

**TOTAL SYNTHESIS OF ARDISIAQUINONE A, A POTENT 5-LIPOXYGENASE INHIBITOR, ISOLATED FROM *ARDISIA SIEBOLDII*, AND DEGREE OF 5-LIPOXYGENASE INHIBITORY ACTIVITY OF ITS DERIVATIVES**

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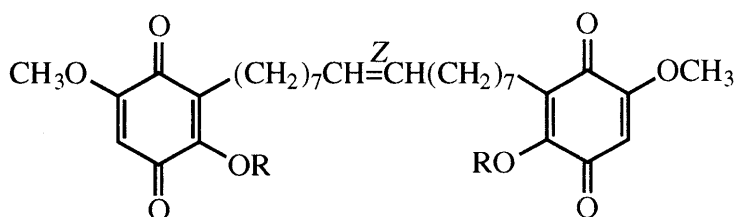
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Ardisiaquinone A (**1**), isolated as a potent 5-lipoxygenase inhibitor from the woods of *Ardisia sieboldii*, has been synthesized efficiently via a cross-coupling reaction between the yne **5** and the iodide **6** derived from the common intermediate **4**. Inhibitory activity for **1** and its derivatives is also reported.

**KEYWORDS** *Ardisia sieboldii*; ardisiaquinone A; 1,4-benzoquinone; 1,4-benzoquinone synthesis; 5-lipoxygenase inhibitor

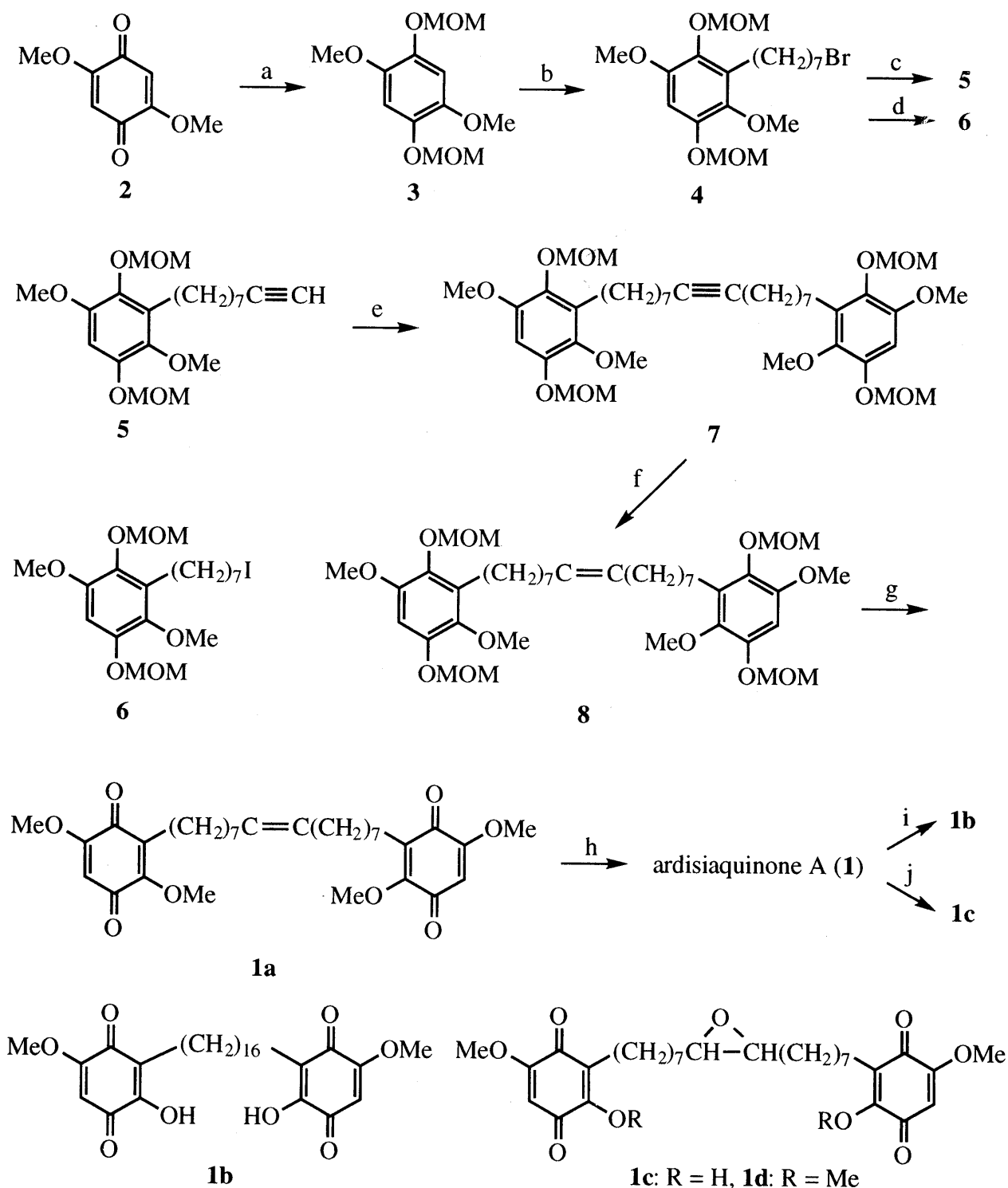
In pursuit of new 5-lipoxygenase inhibitors in natural products,<sup>1)</sup> we have continued to screen inhibitory activity of the plant extracts collected in Yaeyama islands against 5-lipoxygenase by using the enzyme from guinea pig peritoneal polymorphonuclear leukocytes.<sup>2)</sup> As a result, the methanol extract of *Ardisia sieboldii* exhibited a promising inhibitory activity. Activity-guided fractionation of the methanol extract led to the isolation of an inhibitor **1** from the strongest inhibitory active fraction. Its spectral data could assign the active principle **1** as ardisiaquinone A, previously reported by Natori.<sup>3,4)</sup> This simple dimeric structure with unique biological activity aroused our interest for its synthetic possibilities. In this communication, we report the efficient synthesis of ardisiaquinone A (**1**)<sup>5)</sup> and the degree of 5-lipoxygenase inhibitory activity for its derivatives.

Taking the symmetrical structure of **1** into consideration, we have envisioned a key intermediate **4**, which can be readily prepared from **3** by well-documented directed metallation.<sup>6)</sup> In practice, the commercially available 2,5-dimethoxy-*p*-benzoquinone **2** was converted quantitatively into the reduced form **3**, which was lithiated at -78°C with 1.2 eq of *n*-BuLi in the presence of TMEDA, followed by alkylation with 1,7-dibromoheptane to give **4** in 73% yield. The common intermediate



**1**: R = H, **1a**: R = CH<sub>3</sub>

**4**, thereby prepared on a large scale, is ready to be transformed into **5** and **6**, which are needed for the next cross-coupling reaction. The nucleophilic unit **5** was prepared by displacement of the bromide in **4**



**Reagents and conditions;** (a) i)  $\text{Na}_2\text{S}_2\text{O}_4$ ,  $\text{H}_2\text{O}$ , THF, MeOH; ii) MOMCl,  $i\text{-Pr}_2\text{NEt}$ ,  $\text{CH}_2\text{Cl}_2$ , 97%. (b)  $n\text{-BuLi}$ , TMEDA, toluene,  $-78^\circ\text{C}$ , then  $\text{Br}(\text{CH}_2)_7\text{Br}$ , HMPA, 73%. (c) i)  $\text{LiC}\equiv\text{CTMS}$ , HMPA, THF,  $-78^\circ\text{C}$ –RT; ii) TBAF, 92%. (d) NaI, acetone, 97%. (e) LDA, HMPA, THF,  $-78^\circ\text{C}$ , then **6**, 74%. (f)  $\text{H}_2$ , Lindlar cat., 100%. (g) i) 48% HBr, MeOH; ii)  $\text{O}_2$ ,  $\text{NaHCO}_3$ , MeOH, 96%. (h) 70%  $\text{HClO}_4$ ,  $\text{CH}_2\text{Cl}_2$ , THF, 47%. (i)  $\text{H}_2$ , 10% Pd-C, EtOH, 100%. (j) MCPBA,  $\text{CH}_2\text{Cl}_2$ , 100%.

with lithium trimethylsilylacetylide<sup>7)</sup> followed by desilylation with TBAF in 92% yield. On the other hand, the counter electrophile was set up as the iodide **6**<sup>7)</sup> transformed from **4** for the

forthcoming dimerization. Cross-coupling of **6** with the lithium acetylide *in situ* prepared at  $-78^{\circ}\text{C}$  from **5** with LDA smoothly proceeded to give the requisite dimer **7** in 74% yield. Catalytic hydrogenation of the triple bond in **7** under Lindlar catalyst furnished the *Z* olefin **8** with small contamination of the *E* olefin. The MeOH solution of the hydroquinone, obtained by deprotecting the MOM group in **8** with 48% HBr,<sup>9)</sup> was left exposed to bubble through the stream of oxygen, giving rise to the *p*-benzoquinone **1a** in 96 % yield. Finally, treatment of **1a** with a few drops of 70% HClO<sub>4</sub> extruded selectively the more hindered methoxy group to yield ardisiaquinone A (**1**) in 47% yield, which was identical in all respects to the natural one. Thus, we have accomplished the first synthesis of ardisiaquinone A, and our practical procedure should open one way to produce sufficient ardisiaquinone A and its derivatives to perform pharmacological evaluations.

Inhibition (%) of 5-lipoxygenase by ardisiaquinone A and its derivatives is listed in Table I.

Ardisiaquinone A (**1**) exhibited 43% inhibition of 5-lipoxygenase activity at 0.1  $\mu\text{M}$ , whereas the most potent inhibitor was the derivative **1c** containing an epoxide ring. The dihydrogenated and methylated derivatives such as **1a** and **1b**, however, decreased inhibitory activity, presumably due to a slight loss of hydrophilicity and a free movement of both *p*-benzoquinone units spatially disposed into the same direction by the internal *Z* olefin. Further study on pharmacological evaluations of **1** is under way.

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**Table I.** Inhibition (%) of 5-Lipoxygenase<sup>2)</sup> by Ardisiaquinone A (**1**) and Its Derivatives

Compound	Con. ( $\mu\text{M}$ )	Inhibition (%)
<b>1</b>	0.1	43
	0.3	63
<b>1a</b>	0.1	7
	0.3	54
<b>1b</b>	0.1	17
	0.3	41
<b>1c</b>	0.1	66
	0.3	92
<b>1d</b>	0.1	17
	0.3	24
NDGA <sup>a)</sup>	0.3	24

a) nor-Dihydroguaiaretic acid.

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