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, and all other total syntheses that followed were based on Corey’s landmark strategy. Currently, this target molecule is semi-synthetically derived from antitumor cyanosafracin B (2c), which is obtained by a modified fermentation of Pseudomonas fluorescens.

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) and the identification of trace metabolite renieramycin T (3c) from the Thai and Philippines blue sponge Xestospongia sp. that was pretreated with KCN. We also reported the synthesis of the ABC ring system of safracins and...
We started our preliminary experiment with compound 5, which was prepared from commercially available 2-methynaphthoquinone-1,4-dione 9 via phthiocel (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>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Anhydride</th>
<th>Yield (%)</th>
<th>Recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(MeCO)₂O (1.0 equiv.)</td>
<td>7a: 37</td>
<td>8a: trace</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>(MeCO)₂O (1.5 equiv.)</td>
<td>7a: 42</td>
<td>8a: 32</td>
</tr>
<tr>
<td>3</td>
<td>C₆H₅</td>
<td>(C₆H₅CO)₂O (1.5 equiv.)</td>
<td>7b: 55</td>
<td>8b: 25</td>
</tr>
<tr>
<td>4</td>
<td>C(Me)₃</td>
<td>((Me)₃CCO)₂O (1.5 equiv.)</td>
<td>7c: ND</td>
<td>8c: ND</td>
</tr>
</tbody>
</table>
We then focused on a recent report on the use of biocatalysts with high accessibility and availability in organic synthesis. 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. Furthermore, Sugai and co-workers reported a lipase-catalyzed site-selective deacetylation of 2,5-dimethylnaphthalene-1,4-diol diacetate. 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 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](attachment:image.png)

**Scheme 3.** Biocatalytic site-selective deacetylation of 8a to 7a
Table 2. Biocatalytic site-selective deacetylation of \(7a\) to \(8a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enzyme</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Time</th>
<th>Yield (%)</th>
<th>Recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(B. cepacia) lipase</td>
<td>cyclopentanol:CPME = 1:2</td>
<td>50</td>
<td>19</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7a 5</td>
<td>8a 94</td>
</tr>
<tr>
<td>2</td>
<td>(B. cepacia) lipase</td>
<td>2-propanol:THF = 1:2</td>
<td>50</td>
<td>19</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7a 5</td>
<td>8a 86</td>
</tr>
<tr>
<td>3</td>
<td>(C. antarctica) lipase B</td>
<td>cyclopentanol:CPME = 1:2</td>
<td>50</td>
<td>4</td>
<td>80</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7a 5</td>
<td>8a ND</td>
</tr>
<tr>
<td>4</td>
<td>(C. antarctica) lipase B</td>
<td>cyclopentanol:CPME = 1:2</td>
<td>50</td>
<td>16</td>
<td>56</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7a 5</td>
<td>8a ND</td>
</tr>
<tr>
<td>5</td>
<td>(C. antarctica) lipase B</td>
<td>cyclopentanol:CPME = 1:2</td>
<td>40</td>
<td>7</td>
<td>88</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7a 5</td>
<td>8a ND</td>
</tr>
</tbody>
</table>

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).

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. 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 \(^1H\)-NMR, \(^13C\)-NMR, IR, and MS data. It was consistent with the long-range \(^1H\)-\(^13C\) correlation between C-2 carbon (δ 141.1) and OH proton (δ 6.06) signals.
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 Novozymes Japan Inc. (Chiba, Japan). *Burkholderia cepacia* 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$_2$O$_2$ (2.4 mL), Na$_2$CO$_3$ (90.6 mg, 0.855 mmol) in H$_2$O (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$_2$O (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$_2$SO$_4$, 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$_2$SO$_4$, 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), 7.31 (1H, s, 2-OH), 2.11 (3H, s, 3-CH$_3$).

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

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$_2$O (1.17 g, 5.0 mmol) in CH$_2$Cl$_2$ (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\textsubscript{2} flash column chromatography (n-hexane : AcOEt = 9 : 1) to give 5 (130 mg, 64%) as a yellow solid. \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\): 8.10-8.02 (2H, m, Ar-H), 7.74-7.65 (2H, m, Ar-H), 4.12 (3H, s, 2-OCH\textsubscript{3}), 2.10 (3H, s, 3-CH\textsubscript{3}).

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

Acetic anhydride (28.0 \(\mu\)L, 300 \(\mu\)mol) was added into a mixture of naphthoquinone 10 (39.5 mg, 200 \(\mu\)mol) and zinc powder (129 mg, 1.98 mmol) in CHCl\textsubscript{3} (1 mL). The resulting mixture was heated at 60 °C for 2 h. The reaction mixture was diluted with CHCl\textsubscript{3} (10 mL) and washed with 1.0 M aqueous HCl solution (10 mL). The organic layer was mixed with CHCl\textsubscript{3} (10 mL), dried over Na\textsubscript{2}SO\textsubscript{4}, and filtered. The solvent was removed in vacuo, and the residue (55.7 mg) was purified by SiO\textsubscript{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. \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\): 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\textsubscript{3}), 2.47 (3H, s, 4-OCOCH\textsubscript{3}), 2.28 (3H, s, 3-CH\textsubscript{3}); \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\): 169.3 (s, 4-OCOCH\textsubscript{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\textsubscript{3}), 20.6 (q, 4-OCOCH\textsubscript{3}), 10.4 (q, 3-CH\textsubscript{3}); IR (CHCl\textsubscript{3}) cm\textsuperscript{-1}: 3535, 3022, 1759, 1600, 1454, 1398, 1226; EIMS m/z (%): 246 (M\textsuperscript{+}, 27), 205 (12), 204 (100), 189 (61), 161 (17); HREIMS: calcd for C\textsubscript{14}H\textsubscript{14}O\textsubscript{4} 246.0892; Found 246.0893.

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

\textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\): 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\textsubscript{3}), 2.48 (6H, s, -OCOCH\textsubscript{3}), 2.27 (3H, s, 3-CH\textsubscript{3}); \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\): 168.8 (s, OOCOCH\textsubscript{3}), 167.8 (s, -OCOCH\textsubscript{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\textsubscript{3}), 20.6 (q, -OCOCH\textsubscript{3}), 20.5 (q, -OCOCH\textsubscript{3}), 10.4 (q, 3-CH\textsubscript{3}); IR (CHCl\textsubscript{3}) cm\textsuperscript{-1}: 3074, 2933, 1759, 1747, 1363, 1217, 1205, 1066, 759; EIMS m/z (%): 288 (M\textsuperscript{+}, 11), 246 (19), 205 (13), 204 (100), 189 (29); HREIMS: calcd for C\textsubscript{16}H\textsubscript{16}O\textsubscript{5} 288.0998; Found 288.0996.

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

Benzoic anhydride (34.2 mg, 149 \(\mu\)mol) was added into a mixture of naphthoquinone 5 (20.5 mg, 101 \(\mu\)mol) and zinc powder (63.7 mg, 98.9 \(\mu\)mol) in CHCl\textsubscript{3} (1 mL). The resulting mixture was heated at 60 °C for 2 h. The reaction mixture was diluted with CHCl\textsubscript{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$_2$SO$_4$. 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, OCOPh), 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-diy 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, OCOPh), 164.5 (s, OCOPh), 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, 3069, 2947, 1738, 1599, 1452, 1396, 1250, 1067; 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-diy 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$_2$O (30 mL), dried over Na$_2$SO$_4$. 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$_2$SO$_4$ 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 = 6 : 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$_2$O (3 × 15 mL). The combined extracts were dried over Na$_2$SO$_4$, 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-OCH$_2$OCH$_3$), 3.90 (3H, s, 2-OCH$_3$), 3.65 (3H, s, 1-OCH$_2$OCH$_3$), 2.48 (3H, s, 4-OCOCH$_3$), 2.25 (3H, s, 3-CH$_3$); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ: 169.0 (s, 4-C), 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), 121.5 (d, C-8), 120.7 (d, C-5), 99.5 (t, OCH$_2$OCH$_3$), 60.6 (q, 2-OCH$_3$), 57.9 (q, 1-OCH$_2$OCH$_3$), 9.1 (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$_2$CO$_3$ (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$_2$SO$_4$. 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-OCH$_2$OCH$_3$), 5.02 (1H, brs, 4-OH), 3.89 (3H, s, 2-OCH$_3$), 3.65 (3H, s, 1-OCH$_2$OCH$_3$), 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-OCH$_2$OCH$_3$), 60.6 (q, 2-OCH$_3$), 57.9 (q, 1-OCH$_2$OCH$_3$), 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 mixture 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. 1H-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-OCH_2OCH_3), 3.91 (3H, s, 2-OCH_3), 3.64 (3H, s, 1-OCH_2OCH_3), 2.47 (3H, s, 3-CH_3); 13C-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-OCH_2OCH_3), 60.7 (q, 2-OCH_3), 58.0 (q, 1-OCH_2OCH_3), 11.3 (q, 3-CH_3); IR (CHCl_3) cm⁻¹: 3030, 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_{12}F_{3}O_{6}S 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 Et₂NH (20.6 µL, 197 µmol) in MeOH (1.0 mL) was vigorously stirred at 20 °C under H₂ (balloon) for 3 h. After removal of insoluble material by filtration through a cellulose pad, the combined filtrates were diluted with H₂O (10 mL), and extracted with Et₂O (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried over Na₂SO₄. The solvent was removed in vacuo, and the residue (16.5 mg) was purified by SiO₂ 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%). 1H-NMR (400 MHz, CDCl₃) 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-OCH₂OCH₃), 3.89 (3H, s, 2-OCH₃), 3.64 (3H, s, 1-OCH₂OCH₃), 2.43 (3H, s, 3-CH₃); 13C-NMR (100 MHz, CDCl₃) 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-OCH₂OCH₃), 60.6 (q, 2-OCH₃), 57.9 (q, 1-OCH₂OCH₃), 9.1 (q, 3-CH₃); IR (CHCl₃) 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}O₃ 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 NaHCO₃ (10 mL), and extracted with Et₂O (3 × 15 mL). The combined extracts were washed with H₂O (15 mL), dried over Na₂SO₄. The solvent was removed in vacuo to give a residue (13.9 mg), which was purified by SiO₂ flash column chromatography (n-hexane : AcOEt = 7 : 1) to give phenol 6 (42.7 mg, 79%) as pale yellow oil.

1H-NMR (400 MHz, CDCl₃) 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-OCH₃), 2.47 (3H, s, 3-CH₃); 13C-NMR (100 MHz, CDCl₃) 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-OCH₃), 16.6 (q, 3-CH₃); IR (CHCl₃) 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 C₁₂H₁₂O₂ 188.0837; Found 188.0837.

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REFERENCES AND NOTES


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

![Figure 2. Selected HMBC correlations for compound 6](image-url)