HETEROCYCLES, Vol. 105, No. 1, 2022, pp. 511 - 522. © 2022 The Japan Institute of Heterocyclic Chemistry
Received, 16th March, 2021, Accepted, 19th April, 2021, Published online, 27th May, 2021
DOI: 10.3987/COM-21-S(R)1

LIPASE-CATALYZED SITE-SELECTIVE DEACETYLATION OF 2-METHOXY-3-METHYLNAPHTHALENE-1,4-DIOL DIACETATE FOR CONSTRUCTION OF CHARACTERISTIC SUBSTITUTED 1,2,3,4-TETRAHYDROISOQUINOLINE DERIVATIVE OF NOVEL ECTEINASCIDIN MARINE NATURAL PRODUCT

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This paper is dedicated to Professor Somsak Ruchirawat (Research, Chulabhorn Research Institute) on the occasion of his 80th birthday.

Abstract – We developed a site-selective deacetylation of 2-methoxy-3-methylnaphthalene-1,4-diol diacetate catalyzed by *Candida antarctica* lipase B, which furnished 1-hydroxy-2-methoxy-3-methylnaphthalen-4-yl acetate in 88% yield. This product was transformed into 2-methoxy-3-methylnaphthalen-1-ol in a five-step sequence (30.5% overall yield from **7a**). It is a novel procedure for preparing a characteristic A ring substituted system for both safracin antibiotics (**2**) and ecteinascidin marine natural products (**1**).

One of the most exciting topics in the synthesis of novel anticancer ecteinascidin marine natural products is the preparation of highly substituted A and E ring systems (**Figure 1**). Corey and co-workers reported the first total synthesis of ecteinascidin 743 (**1a**) using a multistep process that started from poly-functionalized tyrosine derivatives,[1] and all other total syntheses that followed were based on Corey's landmark strategy.[2-6] Currently, this target molecule is semi-synthetically derived from antitumor cyanosafracin B (**2c**),[7] which is obtained by a modified fermentation of *Pseudomonas fluorescens*.[8]

We have been interested in the characteristic A ring system of safracins (**2**) and ecteinascidins (**1**) because it is known that the substitution pattern of the A ring has a major impact on the anticancer activity. We succeeded in the isolation of a large amount of renieramycin M (**3b**)[9] and the identification of trace metabolite renieramycin T (**3c**) from the Thai[10] and Philippines[11] blue sponge *Xestospongia* sp. that was pretreated with KCN. We also reported the synthesis of the ABC ring system of safracins and

ecteinascidins.[12-14] However, we are of the opinion that it would be better to produce an alternative A ring from corresponding *p*-quinones because its transformation would generate a large yield of product, as was achieved in **3b**. In this paper, we use 2-methoxy-3-methylnaphthoquinone (**5**) as a model compound for the AB ring moiety of **3b** and **4c**, and report the conversion of *p*-quinone **5** to 2-methoxy-3-methylnaphthalen-1-ol (**6**) with a substitution pattern corresponding to the A ring moiety of **1** via monoacetate **7a** (Scheme 1).

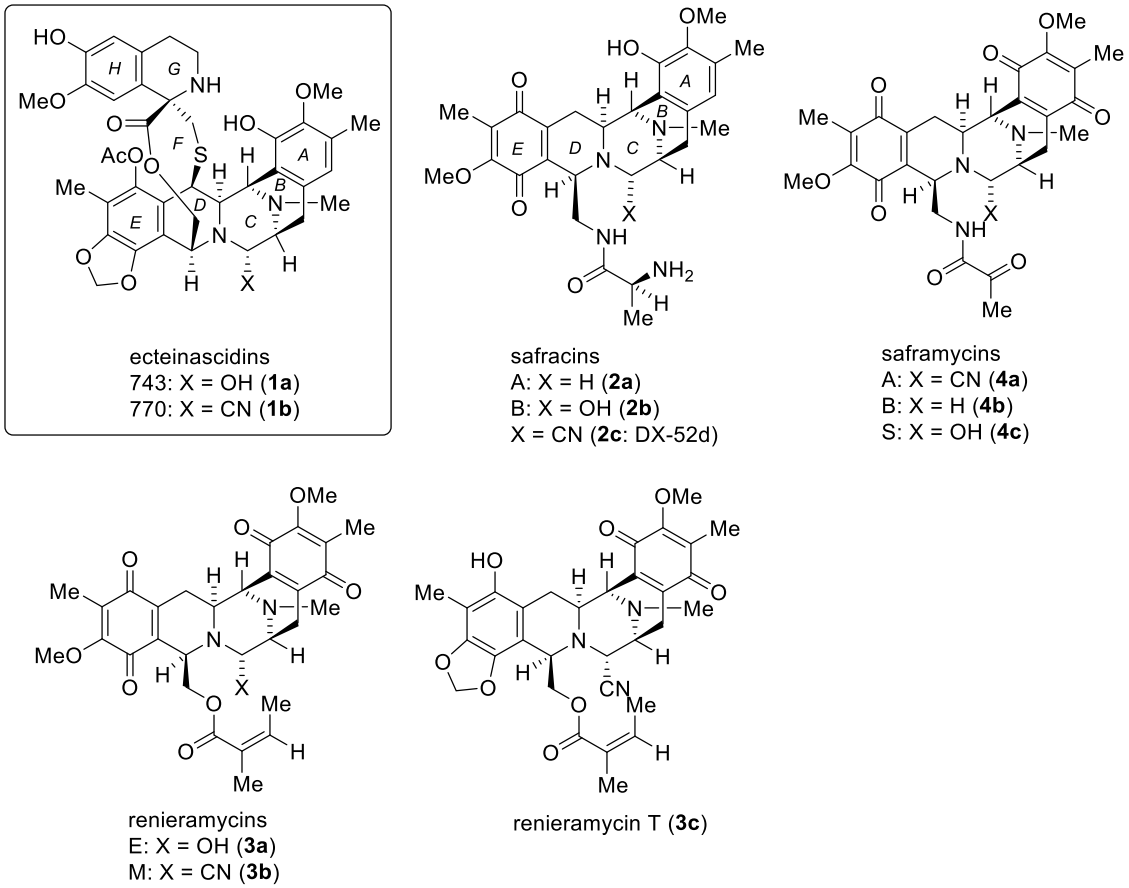
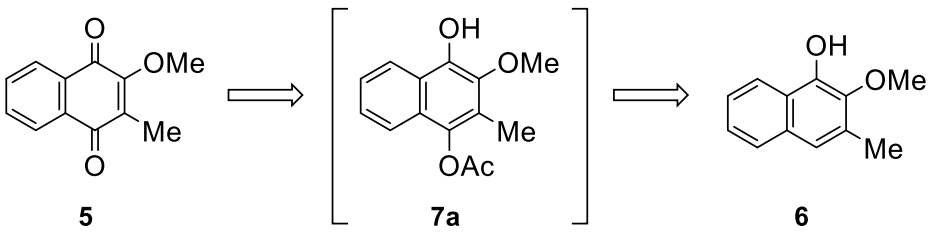


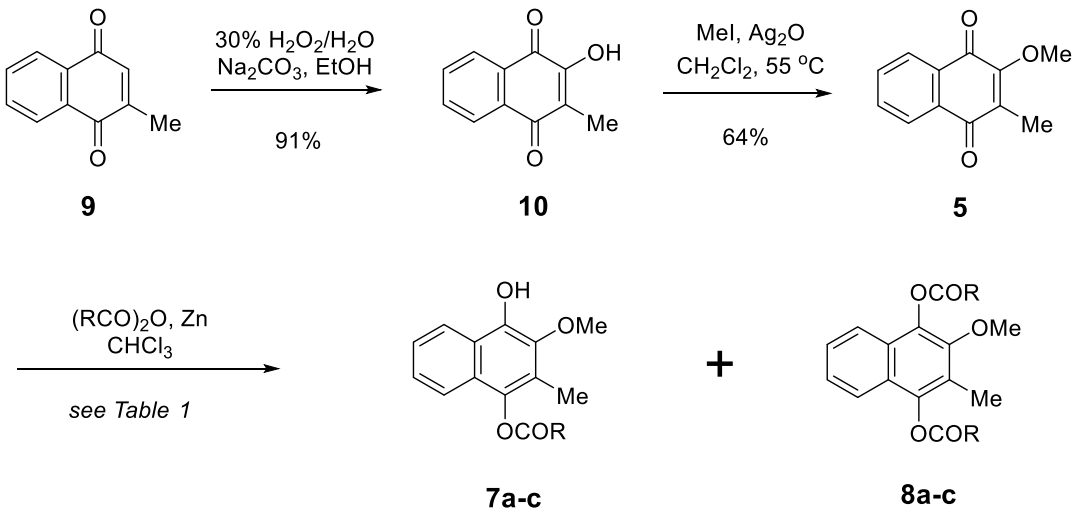
Figure 1. Structures of 1,2,3,4-tetrahydroisoquinoline antitumor natural products



Scheme 1. Outline for the conversion from *p*-quinone **5** to phenol **6**

We started our preliminary experiment with compound **5**,[15] which was prepared from commercially available 2-methylnaphthoquinone-1,4-dione **9** via phthiocol (**10**) in 58% overall yield (Scheme 2).

Treating **5** with acetic anhydride (1 equiv.) in the presence of zinc powder at 60 °C for 2 h gave **7a** (R = Me) in 37% yield, and 47% of starting material **5** was recovered (Table 1). The structure of **7a** was confirmed by the NOE correlations between sharp phenolic OH signal (δ 5.95) and 2-OMe methyl proton (δ 3.87). Thus, the OH group might be located at C-1 in **7a**, and the methoxy group would exert sufficient steric effect on the selective acetylation of the two phenolic hydroxy groups. As we could not produce diacetate **8a**, we tried to increase the yield of **7a** (Entry 2). To reduce the amount of recovered **5**, we carried out the reductive acetylation of **5** with 1.5 equiv. of acetic anhydride in the presence of Zn powder under the same conditions. The yield of **7a** was slightly increased to 42%, but diacetate **8a** was produced in 32% yield. Acylation of **5** with benzoic anhydride (1.5 equiv.) in the presence of Zn powder at 60 °C for 2 h afforded **7b** (55% yield) and **8b** (25% yield) (Entry 3). When **5** was treated with pivalic anhydride in the presence of Zn powder, no acylated compound was obtained due to large steric hindrance (Entry 4).



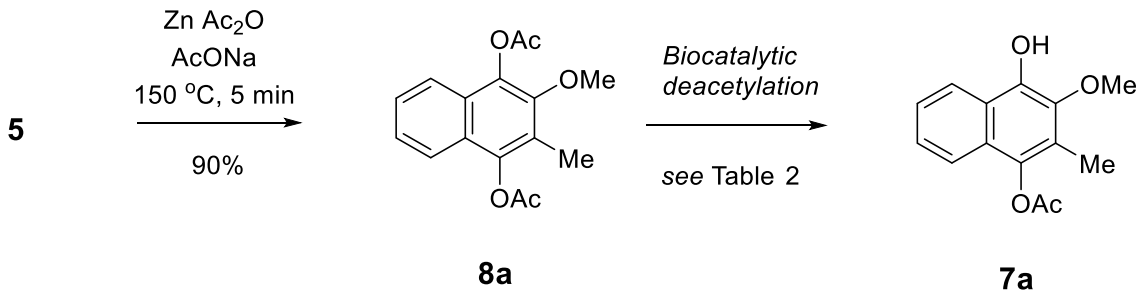
Scheme 2. Preparation of p-quinone **5** and reductive acylation to give **7**

Table 1. Reductive acylation of **5** in the presence of Zn powder to **7** and **8**

Entry	R	Anhydride	Yield (%)		Recovery (%)
			7	**8**	**5**
1	Me	$(MeCO)_2O$ (1.0 equiv.)	**7a**: 37	**8a**: trace	47
2	Me	$(MeCO)_2O$ (1.5 equiv.)	**7a**: 42	**8a**: 32	12
3	C_6H_5	$(C_6H_5CO)_2O$ (1.5 equiv.)	**7b**: 55	**8b**: 25	ND
4	$C(Me)_3$	$((Me)_3CCO)_2O$ (1.5 equiv.)	**7c**: ND	**8c**: ND	71

We then focused on a recent report on the use of biocatalysts with high accessibility and availability in organic synthesis.[16] For example, Mastihubová and co-workers reported mild and selective enzymatic method for deacetylation of aromatic acetate without affecting aliphatic ester by using Lipase PS.[17] Furthermore, Sugai and co-workers reported a lipase-catalyzed site-selective deacetylation of 2,5-dimethylnaphthalene-1,4-diol diacetate.[18]

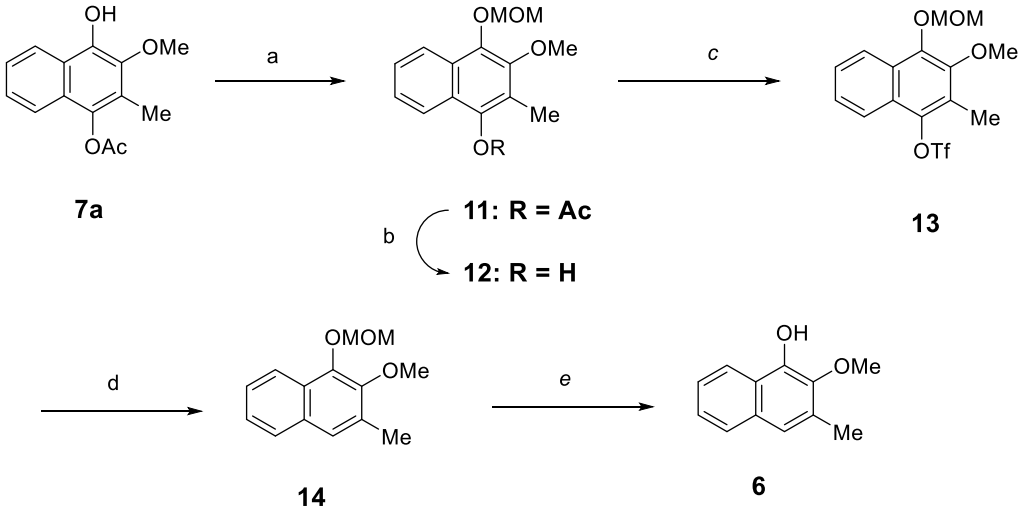
Then, we turned our attention to the preparation of **7a** through the site-selective deacetylation of compound **8a**, which was obtained by the reductive acetylation with acetic anhydride, Zn powder, and sodium acetate at 150 °C for 5 min in 90% yield (Scheme 3). Although the conversion of diacetate **8a** to **7a** by partial deacetylation[19] was considered, we attempted an enzymatic reaction that was expected to be successful, as described above, with a view to applying it to **3b**. In the initial trial, *Burkholderia cepacia* lipase catalyzed deacetylation of **8a** was unsuccessful (Table 2). In contrast, when the reaction was carried out at 50 °C with *C. antarctica* lipase B, desired phenol **7a** was obtained in 80% yield along with *p*-quinone **5** in 3% yield. Compound **5** might be produced by air oxidation of the initial hydroquinone that was generated by the removal of both acetyl groups during work-up. After several investigations of the reaction conditions, we found that the treatment of **8a** in cyclopentanol:cyclopentyl methyl ether (CPME) = 1:2 with *C. antarctica* lipase B as catalyst at 40 °C for 7 h gave **7a** and **5** in 88% and 6% yields, respectively (Entry 5). Bis-acetate **8a** was susceptible to *C. antarctica* lipase B mediated site-selective deacetylation, giving **7a**. Although at present there are no plausible explanations for the results, in general the selectivity of enzymatic reactions is responsible to the difference of potential energy of transition states of enzyme and the substrate. It was found that enzyme could distinguish between the methyl group and the methoxy group present in the *ortho* position of the acetoxy groups, and deacetylation took place predominantly at the *ortho* position of the methoxy group.



Scheme 3. Biocatalytic site-selective deacetylation of **8a** to **7a**

Table 2. Biocatalytic site-selective deacetylation of **8a** to **7a**

Entry	Enzyme	Solvent	Temp. (°C)	Time (h)	Yield (%) **7a**	Yield (%) **5**	Recovery (%) **8a**
1	*B. cepacia* lipase	cyclopentanol:CPME = 1:2	50	19	ND	ND	94
2	*B. cepacia* lipase	2-propanol:THF = 1:2	50	19	ND	ND	86
3	*C. antarctica* lipase B	cyclopentanol:CPME = 1:2	50	4	80	3	ND
4	*C. antarctica* lipase B	cyclopentanol:CPME = 1:2	50	16	56	35	ND
5	*C. antarctica* lipase B	cyclopentanol:CPME = 1:2	40	7	88	6	ND



(a) NaH, DMF, 0 °C, 30 min and then MOMCl, 0 °C, 1 h (80%); (b) K_2CO_3, MeOH, 20 °C, 1 h; (c) Tf_2O, TEA, CH_2Cl_2, 0 °C, 30 min (69%, 2 steps); (d) H_2, 10% Pd/C, Et_2NH, 20 °C, 3 h (70%); (e) *conc.* HCl, EtOH, reflux, 5 min (79%).

Scheme 4. Five-step transformation of **7a** into 1-naphthol **6**

With our target model compound **7a** in hand, we investigated the transformation of **7a** into 1-naphthol derivative **6** on the basis of our previous process (Scheme 4).[13] The reaction of **7a** with sodium hydride in DMF at 0 °C for 30 min, followed by methoxymethyl chloride (MOMCl) treatment afforded **11** in 80% yield. Treating **11** with K_2CO_3 in MeOH at 20 °C for 1 h gave **12**, which was converted into **13** in 69% overall yield. Treatment of **13** with 10% Pd/C in the presence of diethylamine at 20 °C for 3 h produced **14** in 70% yield according to the procedure of Sajiki.[20] Finally, removing the MOM group in **14** by acid hydrolysis gave target 1-naphthol derivative **6** in 79% yield. The structure of **6** was supported by ^{1}H-NMR, ^{13}C-NMR, IR, and MS data. It was consistent with the long-range ^{1}H-^{13}C correlation between C-2 carbon (δ 141.1) and OH proton (δ 6.06) signals.[21]

In conclusion, we efficiently synthesized 1-naphthol derivative **6** from naphthoquinone **5** by using a biocatalytic site-selective deacetylation reaction. We are currently investigating enzyme-catalyzed reactions of right-half tricyclic model compounds for the production of 1,2,3,4-tetrahydroisoquinoline antitumor natural products.

EXPERIMENTAL

General Experimental Procedure

Lipase B from *Candida antarctica* (Novozym 435) immobilized on acrylic resin was purchased from Novozyms Japan Inc. (Chiba, Japan). *Burkholderia capacia* lipase (Amano PS-IM) immobilized on diatomaceous earth was purchased from Amano Enzyme Inc. (Aichi, Japan). IR spectra were obtained with a Shimadzu Prestige 21/IRAffinity-1 FT-IR spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-AL 400 NMR spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C; and a JEOL JNM-AL 300 NMR spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C (ppm, *J* in Hz with TMS as internal standard). All proton and carbon signals were assigned by extensive NMR measurements using COSY, HMBC, and HMQC techniques. Mass spectra were recorded on a JEOL JMS 700 instrument with a direct inlet system operating at 70 eV.

2-Hydroxy-3-methylnaphthalene-1,4-dione (10)

A solution of 30% aqueous H_2O_2 (2.4 mL), Na_2CO_3 (90.6 mg, 0.855 mmol) in H_2O (2.4 mL) was added to a suspension of quinone **9** (1.14 g, 6.63 mmol) in EtOH (4.5 mL). The mixture was stirred at room temperature for 1.5 h. Reaction mixture was diluted with H_2O (3 mL), and the product was extracted with $CHCl_3$ (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated to provide crude epoxide. Sulfuric acid (7.5 mL) was added into the crude, and the reaction mixture was stirred at room temperature for 1 h. Ice water (60 mL) was then added into the reaction mixture, and the resulting mixture was then extracted with $CHCl_3$ (3 × 100 mL). The combined organic layers was washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated to give **10** (1.13 g, 91%) as a yellow solid, which was used in the next step without further purification. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.14-8.07 (2H, m, Ar-H), 7.78-7.66 (2H, m, Ar-H), 7.31 (1H, s, 2-OH), 2.11 (3H, s, 3-CH_3).

2-Methoxy-3-methylnaphthalene-1,4-dione (5)[15]

Methyl iodide (315 µL, 5.0 mmol) was added into a suspension of naphthoquinone **10** (188 mg, 1.0 mmol) in the presence of Ag_2O (1.17 g, 5.0 mmol) in CH_2Cl_2 (20 mL), and the reaction mixture was stirred at 55 °C for 1 h. The insoluble material was removed by filtration and the filtrate was washed with $CHCl_3$.

The combined filtrates were concentrated in vacuo to give a residue, which was purified by SiO_2 flash column chromatography (*n*-hexane : AcOEt = 9 : 1) to give **5** (130 mg, 64%) as a yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.10-8.02 (2H, m, Ar-H), 7.74-7.65 (2H, m, Ar-H), 4.12 (3H, s, 2-OCH_3), 2.10 (3H, s, 3-CH_3).

1-Hydroxy-2-methoxy-3-methylnaphthalen-4-yl acetate (7a)

Acetic anhydride (28.0 µL, 300 µmol) was added into a mixture of naphthoquinone **10** (39.5 mg, 200 µmol) and zinc powder (129 mg, 1.98 mmol) in $CHCl_3$ (1 mL). The resulting mixture was heated at 60 °C for 2 h. The reaction mixture was diluted with $CHCl_3$ (10 mL) and washed with 1.0 M aqueous HCl solution (10 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo, and the residue (55.7 mg) was purified by SiO_2 flash column chromatography (*n*-hexane : AcOEt = 3 : 1) to give monoacetate **7a** (20.0 mg, 42%) as a red oil, bisacetate **8a** (18.2 mg, 32%) as a pale yellow oil, and recovered **5** (4.7 mg, 12%) as a yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.17-8.14 (1H, m, Ar-H), 7.66-7.63 (1H, m, Ar-H), 7.46-7.42 (2H, m, Ar-H), 5.95 (1H, s, 1-OH), 3.87 (3H, s, 2-OCH_3), 2.47 (3H, s, 4-$OCOCH_3$), 2.28 (3H, s, 3-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.3 (s, 4-O<u>C</u>OCH_3), 141.8 (s, C-1), 140.2 (s, C-2), 137.7 (s, C-4), 126.1 (d, C-6 or C-7), 125.1 (d, C-6 or C-7), 124.5 (s, C-10), 122.9 (s, C-9), 122.1 (d, C-5 or C-8), 122.0 (s, C-3), 120.5 (d, C-5 or C-8), 61.3 (q, 2-OCH_3), 20.6 (q, 4-OCO<u>C</u>H_3), 10.4 (q, 3-CH_3); IR ($CHCl_3$) cm^{-1}: 3535, 3022, 1759, 1600, 1454, 1398, 1226; EIMS *m/z* (%): 246 (M^+, 27), 205 (12), 204 (100), 189 (61), 161 (17); HREIMS: calcd for $C_{14}H_{14}O_4$ 246.0892; Found 246.0893.

2-Methoxy-3-methylnaphthalene-1,4-diyl diacetate (8a)

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.75 (1H, dd, *J* = 7.1, 1.6 Hz, Ar-H), 7.70 (1H, dd, *J* = 7.9, 1.9 Hz, Ar-H), 7.50-7.42 (2H, m, Ar-H), 3.87 (3H, s, 2-OCH_3), 2.48 (6H, s, -$OCOCH_3$), 2.27 (3H, s, 3-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 168.8 (s, O*C*OCH_3), 167.8 (s, -O*C*OCH_3), 147.6 (s, C-2), 142.9 (s, C-4), 136.2 (s, C-1), 126.5 (d, C-6 or C-7), 125.9 (d, C-6 or C-7), 124.5 (s, C-9, C-10), 123.6 (s, C-3), 121.1 (d, C-5 or C-8), 120.8 (d, C-5 or C-8), 61.0 (q, 2-OCH_3), 20.6 (q, -OCO*C*H_3), 20.5 (q, -OCO*C*H_3), 10.4 (q, 3-CH_3); IR ($CHCl_3$) cm^{-1}: 3074, 2933, 1759, 1747, 1363, 1217, 1205, 1066, 759; EIMS *m/z* (%): 288 (M^+, 11), 246 (19), 205 (13), 204 (100), 189 (29); HREIMS: calcd for $C_{16}H_{16}O_5$ 288.0998; Found 288.0996.

1-Hydroxy-2-methoxy-3-methylnaphthalen-4-yl benzoate (7b)

Benzoic anhydride (34.2 mg, 149 µmol) was added into a mixture of naphthoquinone **5** (20.5 mg, 101 µmol) and zinc powder (63.7 mg, 98.9 µmol) in $CHCl_3$ (1 mL). The resulting mixture was heated at 60 °C for 2 h. The reaction mixture was diluted with $CHCl_3$ (10 mL) and washed with 1.0 M aqueous HCl solution

(10 mL). The organic layer was washed with 5% aqueous $NaHCO_3$ solution (10 mL), and then brine (10 mL), dried over Na_2SO_4. The solvent was removed in vacuo, and the residue (38.9 mg) was purified by SiO_2 flash column chromatography (*n*-hexane : AcOEt = 9 : 1) to give monobenzoate **7b** (17.1 mg, 55%) as a dark orange solid, and bisbenzoate **8b** (10.5 mg, 25%) as a pale yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.35 (2H, dd, *J* = 8.4, 1.5 Hz, Ar-H), 8.18 (2H, dd, *J* = 7.7, 2.0 Hz, Ar-H), 7.58 (2H, t, *J* = 7.3 Hz, Ar-H), 7.60-7.56 (2H, m, Ar-H), 7.47-7.38 (2H, m, Ar-H), 6.04 (1H, brs, 1-OH), 3.89 (3H, s, 2-OCH_3), 2.33 (3H, s, 3-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 165.0 (s, O<u>C</u>OPh), 141.7 (s, C-1), 140.3 (s, C-2), 137.8 (s, C-4), 133.8 (d, Bz), 130.3 (d, Bz), 129.1 (s, Bz), 128.8 (d, Bz), 126.1 (d, C-6 or C-7), 125.1 (d, C-6 or C-7), 124.7 (s, C-10), 122.9 (s, C-9), 122.4 (s, C-3), 121.9 (d, C-5 or C-8), 120.6 (d, C-5 or C-8), 61.3 (q, 2-OCH_3), 10.5 (q, 3-CH_3); IR (KBr) cm^{-1}: 3433, 3069, 2947, 1738, 1599, 1452, 1396, 1250, 1067; EIMS *m/z* (%): 309 (11), 308 (M^+, 53), 203 (11), 105 (100), 77 (15); HREIMS: calcd for $C_{19}H_{16}O_4$ 308.1049; Found 308.1047.

2-Methoxy-3-methylnaphthalene-1,4-diyl dibenzoate (8b)

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.39-8.35 (4H, m, Ar-H), 7.83 (1H, dd, *J* = 7.1, 1.6 Hz, Ar-H), 7.78 (1H, dd, *J* = 7.1, 1.6 Hz, Ar-H), 7.74-7.69 (2H, m, Ar-H), 7.61-7.57 (4H, m, Ar-H), 7.46-7.39 (2H, m, Ar-H), 3.91 (3H, s, 2-OCH_3), 2.35 (3H, s, 3-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 164.6 (s, O<u>C</u>OPh), 164.5 (s, O<u>C</u>OPh), 147.9 (s, C-2), 143.2 (s, C-4), 136.3 (s, C-1), 133.9 (d, Bz), 130.4 (d × 2, Bz), 129.0 (d, C-6 or C-7), 128.9 (d, C-6 or C-7), 128.8 (d × 2, Bz), 126.8 (s, C-9 or C-10), 126.6 (s, Bz), 126.0 (s, Bz), 124.7 (s, C-9 or C-10), 123.9 (s, C-3), 121.2 (d, C-5), 120.9 (d, C-8), 61.3 (q, 2-OCH_3), 10.6 (q, 3-CH_3); IR (KBr) cm^{-1}: 3342, 3068, 2939, 1739, 1600, 1450, 1238, 1172, 1028, 1024, 705; EIMS *m/z* (%): 412 (M^+, 33), 105 (100), 77 (16); HREIMS: calcd for $C_{26}H_{20}O_5$ 412.1311; Found 412.1312.

2-Methoxy-3-methylnaphthalene-1,4-diyl diacetate (8a)

Acetic anhydride (2.0 mL, 21.2 mmol) was added into a mixture of naphthoquinone **5** (302 mg, 1.48 mmol), zinc powder (221 mg, 3.41 mmol) and sodium acetate (271 mg, 3.26 mmol). The resulting mixture was heated at 150 °C for 5 min. The reaction mixture was diluted with $CHCl_3$ (20 mL) and washed with H_2O (30 mL), dried over Na_2SO_4. The solvent was removed in vacuo, and the residue (469 mg) was purified by SiO_2 flash column chromatography (*n*-hexane : AcOEt = 3 : 1) to give bisacetate **8a** (386 mg, 90%) as a colorless solid.

1-Hydroxy-2-methoxy-3-methylnaphthalen-4-yl acetate (7a)

C. antarctica lipase B (Novozym 435, 33.4 mg) was added to a solution of diacetate **8a** (33.4 mg, 116 μmol) in a mixture of cyclopentanol : cyclopentyl methyl ether (CPME) (1 : 2, 1 mL), which was pre-dried

over Na_2SO_4 at room temperature. The reaction mixture was stirred at 40 °C for 7 h under Ar. After removal of insoluble material by filtration with a Celite pad, the combined filtrate and washings were concentrated in vacuo. The residue (31.7 mg) was purified by SiO_2 flash column chromatography (*n*-hexane : AcOEt = 4 : 1) to give monoacetate **7a** (25.2 mg, 88%) as a red oil and restored *p*-quinone **5** (1.4 mg, 6%) as a yellow solid.

2-Methoxy-1-(methoxymethoxy)-3-methylnaphthalen-4-yl acetate (11)

Sodium hydride (39.2 mg, 970 μmol) was added into a stirred solution of phenol **7a** (239 mg, 970 μmol) in DMF (5.0 mL), and the resulting mixture was stirred at 0 °C for 30 min. MOMCl (146 μL, 1.94 mmol) was added over 15 min and the resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with water (10 mL) and extracted with Et_2O (3 × 15 mL). The combined extracts were dried over Na_2SO_4, and then solvent was removed in vacuo. The residue (284 mg) was purified by SiO_2 flash column chromatography (*n*-hexane : AcOEt = 6 : 1) to give MOM ether **11** (225 mg, 80%) as a pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.17 (1H, dd, *J* = 7.8, 1.5 Hz, Ar-H), 7.66 (1H, dd, *J* = 7.3, 1.5 Hz, Ar-H), 7.47 (1H, td, *J* = 7.3, 1.5 Hz, Ar-H), 7.43 (1H, td, *J* = 7.8, 1.5 Hz, Ar-H), 5.28 (2H, s, 1-OC$\underline{H_2}$OCH$_3$), 3.90 (3H, s, 2-OCH$_3$), 3.65 (3H, s, 1-OCH$_2$OC$\underline{H_3}$), 2.48 (3H, s, 4-OCOC$\underline{H_3}$), 2.25 (3H, s, 3-CH$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.0 (s, 4-O*C*OCH$_3$), 147.6 (s, C-1), 142.4 (s, C-2), 141.0 (s, C-4), 128.0 (s, C-10), 125.8 (d, C-6 or C-7), 125.8 (d, C-6 or C-7), 124.6 (s, C-9), 123.8 (s, C-3), 122.0 (d, C-8), 120.7 (d, C-5), 99.5 (t, O*C*H$_2$OCH$_3$), 60.6 (q, 2-OCH$_3$), 57.9 (q, 1-OCH$_2$O*C*H$_3$), 20.6 (q, 4-OCO*C*H$_3$), 10.4 (q, 3-CH$_3$); IR ($CHCl_3$) cm^{-1}: 3026, 1764, 1598, 1458, 1411, 1367; EIMS *m/z* (%): 290 (M+, 23), 248 (22), 204 (12), 203 (100), 175 (13); HREIMS calcd for $C_{16}H_{18}O_5$ 290.1154; Found 290.1153.

2-Methoxy-1-(methoxymethoxy)-3-methylnaphthalen-4-ol (12)

K_2CO_3 (361 mg, 2.61 mmol) was added into a solution of acetate **11** (152 mg, 0.52 mmol) in MeOH (4.0 mL), and the resulting mixture was stirred at 20 °C for 1 h. The reaction mixture was diluted with 5% aqueous $NaHCO_3$ (10 mL) and extracted with $CHCl_3$ (3 × 15 mL). The combined extracts were washed with brine (15 mL), dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was used in the next step without further purification. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.11 (1H, d, *J* = 8.2 Hz, Ar-H), 8.04 (1H, d, *J* = 8.2 Hz, Ar-H), 7.46 (1H, t, *J* = 8.2 Hz, Ar-H), 7.41 (1H, t, *J* = 8.2 Hz, Ar-H), 5.23 (2H, s, 1-OC$\underline{H_2}$OCH$_3$), 5.02 (1H, brs, 4-OH), 3.89 (3H, s, 2-OCH$_3$), 3.65 (3H, s, 1-OCH$_2$OC$\underline{H_3}$), 2.33 (3H, s, 3-CH$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 148.1 (s, C-2), 145.7 (s, C-4), 138.0 (s, C-1), 128.0 (s, C-10), 125.8 (d, C-6), 124.6 (d, C-7), 121.8 (s, C-9), 121.5 (d, C-8), 121.0 (d, C-5), 113.2 (s, C-3), 99.5 (t, 1-O*C*H$_2$OCH$_3$), 60.6 (q, 2-OCH$_3$), 57.9 (q, 1-OCH$_2$O*C*H$_3$), 9.1 (q, 3-CH$_3$); IR ($CHCl_3$) cm^{-1}: 3535, 2939, 1662, 1597, 1458,

1390, 1363; EIMS *m/z* (%): 248 (M+, 41), 247 (10), 204 (16), 203 (100), 202 (14), 175 (24), 171 (11), 160 (10), 115 (12), 45 (32); HREIMS calcd for $C_{14}H_{16}O_4$ 248.1049; Found 248.1047.

2-Methoxy-1-(methoxymethoxy)-3-methylnaphthalen-4-yl trifluoromethanesulfonate (13)

Triflic anhydride (128 µL, 0.78 mmol) was added over 10 min to a mixtue of the obtained above and triethylamine (280 µL, 2.09 mmol) in CH_2Cl_2 (8.0 mL), and the resulting reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with water (5 mL) and extracted with $CHCl_3$ (3 × 15 mL). The combined extracts were washed with brine (20 mL), dried over Na_2SO_4. The solvent was removed in vacuo, and the residue (206 mg) was purified by SiO_2 flash column chromatography (*n*-hexane : AcOEt = 8 : 1) to give triflate **13** (137 mg, 69%, 2 steps from **11**) as a pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.24-8.17 (1H, m, Ar-H), 8.00-7.94 (1H, m, Ar-H), 7.59-7.50 (2H, m, Ar-H), 5.32 (2H, s, 1-OC$\underline{H_2}$OCH$_3$), 3.91 (3H, s, 2-OCH$_3$), 3.64 (3H, s, 1-OCH$_2$OC$\underline{H_3}$), 2.47 (3H, s, 3-CH$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 147.3 (s, C-2), 144.4 (s, C-1), 138.9 (s, C-4), 128.2 (s, C-10), 126.9 (d, C-7), 126.5 (d, C-6), 126.4 (s, C-3), 121.5 (d, C-8), 124.7 (s, C-9), 121.0 (d, C-5), 99.5 (t, 1-O*C*H$_2$OCH$_3$), 60.7 (q, 2-OCH$_3$), 58.0 (q, 1-OCH$_2$O*C*H$_3$), 11.3 (q, 3-CH$_3$); IR ($CHCl_3$) cm^{-1}: 3003, 2939, 1600, 1458, 1411, 1240, 1138; EIMS *m/z* (%): 381 (16), 380 (M$^+$, 100), 335 (15), 248 (13), 247 (95), 243 (10), 217 (17), 215 (16), 202 (45), 201 (11), 187 (10), 172 (15), 159 (15), 116 (11), 117 (20), 103 (10), 45 (81); HREIMS calcd for $C_{15}H_{15}F_3O_6S$ 380.0541; Found 380.0542.

2-Methoxy-1-(methoxymethoxy)-3-methylnaphthalene (14)

A mixture of triflate **13** (31.2 mg, 82 µmol), 10% Pd/C (6.2 mg) and Et_2NH (20.6 µL, 197 µmol) in MeOH (1.0 mL) was vigorously stirred at 20 °C under H_2 (balloon) for 3 h. After removal of insoluble material by filtration through a cellulose pad, the combined filtrates were diluted with H_2O (10 mL), and extracted with Et_2O (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried over Na_2SO_4. The solvent was removed in vacuo, and the residue (16.5 mg) was purified by SiO_2 flash column chromatography (*n*-hexane : AcOEt = 19 : 1) to give phenol **14** (13.4 mg, 70%) as a pale yellow oil and recovered **13** (0.8 mg, 3%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.13 (1H, d, *J* = 7.7 Hz, Ar-H), 7.70 (1H, dd, *J* = 7.3, 1.8 Hz, Ar-H), 7.45-7.35 (3H, m, Ar-H), 5.30 (2H, s, 1-OC$\underline{H_2}$OCH$_3$), 3.89 (3H, s, 2-OCH$_3$), 3.64 (3H, s, 1-OCH$_2$OC$\underline{H_3}$), 2.43 (3H, s, 3-CH$_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 148.3 (s, C-2), 144.0 (s, C-1), 132.1 (s, C-3), 131.1 (s, C-9), 128.3 (s, C-10), 126.9 (d, C-8), 125.1 (d, 6-C or 7-C), 125.0 (d, 6-C or 7-C), 124.5 (d, C-4), 121.6 (d, C-5), 99.5 (t, 1-O*C*H$_2$OCH$_3$), 60.6 (q, 2-OCH$_3$), 57.9 (q, 1-OCH$_2$O*C*H$_3$), 9.1 (q, 3-CH$_3$); IR ($CHCl_3$) cm^{-1}: 3014, 2937, 1597, 1500, 1371, 1247, 1157; EIMS *m/z* (%): 233 (11), 232 (M$^+$, 77), 202 (21), 188 (12), 187 (100), 159 (38), 144 (22), 141 (12), 128 (11), 116 (10), 115 (21), 45 (35); HREIMS calcd for $C_{14}H_{16}O_3$ 232.1099; Found 232.1099.

2-Methoxy-3-methylnaphthalen-1-ol (6)

Conc. HCl (18.0 µL) was added into a solution of MOM ether **14** (66.5 mg, 286 µmol) in EtOH (5.0 mL), and the reaction mixture was refluxed for 5 min. After solvent was removed in vacuo, the residue was diluted with *sat*. aqueous $NaHCO_3$ (10 mL), and extracted with Et_2O (3 × 15 mL). The combined extracts were washed with H_2O (15 mL), dried over Na_2SO_4. The solvent was removed in vacuo to give a residue (13.9 mg), which was purified by SiO_2 flash column chromatography (*n*-hexane : AcOEt = 7 : 1) to give phenol **6** (42.7 mg, 79%) as pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.14-8.10 (1H, m, Ar-H), 7.70-7.63 (1H, m, Ar-H), 7.43-7.35 (2H, m, Ar-H), 7.20 (1H, s, 4-H), 6.06 (1H, brs, 1-OH), 3.86 (3H, s, 2-OCH_3), 2.47 (3H, s, 3-CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 143.2 (s, C-1), 141.1 (s, C-2), 131.1 (s, C-10), 130.2 (s, C-3), 126.7 (d, C-5), 125.4 (d, C-6 or C-7), 124.4 (d, C-6 or C-7), 123.2 (s, C-9), 121.6 (d, C-8), 120.2 (d, C-4), 60.9 (q, 2-OCH_3), 16.6 (q, 3-CH_3); IR ($CHCl_3$) cm^{-1}: 3014, 2937, 1597, 1500, 1371, 1247, 1157; EIMS *m/z* (%): 189 (12), 188 (M^+, 96), 174 (12), 173 (100), 145 (49), 115 (23); HREIMS calcd for $C_{12}H_{12}O_2$ 188.0837; Found 188.0837.

ACKNOWLEDGEMENTS

We acknowledge Professor Hironao Sajiki (Gifu Pharmaceutical University) for useful comments on the palladium on carbon-diethylamine-mediated hydrodeoxygenation reaction. This work was supported by the Japan Society for the Promotion of Science (JSPS) Grant-in Aid for Scientific Research (C) (No. 20K06977 to Y. M.).

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21. Selected ^{1}H-detected heteronuclear multiple bond coherence (HMBC) correlations for compound **6** are shown in Figure 2.

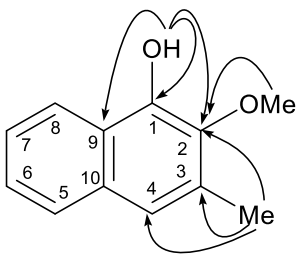

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Figure 2. Selected HMBC correlations for compound **6**