affected the ratio and yield of the product (Table 5, entries 1–4). Fortunately, the selectivity and yield of **6** dramatically improved when DMA was selected as the solvent (Table 5, entry 5). On the other hand, the reaction utilizing a weaker base gave compound **5** by the usual O-methoxymethylation (Table 5, entry 6). Thus, we were able to successfully demonstrate the chemoselective O-methylation, with compound **6** being obtained as the sole product in good yield.

Compound **6** is an important synthetic intermediate for the synthesis of biologically active natural products. As the last part of the study, we tried to synthesize (±)-lantalucratin C[9] (**12**) to demonstrate the utility of compound **6**. Recently, we reported the first example of stereoselective synthesis of *R*-(−)-lantalucratin C in 7% overall yield.[5e] We thought that the overall yield could be improved by using compound **6** although **12** would obtain as a racemic mixture. The actual synthetic route is summarized in Fig. 2. Compound **6** was first converted to tetra-substituted naphthalene **8** by reductive methylation, and the prenyl side chain was introduced by *ortho*-lithiation-alkylation reaction to afford **9**. The precursor **11** for cyclization was afforded by olefin epoxidation and subsequent epoxy-ring opening reaction in the presence of acid catalyst. The target compound was successfully obtained by diammonium cerium(IV) nitrate (CAN) oxidative cyclization followed by deprotection of the MOM group. Thus, the total synthesis of (±)-**12** was achieved in six steps from the known compound **1n** with 22% overall yield.

## 3. Conclusion

In summary, we have developed a novel etherification of 2-hydroxy-1,4-naphthoquinone derivatives with alkoxyalkyl chlorides and hydride bases. Precise study of the conditions and substrate scope suggested that the reaction occurred specifically in the

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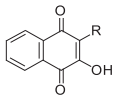
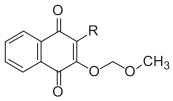
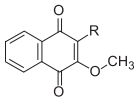
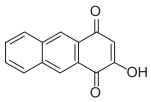
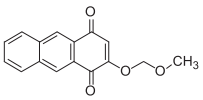
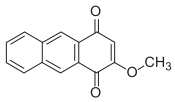
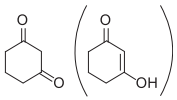
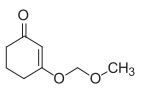
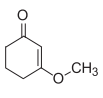
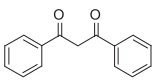
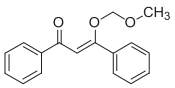
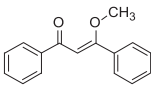
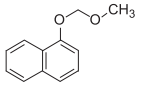
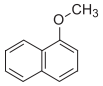
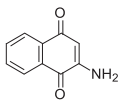
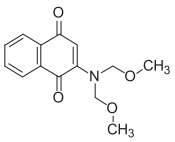
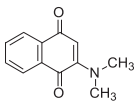
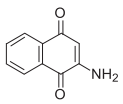
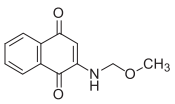
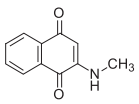
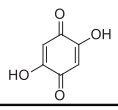
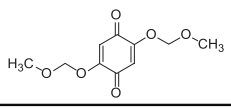
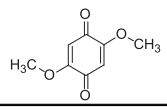
**Table 4**
Substrate scope[a]

| Entry | Substrate (1) | Product (2) | Yield (%) | Product (3) | Yield (%) |
|---|---|---|---|---|---|
| |  |  | |  | |
| 1 | e: R=$CH_3$ | | 65 | | 19 |
| 2 | f: R=Bn | | 51 | | 45 |
| 3 |  |  | 35 |  | 32 |
| 4 |  |  | 44 |  | 0 |
| 5 |  |  | 17 |  | 0 |
| 6 |  |  | Quant |  | 0 |
| 7 |  |  | 40 |  | 0 |
| 8[b] |  |  | 32 |  | 0 |
| 9 |  |  | 43 |  | 16 |

[a] The reaction was carried out using a flame-dried round bottom flask and filled with argon gas. **1a** (2.0 mmol), NaH (2 equiv), MOMCl (2 equiv) and activated MS3A (500 mg) were stirred at rt for 1 h.
[b] LiH was used instead of NaH.

molecule having a 2-hydroxy-1,4-benzoquinone skeleton. In addition, chemoselective O-methylation reaction was achieved to afford the synthetically important intermediate **6**. Use of **6** for the synthesis of **12** resulted in significant improvement of the overall yield. Further study of the applicability of this process is in progress.

## 4. Experimental

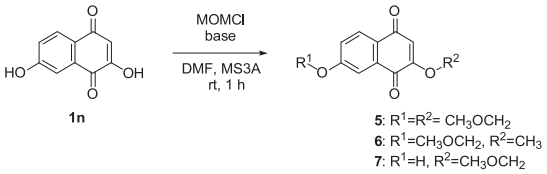
### 4.1. General

All materials not explicitly mentioned were purchased from Wako Pure Chemical Products Co., Kanto Chemical Co., TCI Laboratory Chemical Co., Nacalai Tesque Co. and Aldrich Chemical Co. Activated MS3A was prepared by heating to dryness under reduced pressure for a few hours. Activated $NaHSO_4 \cdot SiO_2$ was prepared by heating at 120 °C in a drying oven for 2 days. $^1H$ NMR (400 MHz) and $^{13}C$ NMR (100 MHz) were recorded on a JEOL JNM-ECP400 spectrometer. Chemical shift values were expressed in ppm relative to an internal reference of tetramethylsilane (0 ppm) in $^1H$ NMR and $CDCl_3$ (77.0 ppm) in $^{13}C$ NMR. Coupling constants are shown in Hertz. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; br, broad. IR spectra were recorded on an SHIMADZU IR Affinity-1. Mass spectra (MS) were obtained on JEOL JMS-700 instruments. Melting points were measured on a Yanaco micro melting point apparatus and are uncorrected. Flash chromatography was performed with silica gel (Wakosil C-200) obtained from Wako Pure Chemical Products Co. or Silica gel 60 N (spherical, neutral) obtained from Kanto Chemical Co. Analytical thin layer chromatography was performed on Merck Silica Gel 60 F254 aluminum sheets and the visualization was accompanied by UV lamp.

### 4.2. Typical procedure for O-alkylation of 2-hydroxy-1,4-naphthoquinones (example for the reaction in Table 1, entry 10)

To a flame-dried round bottom flask was added 2-hydroxy-1,4-naphthoquinone (348 mg, 2 mmol) and activated MS3A (500 mg) followed by filling with argon gas. Anhydrous DMF (2.0 mL) was added and the mixture was stirred at rt for 1 h to allow complete

**Table 5**
Reaction of 1n with NaH and MOMCl[a]




| Entry | Base (equiv) | MOMCl (equiv) | DMF (mol/L) | Product (isolated yield) | | |
|---|---|---|---|---|---|---|
| | | | | **5** (%) | **6** (%) | **7** (%) |
| 1 | NaH (3.0) | 3.0 | 1.0 | 6 | 36 | 6 |
| 2 | NaH (5.0) | 5.0 | 1.0 | 0 | 32 | 0 |
| 3 | NaH (3.0) | 3.0 | 0.2 | 59 | 23 | 9 |
| 4 | NaH (5.0) | 5.0 | 0.2 | 16 | 40 | Trace |
| 5 | NaH (5.0) | 5.0 | 0.2[b] | 0 | 69 | 0 |
| 6 | *i*Pr$_2$NEt (3.0) | 3.0 | 1.0 | 74 | 0 | 2 |

[a] The reaction was carried out using a flame-dried round bottom flask and filled with argon gas. **1n** (0.5 mmol) and activated MS3A (125 mg) were used.
[b] DMA was used instead of DMF.

absorption of the moisture. After stirring for 10 min by adding sodium hydride 60% dispersion in mineral oil (160 mg, 4 mmol) in one portion, methoxymethyl chloride (320 mg, 4 mmol) was added dropwise. The reaction mixture was warmed up to rt and stirred for 1 h. After complete consumption of the substrate confirmed by TLC analysis, the reaction mixture was poured onto ice water. The reaction mixture was diluted with ethyl acetate and the solution was filtered through a Celite® pad. The filtrate was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was successively washed with water (×3), brine (×1) and then dried over $Na_2SO_4$. Filtration and concentration under reduced pressure gave a dark brown crude oil, which was purified by flash column chromatography eluting with hexane and ethyl acetate in 5/1 to 1/1 ratio to obtain a mixture of **2a** and **3a** as a yellow solid. The product yield was calculated based on $^1$H NMR analysis results.

*4.2.1. 2-Methoxymethoxy-1,4-naphthoquinone (**2a**).*[10] $^1$H NMR ($CDCl_3$) $\delta$: 3.53 (3H, s, $OCH_3$), 5.30 (2H, s, $CH_2$), 6.47 (1H, s, CH), 7.69–7.77 (2H, m, Ar–H), 8.07–8.15 (2H, m, Ar–H).

*4.2.2. 2-Methoxy-1,4-naphthoquinone (**3a**).*[11] $^1$H NMR ($CDCl_3$) $\delta$: 3.91 (3H, s, $OCH_3$), 6.18 (1H, s, CH), 7.69–7.77 (2H, m, Ar–H), 8.08–8.15 (2H, m, Ar–H).

### 4.3. Alternative method for the synthesis of 3a

To a solution of lawsone (30 g, 172 mmol) in methanol (1 l) was added conc. HCl (100 mL), and the mixture was gently warmed with stirring until all of the substrate had completely dissolved. Stirring of the reaction mixture was continued at rt overnight. The resulting yellow suspension was cooled to 0 °C and yellow solid was collected by vacuum filtration. The filtrate was concentrated in vacuo and ethyl acetate was added to obtain a yellow suspension, and, which was collected by vacuum filtration. The obtained yellow solid was combined and dried by heating at 60 °C under reduced pressure for 2 days to obtain 26.4 g (82%) of yellow powder.

### 4.4. 2-Benzyloxymethoxy-1,4-naphthoquinone (2b)

A yellow solid of mp 98.2–98.8 °C. IR (KBr): 1678, 1655, 1613, 1593, 1578, 1499, 1331, 1262, 1231, 1196, 1167, 1107, 1082, 1034 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$: 4.76 (2H, s, $OCH_2$), 5.42 (2H, s, $OCH_2$), 6.53 (1H, s, CH), 7.27–7.36 (5H, m, Ph-H), 7.69–7.77 (2H, m, Ar–H), 8.07–8.15 (2H, m, Ar–H). $^{13}$C NMR ($CDCl_3$) $\delta$: 71.4 ($CH_2$), 92.7 ($CH_2$), 113.4 (CH), 126.1 (CH), 126.6 (CH), 128.0 (CH), 128.2 (CH), 128.5 (CH), 131.1 (C), 131.9 (C), 133.3 (CH), 134.2 (CH), 136.2 (C), 157.9 (C), 180.2 (C), 184.9 (C). FABMS *m/z*: 295 ($M^+$+H). HRMS-FAB *m/z*: ($M^+$+H) calcd for $C_{18}H_{15}O_4$, 295.0970; found, 295.0970.

*4.4.1. 2-Benzyloxy-1,4-naphthoquinone (**3b**).*[12] $^1$H NMR ($CDCl_3$) $\delta$: 5.14 (2H, s, $OCH_2$), 6.23 (1H, s, CH), 7.35–7.45 (5H, m, Ph-H), 7.68–7.76 (2H, m, Ar–H), 8.06–8.15 (2H, m, Ar–H).

### 4.5. 2-Ethoxymethoxy-1,4-naphthoquinone (2c)

A yellow solid of mp 129.3–129.7 °C. IR (KBr): 1684, 1647, 1603, 1337, 1302, 1267, 1233, 1202, 1117 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$: 1.24 (3H, t, *J*=7.0, $CH_3$), 3.77 (2H, q, *J*=7.0, $CH_2$), 5.35 (2H, s, $OCH_2O$), 6.50 (1H, s, CH), 7.69–7.76 (2H, m, Ar–H), 8.06–8.13 (2H, m, Ar–H). $^{13}$C NMR ($CDCl_3$) $\delta$: 14.9 ($CH_3$), 65.7 ($CH_2$), 93.6 ($CH_2$), 113.2 (CH), 126.1 (CH), 126.6 (CH), 131.1 (C), 131.9 (C), 133.3 (CH), 134.2 (CH), 158.0 (C), 180.3 (C), 185.0 (C). EIMS *m/z*: 232 ($M^+$). HRMS-EI *m/z*: ($M^+$) calcd for $C_{13}H_{12}O_4$, 232.0736; found, 232.0735.

*4.5.1. 2-Ethoxy-1,4-naphthoquinone (**3c**).*[13] $^1$H NMR ($CDCl_3$) $\delta$: 1.24 (3H, t, *J*=7.0, $CH_3$), 3.77 (2H, q, *J*=7.0, $-OCH_2$), 6.15 (1H, s, CH), 7.68–7.75 (2H, m, Ar–H), 8.06–8.14 (2H, m, Ar–H).

### 4.6. Preparation of 2-hydroxy-3-methyl-1,4-naphthoquinone (1e)[14]

According to a literature procedure,[14] to an ice-cooled suspension of 3-methyl-1,4-naphthoquinone (757 mg, 4.4 mmol) in ethanol (3 mL) was added 30% $H_2O_2$ (1.5 mL), $Na_2CO_3$ (60 mg, 0.57 mmol) and water (0.6 mL). After stirring for 1.5 h at rt, water (20 mL) was added and then the reaction mixture was extracted with $CHCl_3$ (×3). The combined organic layer was dried over $Na_2SO_4$, filtered and concentrated in vacuo to give epoxide. To the epoxide was then added conc. $H_2SO_4$ (5 mL) and stirred for 1 h. The

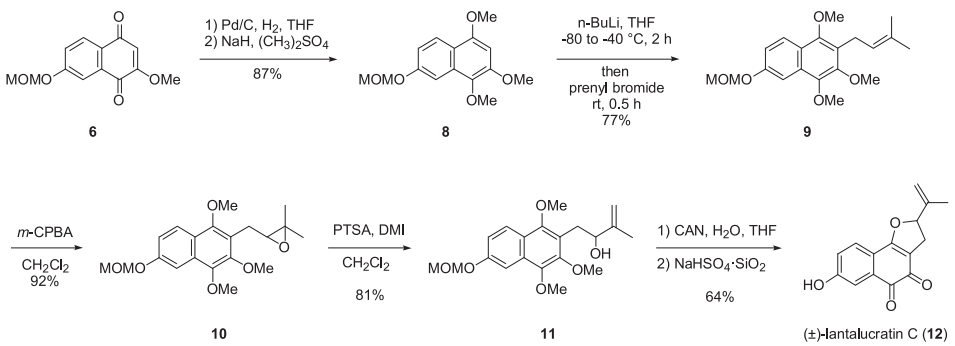



**Fig. 2.** Synthetic application of compound 6 toward the biologically active natural product (±)-lantalucratin C.

reaction mixture was carefully added to ice water, and the whole mixture was extracted with $CHCl_3$ (×3). The combined organic layer was dried over $Na_2SO_4$, filtered and concentrated in vacuo to give a crude product, which was purified by flash column chromatography by eluting with hexane and ethyl acetate in 2/1 ratio to yield 551 mg (67%) of the target product as a yellow solid. $^1$H NMR ($CDCl_3$) $\delta$: 2.11 (3H, s, $CH_3$), 7.28 (1H, s, OH), 7.66–7.77 (2H, m, Ar–H), 8.07–8.14 (2H, m, Ar–H).

### 4.7. 2-Methoxymethoxy-3-methyl-1,4-naphthoquinone (2e)

A yellow solid of mp 52.3–53.9 °C. IR (KBr): 1674, 1659, 1622, 1593, 1333, 1298, 1263, 1225, 1173, 1156, 1092, 1071 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$: 2.17 (3H, s, $CH_3$), 3.56 (3H, s, $OCH_3$), 5.45 (2H, s, $OCH_2$), 7.66–7.72 (2H, m, Ar–H), 8.03–8.10 (2H, m, Ar–H). $^{13}$C NMR ($CDCl_3$) $\delta$: 9.5 ($CH_3$), 57.5 ($CH_3$), 98.3 ($CH_2$), 126.2 (CH), 126.3 (CH), 131.4 (C), 132.1 (C), 133.1 (C), 133.3 (CH), 133.8 (CH), 155.5 (C), 181.2 (C), 185.5 (C). EIMS *m/z*: 232 ($M^+$). HRMS-EI *m/z*: ($M^+$) calcd for $C_{13}H_{12}O_4$, 232.0736; found, 232.0734.

*4.7.1. 2-Methoxy-3-methyl-1,4-naphthoquinone (**3e**).*[15] $^1$H NMR ($CDCl_3$) $\delta$: 2.11 (3H, s, $CH_3$), 4.12 (3H, s, $OCH_3$), 7.68–7.70 (2H, m, Ar–H), 8.04–8.08 (2H, m, Ar–H).

### 4.8. Preparation of 2-benzyl-3-hydroxy-1,4-naphthoquinone (1f)[16]

According to a literature procedure,[16] a mixture of lawsone (348 mg, 2 mmol) and potassium carbonate (312 mg, 2.26 mmol) in anhydrous DMF (10 mL) was stirred at rt for 15 min under argon gas atmosphere. The resulting red suspension was combined with potassium iodide (349 mg, 2.1 mmol), and then benzyl bromide (360 mg, 2.1 mmol) in anhydrous DMF (2 mL) was added dropwise. The mixture was heated to 150 °C and stirred for 2 h. The reaction mixture was cooled to rt, and then poured into ice water. The resulting dark reddish violet solution was washed with hexane (×1), and the aqueous layer was acidified with 10% HCl to become a yellow suspension, which was extracted with ethyl acetate (×2). The organic layer was dried over $Na_2SO_4$, filtered and concentrated in vacuo gave a yellow crude solid, which was purified by flash column chromatography eluting with hexane and ethyl acetate in 5/1 ratio to obtain 228 mg, 43% yield of the target compound as a yellow solid. $^1$H NMR ($CDCl_3$) $\delta$: 3.95 (2H, s, $CH_2$), 7.14–7.27 (2H, m, Ph–H), 7.36–7.39 (3H, m, Ph–H), 7.64–7.76 (2H, m, Ar–H), 8.05–8.13 (2H, m, Ar–H).

### 4.9. 2-Benzyl-3-methoxymethoxy-1,4-naphthoquinone (2f)

A yellow solid of mp 90.5–90.9 °C. IR (KBr): 1663, 1601, 1491, 1445, 1335, 1300, 1217, 1169, 1032 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$: 3.49 (3H, s, $OCH_3$), 4.02 (2H, s, $CH_2$), 5.52 (2H, s, $OCH_2$), 7.14–7.27 (3H, m, Ph–H), 7.35 (2H, d, *J*=7.3, Ph–H), 7.66–7.71 (2H, m, Ar–H), 8.03–8.07 (2H, m, Ar–H). $^{13}$C NMR ($CDCl_3$) $\delta$: 29.6 ($CH_2$), 57.7 ($CH_3$), 98.6 ($CH_2$), 126.26 (CH), 126.30 (CH), 126.4 (CH), 128.4 (CH), 129.1 (CH), 131.4 (C), 131.9 (C), 133.3 (CH), 133.9 (CH), 134.4 (C), 138.8 (C), 155.5 (C), 181.8 (C), 184.9 (C). EIMS *m/z*: 308 ($M^+$). HRMS-EI *m/z*: ($M^+$) calcd for $C_{19}H_{16}O_4$, 308.1049; found, 308.1041.

*4.9.1. 2-Benzyl-3-methoxy-1,4-naphthoquinone (**3f**).*[17] $^1$H NMR ($CDCl_3$) $\delta$: 3.94 (2H, s, $CH_2$), 4.13 (3H, s, $OCH_3$), 7.14–7.34 (5H, m, Ph–H), 7.63–7.71 (2H, m, Ar–H), 8.02–8.08 (2H, m, Ar–H).

### 4.10. Preparation of 2-hydroxyanthracene-1,4-dione (1g)[18]

The reaction was performed in the same manner as shown above (preparation of **1e**). $^1$H NMR (DMSO-$d_6$) $\delta$: 5.59 (1H, s), 7.58–7.66 (2H, m), 8.08–8.14 (2H, m), 8.36 (1H, s), 8.41 (1H, s).

*4.10.1. 2-Methoxymethoxyanthracene-1,4-dione (**2g**).* A yellow solid of mp 144.3–145.6 °C. IR (KBr): 1680, 1649, 1613, 1601, 1458, 1289, 1242, 1155, 1061 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$: 3.56 (3H, s, $OCH_3$), 5.34 (2H, s, $OCH_2$), 6.58 (1H, s, Ar–H), 7.64–7.70 (2H, m, Ar–H), 8.03–8.06 (2H, m, Ar–H), 8.58 (1H, s, Ar–H), 8.66 (1H, s, Ar–H). $^{13}$C NMR ($CDCl_3$) $\delta$: 57.2 ($CH_3$), 94.9 ($CH_2$), 114.9 (CH), 127.8 (C), 128.2 (CH), 128.3 (C), 129.29 (CH), 129.32 (CH), 129.7 (CH), 130.1 (CH), 130.2 (CH), 134.6 (C), 135.1 (C), 159.1 (C), 179.9 (C), 184.6 (C). EIMS *m/z*: 268 ($M^+$). HRMS-EI *m/z*: ($M^+$) calcd for $C_{16}H_{12}O_4$, 268.0736; found, 268.0732.

### 4.11. 2-Methoxyanthracene-1,4-dione (3g)[19]

$^1$H NMR ($CDCl_3$) $\delta$: 3.94 (3H, s, $OCH_3$), 6.29 (1H, s, Ar–H), 7.64–7.71 (2H, m, Ar–H), 8.04–8.06 (2H, m, Ar–H), 8.60 (1H, s, Ar–H), 8.68 (1H, s, Ar–H).

### 4.12. 3-Methoxymethoxycyclohex-2-enone (2h)[20]

$^1$H NMR ($CDCl_3$) $\delta$: 2.00 (2H, quint, *J*=6.2, $CH_2$), 2.35 (2H, t, *J*=6.2, $CH_2$), 2.43 (2H, t, *J*=6.2, $CH_2$), 3.47 (3H, s, $OCH_3$), 5.06 (2H, s, $OCH_2$), 5.49 (1H, s, CH).

### 4.13. 3-Methoxymethoxy-1,3-diphenylpropenone (2i)

As a pale yellow oil. IR (neat): 1651, 1591, 1564, 1491, 1449, 1408, 1354, 1302, 1271, 1213, 1157, 1069, 1003 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$: 3.53 (3H, s, $OCH_3$), 5.19 (2H, s, $OCH_2$), 6.63 (1H, s, CH), 7.41–7.56 (6H, m, Ar–H), 7.71–7.73 (2H, m, Ar–H), 7.97 (2H, d, *J*=7.3, Ar–H). $^{13}$C NMR ($CDCl_3$) $\delta$: 57.6 ($CH_3$), 99.1 ($CH_2$), 105.0 (CH), 127.6 (CH), 128.2 (CH), 128.4 (CH), 128.6 (CH), 130.7 (CH), 132.4 (CH), 135.4 (C), 139.3 (C), 165.6 (C), 189.2 (C). EIMS *m/z*: 268 ($M^+$). HRMS-EI *m/z*: ($M^+$) calcd for $C_{17}H_{16}O_3$, 268.1099; found, 268.1099.

### 4.14. 1-Methoxymethoxynaphthalene (2j)[21]

$^1$H NMR ($CDCl_3$) $\delta$: 3.55 (3H, s, $OCH_3$), 5.39 (2H, s, $OCH_2$), 7.09 (1H, d, *J*=7.7, Ar–H), 7.37 (1H, t, *J*=7.7, Ar–H), 7.47–7.49 (3H, m, Ar–H), 7.79–7.82 (1H, m, Ar–H), 8.26–8.28 (1H, m, Ar–H).

### 4.15. Preparation of 2-amino-1,4-naphthoquinone (1k)[22]

According to a literature procedure,[22a] to a solution of 1,4-naphthoquinone (2.5 g, 15.8 mmol) in glacial acetic acid (25 mL) was added sodium azide (1.7 g, 26.2 mmol) in water (5 mL) dropwise at 40 °C, and then stirred for 1.5 h at the same temperature. The reaction was quenched with large volume of water, and basified with satd aqueous sodium bicarbonate. The reaction mixture was extracted with ethyl acetate (×2), and the organic layer was dried over $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography eluting with hexane and ethyl acetate in 10/1 ratio to obtain 1.14 g, 42% of the target compound as an orange solid. $^1$H NMR ($CDCl_3$) $\delta$: 5.12 (2H, br-s, $NH_2$), 6.00 (1H, s, CH), 7.63 (1H, ddd, *J*=1.5, 7.3, 7.7, Ar–H), 7.72 (1H, ddd, *J*=1.5, 7.3, 7.7, Ar–H), 8.05–8.09 (2H, m, Ar–H).

### 4.16. 2-(Bismethoxymethylamino)-1,4-naphthoquinone (2k)

As a dark brown oil. IR ($CHCl_3$): 1676, 1640, 1595, 1568, 1470, 1397, 1331, 1302, 1260, 1217, 1119, 1076 cm$^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$: 3.38 (6H, s, 2×$OCH_3$), 4.89 (4H, s, 2×$CH_2$), 6.42 (1H, s, CH), 7.64–7.72 (2H, m, Ar–H), 8.02–8.04 (2H, m, Ar–H). $^{13}$C NMR ($CDCl_3$) $\delta$: 55.8 ($CH_3$), 82.6 ($CH_2$), 114.7 (CH), 125.5 (CH), 126.7 (CH), 131.9 (C), 132.6

(CH), 132.7 (C), 133.8 (CH), 150.6 (C), 182.7 (C), 184.3 (C). FABMS *m/z*: 262 ($M^+$+H). HRMS-FAB *m/z*: ($M^+$+H) calcd for $C_{14}H_{16}NO_4$, 262.1079; found, 262.1079.

### 4.17. 2-(Methoxymethylamino)-1,4-naphthoquinone (2l)[23]

$^1$H NMR ($CDCl_3$) $\delta$: 3.35 (3H, s, $OCH_3$), 4.70 (2H, d, $J$=6.6, $CH_2$), 6.09 (1H, s, CH), 6.46 (1H, br-s, NH), 7.64 (1H, ddd, $J$=1.5, 7.3, 7.7, Ar−H), 7.73 (1H, ddd, $J$=1.5, 7.3, 7.7, Ar−H), 8.06 (1H, dd, $J$=1.5, 7.7, Ar−H), 8.09 (1H, dd, $J$=1.5, 7.7, Ar−H). $^{13}$C NMR ($CDCl_3$) $\delta$: 55.4 ($CH_3$), 74.6 ($CH_2$), 104.6 (CH), 126.20 (CH), 126.24 (CH), 130.5 (C), 132.3 (CH), 133.1 (C), 134.7 (CH), 147.3 (C), 181.7 (C), 183.5 (C).

### 4.18. 2,5-Bismethoxymethoxy-1,4-benzoquinone (2m)

As a yellow solid of mp 160.4−160.9 °C. IR (KBr): 3447, 3071, 2969, 2949, 2914, 1668, 1595, 1364, 1221, 1186, 1150, 1090 $cm^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$: 3.49 (6H, s, 2×$OCH_3$), 5.23 (4H, s, 2×$OCH_2$), 6.17 (2H, s, CH). $^{13}$C NMR ($CDCl_3$) $\delta$: 57.2 ($CH_3$), 95.0 ($CH_2$), 109.0 (CH), 156.5 (C), 182.1 (C). EIMS *m/z*: 228 ($M^+$). HRMS-EI *m/z*: ($M^+$) calcd for $C_{10}H_{12}O_6$, 228.0634; found, 228.0627.

### 4.19. 2,5-Dimethoxy-1,4-benzoquinone (3m)[24]

$^1$H NMR ($CDCl_3$) $\delta$: 3.84 (6H, s, 2×$OCH_3$), 5.87 (2H, s, Ar−H).

### 4.20. Preparation of 2,7-dihydroxy-1,4-naphthoquinone (1n)[25]

According to the literature procedure,[24] a solution of potassium *tert*-butoxide (8.8 g, 78 mmol) in *tert*-butanol (88 mL) was vigorously stirred for 1 h in a flask equipped with an $O_2$ gas balloon. To the reaction mixture was added 7-methoxy-1-tetralone (1.76 g, 10 mmol), and stirring was continued at rt overnight. The resulting red color suspension was poured into ice water, and then acidified with 1M HCl to form a yellow solid, which was collected by vacuum filtration. The filtrate was extracted with chloroform (×3), and the organic layer and the yellow solid were combined and basified with 1M NaOH to form a red solution. The red aqueous layer was washed with chloroform (×2), and separated aqueous layer was acidified with conc. HCl to form a yellow solid again, which was collected by vacuum filtration. After completely drying the solid at 80 °C under reduced pressure, 1.57 g, 76% of 2-hydroxy-7-methoxy-1,4-naphthoquinone was obtained as a yellow solid. A 100 mL of Erlenmeyer flask was charged with finely grounded anhydrous aluminum trichloride (6.2 g, 46.6 mmol) and sodium chloride (1.45 g, 25 mmol), and heated to 180 °C (oil bath temp) until these solids melted completely. A fine powder of 2-hydroxy-7-methoxy-1,4-naphthoquinone was added to the flask, and heating was continued for 15 min at the same temperature. After cooling to about 100 °C, conc. HCl in crushed ice (40 mL) was carefully added to the flask, and the mixture was filtered through a Celite® pad to remove insoluble black materials. The filtrate was extracted with ether (×3), and the rest of the target compound was extracted by Soxhlet extraction using ether from the insoluble materials. The combined organic extracts were dried over $Na_2SO_4$, filtered and concentrated to obtain a yellow solid, which was then completely dried at 60 °C under reduced pressure to furnish the target compound 930 mg in 98% yield. $^1$H NMR (DMSO-$d_6$) $\delta$: 6.04 (1H, s, CH), 7.14 (1H, dd, $J$=2.6, 8.4, Ar−H), 7.31 (1H, d, $J$=2.6, Ar−H), 7.80 (1H, d, $J$=8.4, Ar−H), 10.7 (1H, br-s, OH).

### 4.21. 2,7-Bismethoxymethoxy-1,4-naphthoquinone (5)

As a yellow solid of mp 106.6−108.2 °C. IR (KBr): 1684, 1645, 1613, 1597, 1491, 1348, 1317, 1304, 1271, 1236, 1200, 1165, 1090 $cm^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$: 3.50 (3H, s, $OCH_3$), 3.52 (3H, s, $OCH_3$), 5.28 (2H, s, $OCH_2$), 5.29 (2H, s, $OCH_2$), 6.41 (1H, s, CH), 7.33 (1H, dd, $J$=2.6, 8.4, Ar−H), 7.71 (1H, d, $J$=2.6, Ar−H), 8.02 (1H, d, $J$=8.4, Ar−H). $^{13}$C NMR ($CDCl_3$) $\delta$: 56.4 ($CH_3$), 57.1 ($CH_3$), 94.2 ($CH_2$), 94.8 ($CH_2$), 113.0 (CH), 113.2 (CH), 121.8 (CH), 126.1 (C), 128.5 (CH), 132.9 (CH), 157.7 (C), 161.3 (C), 180.1 (C), 184.3 (C). EIMS *m/z*: 278 ($M^+$). HRMS-EI *m/z*: ($M^+$) calcd for $C_{14}H_{14}O_6$, 278.0790; found, 278.0787.

### 4.22. 2-Methoxy-7-methoxymethoxy-1,4-naphthoquinone (6)

As a yellow solid of mp 137.0−137.5 °C. IR (KBr): 1682, 1647, 1601, 1489, 1441, 1350, 1304, 1275, 1246, 1206, 1167, 1084, 1038 $cm^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$: 3.50 (3H, s, $OCH_3$), 3.89 (3H, s, $OCH_3$), 5.29 (2H, s, $OCH_2$), 6.11 (1H, s, CH), 7.33 (1H, dd, $J$=2.6, 8.4, Ar−H), 7.71 (1H, d, $J$=2.6, Ar−H), 8.03 (1H, d, $J$=8.4, Ar−H). $^{13}$C NMR ($CDCl_3$) $\delta$: 56.3 ($CH_3$), 56.4 ($CH_3$), 94.3 ($CH_2$), 109.8 (CH), 113.1 (CH), 121.8 (CH), 126.3 (C), 128.5 (CH), 132.9 (CH), 160.3 (C), 161.3 (C), 180.0 (C), 184.1 (C). EIMS *m/z*: 248 ($M^+$). HRMS-EI *m/z*: ($M^+$) calcd for $C_{13}H_{12}O_5$, 248.0685; found, 248.0681.

### 4.23. 7-Hydroxy-2-methoxymethoxy-1,4-naphthoquinone (7)

As a yellowish green solid of mp 169.0−170.1 °C. The position of the methoxymethyl substituent group was determined by NOE measurement and analysis. IR (KBr): 3190, 1690, 1634, 1559, 1468, 1343, 1308, 1233, 1173, 1084, 1022 $cm^{-1}$.$^1$H NMR (DMSO-$d_6$) $\delta$: 3.41 (3H, s, $OCH_3$), 5.28 (2H, s, $OCH_2$), 6.24 (1H, s, CH), 7.14 (1H, dd, $J$=2.6, 8.4, Ar−H), 7.29 (1H, d, $J$=2.6, Ar−H), 7.81 (1H, d, $J$=8.4, Ar−H), 10.8 (1H, br-s, OH). $^{13}$C NMR ($CDCl_3$) $\delta$: 56.7 ($CH_3$), 94.7 ($CH_2$), 111.9 (CH), 112.2 (CH), 120.9 (CH), 123.4 (C), 128.3 (CH), 132.8 (C), 157.1 (C), 162.2 (C), 179.7 (C), 183.6 (C). EIMS *m/z*: 234 ($M^+$). HRMS-EI *m/z*: ($M^+$) calcd for $C_{12}H_{10}O_5$, 234.0528; found, 234.0529.

### 4.24. 1,2,4-Trimethoxy-7-methoxymethoxynaphthalene (8)

To a 100 mL round-bottom flask was added 10% wet-Pd/C (620 mg) in THF (25 mL) followed by addition of **6** (620 mg, 2.5 mmol). After the flask had been fully purged with hydrogen gas, the reaction mixture was vigorously stirred at rt overnight, with the flask being equipped with a hydrogen gas balloon. To the reaction mixture was added sodium hydride at 60% dispersion in mineral oil (250 mg, 6.25 mmol) and dimethyl sulfate (1.58 g, 12.5 mmol) under hydrogen gas atmosphere. After stirring for 1 h, sodium hydride (6.25 mmol) and dimethyl sulfate (12.5 mmol) were added to the reaction mixture, and stirring was continued for about 1 h at the same temperature until **6** was fully converted to **8** as confirmed by the results of TLC analysis. The catalyst was filtered off by using Celite® followed by thorough washing with ether. To the filtrate was added 10w/v% NaOH (75 mL) with vigorous stirring for 4 h to destroy any excess dimethyl sulfate. The reaction mixture was separated and the aqueous layer was extracted with ether (×2). The combined ethereal layer was successively washed with water (×1), brine (×1) and then dried over $Na_2SO_4$. Filtration and concentration under reduced pressure gave a pale yellow oil, which was then purified by flash column chromatography by eluting with hexane and ethyl acetate in 5/1 ratio to obtain 605 mg (87%) of **8** as a white solid of mp 53.2−53.5 °C. IR (KBr): 2959, 2903, 2841, 1630, 1603, 1516, 1466, 1445, 1356, 1262, 1221, 1194, 1157, 1105, 1084, 1059, 1009 $cm^{-1}$. $^1$H NMR ($CDCl_3$) $\delta$: 3.52 (3H, s, $OCH_3$), 3.90 (3H, s, $OCH_3$), 3.96 (3H, s, $OCH_3$), 3.99 (3H, s, $OCH_3$), 5.31 (2H, s, $OCH_2$), 6.51 (1H, s, C3−H), 7.07 (1H, dd, $J$=2.6, 9.2, C6−H), 7.54 (1H, d, $J$=2.6, C8−H), 8.07 (1H, d, $J$=9.2, C5−H). $^{13}$C NMR ($CDCl_3$) $\delta$: 55.7 ($CH_3$), 56.1 ($CH_3$), 57.3 ($CH_3$), 61.0 ($CH_3$), 93.9 ($CH_2$), 94.5 (CH), 103.8 (CH), 116.0 (CH), 117.4 (C), 124.0 (CH), 130.7 (C), 136.4 (C), 149.0 (C), 152.6 (C), 156.3 (C). EIMS *m/z*: 278

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($M^+$). HRMS-EI *m/z*: ($M^+$) calcd for $C_{15}H_{18}O_5$, 278.1154; found, 278.1157.

### 4.25. 1,3,4-Trimethoxy-6-methoxymethoxy-2-(3-methyl-2-butenyl)naphthalene (9)

To a solution of **8** (1.30 g, 4.68 mmol) in anhydrous THF (23 mL) was added dropwise 1.6 M *n*-butyllithium in hexane solution (8.8 mL, 14.0 mmol) at −80 °C under an argon atmosphere. The reaction mixture was warmed to −40 °C, and then was stirred for 2 h. The reaction mixture was cooled to −80 °C, and prenyl bromide (2.09 g, 14.0 mmol) was added dropwise. The reaction mixture was warmed to rt and stirred for 30 min. The reaction was quenched with satd. $NH_4Cl$ aq under ice bath cooling, and the entire mixture was extracted with ethyl acetate (×3). The organic layer was successively washed with 1w/v% $Na_2S_2O_3$ aq (×1), water (×1) and brine (×1), dried over $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography by eluting with hexane and ethyl acetate in 10/1 to 5/1 ratio to obtain 1.25 g (77%) of **9** as a colorless oil with recovery of starting material **8** (21%). IR (neat): 2934, 1626, 1597, 1501, 1449, 1404, 1379, 1343, 1263, 1223, 1192, 1152, 1111, 1080, 1063 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$: 1.70 (3H, d, *J*=1.1, $CH_3$), 1.83 (3H, s, $CH_3$), 3.50 (2H, d, *J*=7.0, $CH_2$), 3.52 (3H, s, $OCH_3$), 3.87 (3H, s, $OCH_3$), 3.95 (6H, s, 2×$OCH_3$), 5.21–5.25 (1H, m, CH), 5.30 (2H, s, $OCH_2$), 7.15 (1H, dd, *J*=2.6, 9.2, C7−H), 7.60 (1H, d, *J*=2.6, C5−H), 7.93 (1H, d, *J*=9.2, C8−H). $^{13}C$ NMR ($CDCl_3$) $\delta$: 17.9 ($CH_2$), 23.9 ($CH_3$), 25.7 ($CH_3$), 56.1 ($CH_3$), 60.6 ($CH_3$), 62.2 ($CH_3$), 94.6 ($CH_2$), 104.4 (CH), 117.6 (CH), 121.5 (C), 123.6 (CH), 123.9 (CH), 125.0 (C), 129.4 (C), 131.3 (C), 143.1 (C), 149.1 (C), 150.1 (C), 155.2 (C). EIMS *m/z*: 346 ($M^+$). HRMS-EI *m/z*: ($M^+$) calcd for $C_{20}H_{26}O_5$, 346.1780; found, 346.1780.

### 4.26. 2,2-Dimethyl-3-(1,3,4-trimethoxy-6-methoxymethoxy-2-naphthalenylmethyl)oxirane (10)

To a solution of **9** (1.67 g, 4.82 mmol) in $CH_2Cl_2$ (15 mL) was added *m*-chloroperoxybenzoic acid, wet, 75% purity (1.22 g, 5.30 mmol) at 0 °C, and the reaction mixture was warmed to rt and stirred for 1 h. The reaction was quenched with water with ice bath cooling, and the mixture was extracted with $CHCl_3$ (×3). The combined organic layer was successively washed with 1w/v% $Na_2S_2O_3$ aq (×1) and brine (×1), dried over $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography by eluting with hexane and ethyl acetate in 5/1 to 2/1 ratio to give 1.61 g (92%) of **10** as a colorless oil. IR (neat): 2938, 2839, 1738, 1626, 1599, 1503, 1451, 1404, 1381, 1343, 1265, 1246, 1223, 1196, 1152, 1117, 1082, 1061, 1005 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$: 1.31 (3H, s, $CH_3$), 1.46 (3H, s, $CH_3$), 2.96–3.11 (3H, m), 3.53 (3H, s, $OCH_3$), 3.91 (3H, s, $OCH_3$), 3.95 (3H, s, $OCH_3$), 4.00 (3H, s, $OCH_3$), 5.31 (2H, s, $OCH_2$), 7.17 (1H, dd, *J*=2.6, 9.2, C7−H), 7.62 (1H, d, *J*=2.6, C5−H), 7.94 (1H, d, *J*=9.2, C8−H). $^{13}C$ NMR ($CDCl_3$) $\delta$: 19.0 ($CH_2$), 24.7 ($CH_3$), 24.8 ($CH_3$), 56.1 ($CH_3$), 59.0 (C), 60.61 ($CH_3$), 60.64 ($CH_3$), 62.4 ($CH_3$), 64.1 (CH), 94.5 ($CH_2$), 104.4 (CH), 117.7 (CH), 121.27 (C), 121.30 (C), 124.1 (CH), 129.9 (C), 142.9 (C), 149.0 (C), 150.9 (C), 155.5 (C). EIMS *m/z*: 362 ($M^+$). HRMS-EI *m/z*: ($M^+$) calcd for $C_{20}H_{26}O_6$, 362.1729; found, 362.1729.

### 4.27. 3-Methyl-1-(1,3,4-trimethoxy-6-methoxymethoxy-2-naphthalenyl)-but-3-en-2-ol (11)

According to a literature procedure,[26] to a solution of **10** (1.35 g, 3.73 mmol) in $CH_2Cl_2$ (18.7 mL) was added 1,3-dimethylimidazolidin-2-one (850 mg, 7.46 mmol) and *p*-toluenesulfonic acid monohydrate (353 mg, 1.86 mmol), and the solution was stirred at rt for 1 h. The reaction was quenched with water, and the reaction mixture was extracted with $CHCl_3$ (×2). The combined organic layer was successively washed with water (×1) and brine (×1), dried over $Na_2SO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography by eluting with hexane and ethyl acetate in 5/1 to 2/1 ratio to give 1.092 g (81%) of **11** as a colorless oil. IR (neat): 3489, 2938, 2839, 1626, 1599, 1503, 1451, 1404, 1379, 1343, 1265, 1223, 1196, 1152, 1111, 1080, 1067, 1003 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$: 1.88 (3H, s, $CH_3$), 2.94 (1H, dd, *J*=4.4, 13.9, C1−$H_a$), 2.97 (1H, d, *J*=4.4, OH), 3.16 (1H, dd, *J*=3.3, 13.9, C1−$H_b$), 3.53 (3H, s, $OCH_3$), 3.92 (3H, s, $OCH_3$), 3.95 (3H, s, $OCH_3$), 4.00 (3H, s, $OCH_3$), 4.28–4.32 (1H, m, C2−H), 4.85 (1H, d, *J*=1.4, C4−$H_a$), 5.04 (1H, d, *J*=1.4, C4−$H_b$), 5.31 (2H, s, $OCH_2$), 7.18 (1H, dd, *J*=2.6, 9.2, C7−H), 7.62 (1H, d, *J*=2.6, C5−H), 7.93 (1H, d, *J*=9.2, C8−H). $^{13}C$ NMR ($CDCl_3$) $\delta$: 18.1 ($CH_3$), 31.7 ($CH_2$), 56.1 ($CH_3$), 60.65 ($CH_3$), 60.70 ($CH_3$), 62.1 ($CH_3$), 76.3 (CH), 94.5 ($CH_2$), 104.4 (CH), 110.2 ($CH_2$), 117.9 (CH), 121.2 (C), 121.8 (C), 124.0 (CH), 129.9 (C), 143.0 (C), 147.8 (C), 148.6 (C), 150.8 (C), 155.5 (C). EIMS *m/z*: 362 ($M^+$). HRMS-EI *m/z*: ($M^+$) calcd for $C_{20}H_{26}O_6$, 362.1729; found, 362.1727.

### 4.28. (±)-7-Hydroxy-2-isopropenyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (racemic lantalucratin C: 12)[5e]

According to our reported method,[5] to a solution of **11** (109 mg, 0.3 mmol) in MeCN (5.0 mL) was gently added diammonium cerium nitrate (411 mg, 0.75 mmol) in 1.8 mL of water at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h while the color of the solution changed to a dark red. The reaction mixture was diluted with water and $CHCl_3$, and the entire mixture was extracted with $CHCl_3$ (×3). The combined organic layer was successively washed with water (×1) and brine (×1), dried over $Na_2SO_4$, filtered and concentrated in vacuo to give 104 mg of a crude dark red gum. According to the literature procedure,[27] to a solution of crude in anhydrous $CH_2Cl_2$ (6 mL) was added pre-activated $NaHSO_4 \cdot SiO_2$ (120 mg) and the mixture was stirred at rt for 5 h. The resulting purple solution was filtered in vacuo and the filtrate was evaporated. The residue was purified by flash column chromatography using neutral silica gel by eluting with hexane and ethyl acetate in 5/1 to 1/1 ratio to obtain 49 mg (64%) of **12** as a purple solid. $^1H$ NMR (acetone-$d_6$) $\delta$: 1.81 (3H, s, $CH_3$), 2.81 (1H, dd, *J*=7.7, 15.0, C3−$H_a$), 3.21 (1H, dd, *J*=10.2, 15.0, C3−$H_b$), 5.00 (1H, s, C11−$H_a$), 5.16 (1H, s, C11−$H_b$), 5.57 (1H, dd, *J*=7.7, 10.2, C2−H), 7.16 (1H, dd, *J*=2.6, 8.1, C8−H), 7.44 (1H, d, *J*=2.6, C6−H), 7.57 (1H, d, *J*=8.1, C9−H), 9.45 (1H, br-s, OH).

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### Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.01.040.

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