

# Synthesis of (–)-Ilimaquinone via a Radical Decarboxylation and Quinone Addition Reaction

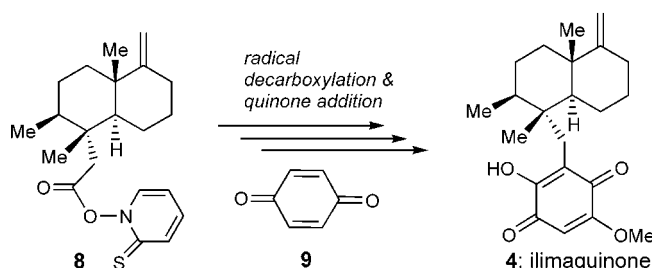
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## ABSTRACT



A stereoselective synthesis of (–)-ilimaquinone (4) is presented. The synthetic strategy is based on a novel radical decarboxylation and quinone addition methodology that produces quinone 7 from reaction of thiohydroxamic acid derivative 8 with benzoquinone (9). Final functionalization of 7 to ilimaquinone (4) is achieved by exploring the electronic effects of the residual thiopyridyl group.

Marine organisms represent a rich source of natural products that often possess novel chemical structures and interesting biological and pharmacological properties.<sup>1</sup> Among these products is included a family of quinone sesquiterpenes, selected members of which are avarol (1),<sup>2</sup> avarone (2),<sup>2</sup> nakijiquinone A (3),<sup>3</sup> ilimaquinone (4),<sup>4</sup> smenospongine (5),<sup>5</sup> and smenospongidine (6)<sup>5</sup> (Figure 1).

All members of this family are distinguished by a common chemical architecture in which the C9 position of a trans-decalin ring is attached to a variably hydroxylated (or

heteroatom substituted) quinone or hydroquinone unit. Interestingly, this nearly identical structural motif translates to a variety of exciting biological properties often unique to each family member. For example, avarol (1) and avarone (2) have been shown to exhibit anti-HIV properties,<sup>6</sup> while nakijiquinone A (3) was found to inhibit selectively the Her-2/Neu protooncogene.<sup>3,7</sup> On the other hand, ilimaquinone (4) was found to exhibit anti-HIV, antimitotic, and antiinflammatory activities,<sup>8</sup> in addition to promoting a reversible vesiculation of the Golgi apparatus and interfering with intracellular protein trafficking.<sup>9</sup>

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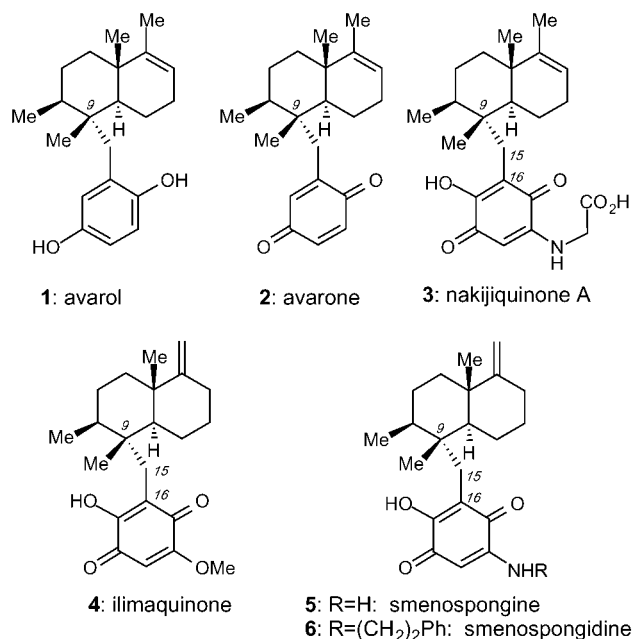
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**Figure 1.** Selected structures of quinone sesquiterpenes.

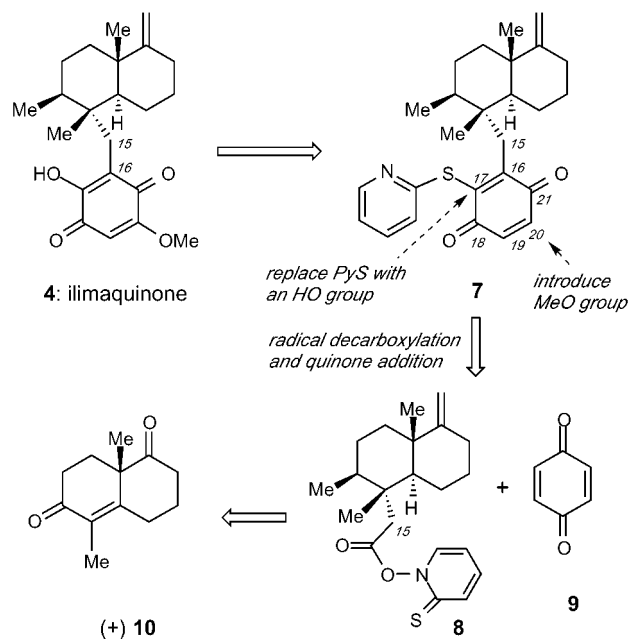
Inspired by the interesting chemical structures and promising biological activities, we sought to design a “unified” approach to these quinone sesquiterpenes. Our synthetic strategy is based on a novel radical decarboxylation and quinone addition method, the validity of which was initially demonstrated with the synthesis of avarol (**1**) and avarone (**2**).<sup>10</sup> Herein we further expand this method to the synthesis of ilimaquinone (**4**).<sup>11</sup>

The retrosynthetic analysis of ilimaquinone is shown in Figure 2 and rests upon a photochemical decarboxylation of thiohydroxamic ester **8** and trapping of the derived C15 radical with benzoquinone (**9**) to produce quinone **7**. It was expected that further functionalization of adduct **7** by introducing a methoxy group at the C20 carbon center and replacing the thiopyridyl group at C17 with a hydroxide species could form the ilimaquinone structure. Starting material for this venture would then be the Wieland–Miescher enone **10**, which upon additional functionalizations could provide activated ester **8**.

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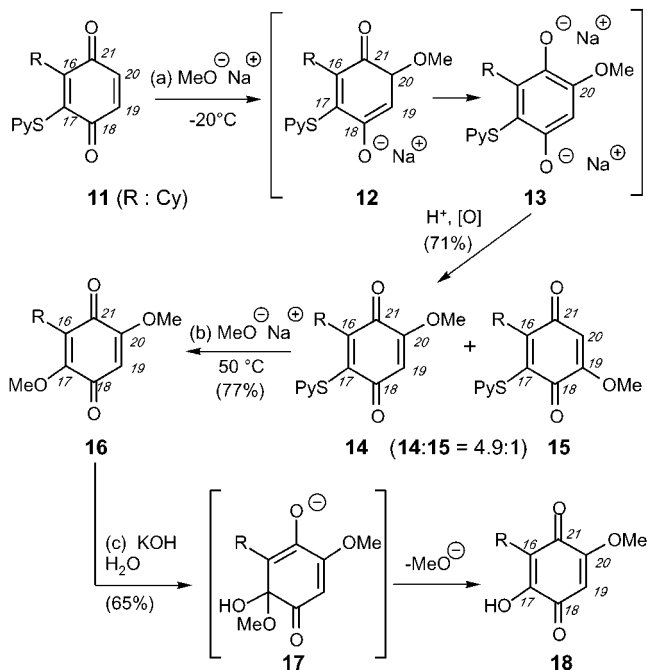
**Figure 2.** Retrosynthetic analysis of ilimaquinone (**4**).

At the onset of our studies we were concerned with the regiochemistry of the sodium methoxide addition as well as the replacement of the thiopyridyl group by a hydroxide anion. In principle, sodium methoxide can either replace the thiopyridyl group at the C17 carbon center of **7** via an addition–elimination process or add in a conjugate fashion on the C19–20 double bond (ilimaquinone numbering). In the latter case one could envision the formation of two regioisomers arising from addition at the C19 or C20 centers, the ratio of which would be dependent on the relative reactivity of the two carbonyl groups. To examine the sodium methoxide addition, we investigated its reaction with a similarly functionalized quinone, **11**<sup>12</sup> (R = cyclohexyl group, PyS = thiopyridyl group). Our initial studies revealed that this addition produces a mixture of hydroquinone adducts that are slowly oxidized upon exposure to air to the corresponding quinones (Scheme 1). To facilitate the products isolation and characterization, we decided to treat the mixture with excess MnO<sub>2</sub>, thus driving the oxidation process to completion. This sequence afforded best results using 5 equivs of sodium methoxide at –20 °C followed by acid extraction and subsequent treatment with 5 equiv of MnO<sub>2</sub>. Under these conditions we obtained a mixture of isomeric quinones **14** and **15** in a 4.9:1 ratio in favor of **14** (71% combined yield).<sup>13</sup> Formation of the major product **14** is proposed to occur via the intermediacy of adducts **12** (or **13**), in which the crucial addition of methoxide anion to the C20 center has been accomplished. The regioselectivity of the methoxide addition can be mechanistically rationalized by comparing the relative electron deficiency of the C18 and

(12) For the synthesis of **11**, see Supporting Information.

(13) The structures of the quinone addition products were assigned by NOE and HMBC experiments. See Supporting Information for details.

**Scheme 1.** Studies on the Regiochemistry of the Sodium Methoxide Addition to Quinones<sup>a</sup>



<sup>a</sup> Reagents and conditions: [R = cyclohexyl]; (a) 5.0 equiv of MeONa (0.5 M in MeOH), THF,  $-20^\circ\text{C}$ , 2 h; then aqueous  $\text{NH}_4\text{Cl}$ , AcOEt, 5.0 equiv of  $\text{MnO}_2$ ,  $25^\circ\text{C}$ , 1 h, 59% for **14** and 12% for **15**; (b) 3.0 equiv of MeONa (0.5 M in MeOH), MeOH,  $50^\circ\text{C}$ , 1 h; 77%; (c) 3.0 equiv of KOH, MeOH/ $\text{H}_2\text{O}$  (1/1), 65%.

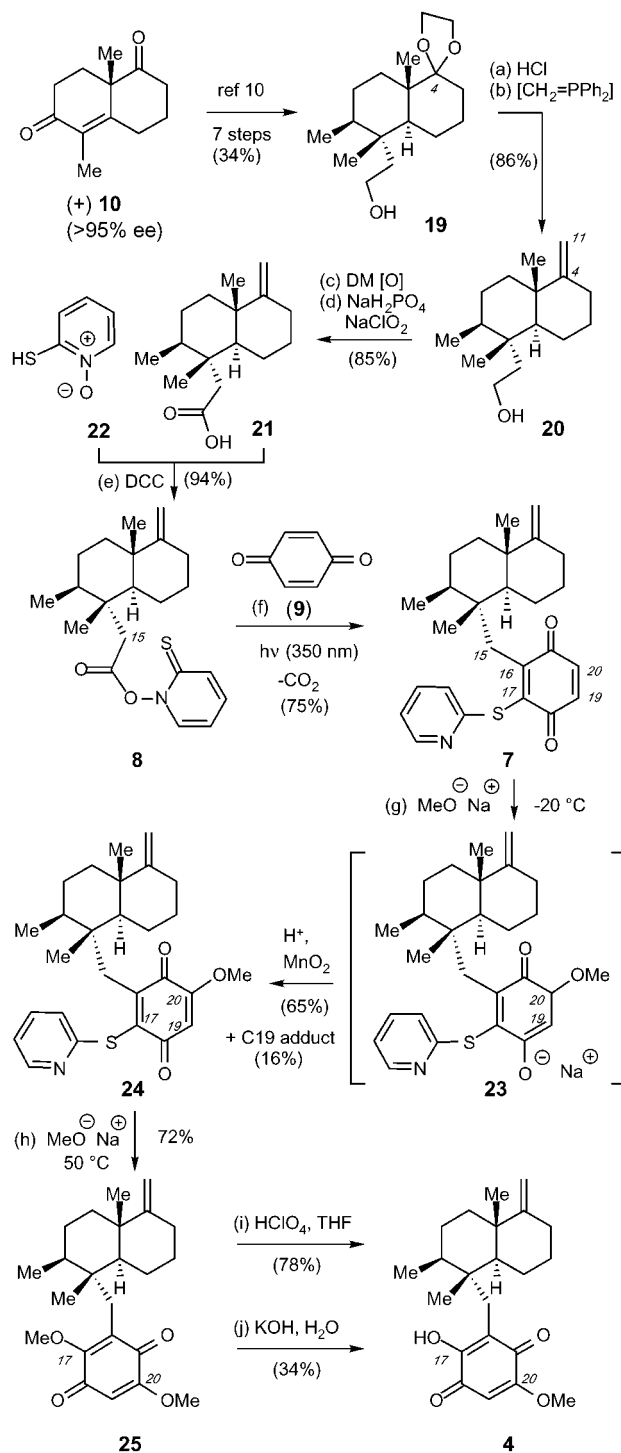
C21 carbonyl groups. Among them, the C21 carbonyl group is electronically richer due to the electron-donating effect of the thiopyridyl group at the C17 center (vinylogous ester functionality).<sup>14</sup> By virtue of this effect, the C18 carbonyl group is more electronically deficient and consequently the C20 center becomes a better electrophilic center for conjugate additions. Hence, the preferred site for the methoxide addition is the C20 carbon atom (Scheme 1).<sup>15</sup>

The next task was the exchange of the thiopyridyl group with a hydroxyl equivalent. However, all attempts to perform this displacement in a direct way, by reacting **14** with hydroxide anion, led to formation of multiple products, arising presumably by reaction of hydroxide anions both at the C17 and C20 centers. This problem was circumvented by using a two-step procedure that involved reaction of **14** with sodium methoxide (3 equiv at  $50^\circ\text{C}$ ) to afford dimethoxy quinone **16** (77% yield), followed by selective monodeprotection of the C17 center to produce the desired compound **18** (Scheme 1). The selectivity observed during the last step may be explained by considering the relative stability of the tetrasubstituted enolate **17** versus the less

(14) The "vinylogous ester" effect of alkoxy groups in benzoquinone and related compounds has been explored in regioselective Diels–Alder reactions. For selected reviews on this topic, see: Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, New York, 1991; pp 315–399. Woodward, R. B.; Katz, T. J. *Tetrahedron* **1959**, *5*, 70–89.

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**Scheme 2.** Total Synthesis of Ilimaquinone (**4**)<sup>a</sup>



<sup>a</sup> Reagents and conditions: (a) 0.1 N HCl, THF, 3 h,  $25^\circ\text{C}$ , 93%; (b) 3.0 equiv of  $\text{CH}_3\text{PPh}_3\text{Br}$ , 2.5 equiv of NaHMDS, THF,  $65^\circ\text{C}$ , 10 h, 92%; (c) 1.2 equiv of Dess–Martin periodinane,  $\text{CH}_2\text{Cl}_2$ , 1 h,  $25^\circ\text{C}$ , 96%; (d) 2.0 equiv of  $\text{NaClO}_2$ , 2.0 equiv of  $\text{NaH}_2\text{PO}_4$ , 2.0 equiv of  $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)_2$ , tBuOH/ $\text{H}_2\text{O}$ : 2/1  $25^\circ\text{C}$ , 1 h, 89%; (e) 1.0 equiv of **21**, 1.0 equiv of **22**, 1.0 equiv of DCC,  $\text{CH}_2\text{Cl}_2$ , 12 h,  $25^\circ\text{C}$ , (dark), 94%; (f) 3.0 equiv of **9**,  $\text{CH}_2\text{Cl}_2$ , hv ( $2 \times 500 \text{ W}$ ), 2 h,  $0^\circ\text{C}$ , 75%; (g) 5.0 equiv of MeONa (0.5 M in MeOH), MeOH,  $-20^\circ\text{C}$ , 2 h; then aqueous  $\text{NH}_4\text{Cl}$ ,  $\text{CH}_2\text{Cl}_2$ , 5.0 equiv of  $\text{MnO}_2$ , 1 h, 65% for **24** and 16% for C19-adduct; (h) 3.0 equiv of MeONa (0.5 M in MeOH), MeOH,  $50^\circ\text{C}$ , 1 h; 77%; (i) 1.2 equiv of oHClO<sub>4</sub> (70% aq.), THF,  $25^\circ\text{C}$ , 4 h, 78%.

substituted one arising from conjugate addition at the C20 center.<sup>16</sup>

Application of the above strategy to the synthesis of ilimaquinone (**4**) is illustrated in Scheme 2. Enantiomerically enriched enone **10** was converted to alcohol **19**,<sup>10</sup> which upon acid-catalyzed deprotection of the C4 ketal and Wittig methylenation afforded compound **20** (86% combined yield). The C15 hydroxyl group of **20** was then oxidized to the corresponding carboxylic acid **21** (Dess–Martin periodinane<sup>17</sup> and sodium chlorite, 85% combined yield), which upon DCC-induced coupling with commercially available *N*-hydroxy-2-thiopyridone (**22**) furnished adduct **8** (94% yield).<sup>18</sup> Light-induced decarboxylation (>350 nm) of **8** in the presence of excess benzoquinone (**9**) produced the substituted quinone **7** in 75% yield.<sup>19</sup> The structure of **7** can be mechanistically explained by considering an initial formation of a semiquinone adduct that is further oxidized to **7** with an excess of **9**.<sup>20</sup> Treatment of adduct **7** with sodium methoxide at –20 °C followed by one-pot oxidation with MnO<sub>2</sub> afforded quinone **24**, presumably via intermediate **23**, in 65% yield. Under these conditions the C19-methoxylated adduct was also isolated as a minor product (16% yield) and was chromatographically separated from the desired compound **24**. Further exposure of **24** with excess of sodium methoxide at 50 °C produced dimethoxyquinone **25** in 72% yield. The spectroscopic and analytical data of **25** were

(16) Although the regioselective hydrolysis of a more hindered methoxy group under basic conditions has been reported in the literature (ref 7), no explanation for this effect was offered.

(17) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287. Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(18) For selected reviews on the photochemistry of thiohydroxamic acid derivatives, see: Crich, D. *Aldrichimica Acta* **1987**, *20*, 35–49. Barton, D. H. R. *Pure Appl. Chem.* **1994**, *66*, 1943–1954. Barton, D. H. R. *Tetrahedron* **1992**, *48*, 2529–2544.

(19) Barton, D. H. R.; Sas, W. *Tetrahedron* **1990**, *46*, 3419–3430. Barton, D. H. R.; Bridon, D.; Zard, S. Z. *Tetrahedron* **1987**, *43*, 5307–5314.

(20) Alkyl-substituted quinones are known to have a lower oxidation potential than the unsubstituted counterparts. For recent reviews on this topic, see: (a) *The Chemistry of the Quinonoid Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1988; Vol. 1, p 2. (b) *Naturally Occurring Quinones IV: Recent Advances*, 4th ed.; Thomson, R. H., Ed.; Blackie Academic & Professional: London, 1997.

identical with the literature values, thereby supporting the prediction that the methoxide functionalities were appropriately incorporated at the C20 and C17 centers.<sup>11</sup> Selective hydrolysis of **25** at the C17 center was then attempted under basic conditions (aqueous KOH). Despite our encouraging results in model studies (see Scheme 1) this reaction produced a complex mixture of quinones, containing ilimaquinone **4** in 34% yield (calculated by NMR). Gratifyingly, treatment of **26** under dilute perchloric acid conditions produced the desired natural product **4** in 78% yield.<sup>21</sup> Compound **4** was spectroscopically and analytically identical with the natural ilimaquinone.<sup>22</sup>

In conclusion, we have developed an efficient synthesis of (–) ilimaquinone (**4**). Our synthesis is based on a novel radical decarboxylation and quinone addition methodology that was used to construct the carbocyclic framework of the natural product. Taking advantage of both the electronic effects and the leaving ability of the residual thiopyridyl group we developed conditions for sequential regioselective oxygenations of the quinone ring. Our strategy extends the scope, applicability, and versatility of the above methodology and opens the way for the construction of differentially substituted derivatives of the natural product.

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**Supporting Information Available:** <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra for compounds **4**, **7–8**, **11**, **14–16**, **18–21**, and **24–25**. Experimental procedures for compounds **8** and **11**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(21) Fukuyama, Y.; Kiriya, Y.; Kodama, M. *Chem. Pharm. Bull.* **1998**, *46*, 1770–1775. Kubo, I.; Kamikawa, T.; Miura, I. *Tetrahedron Lett.* **1983**, *24*, 3825–3828.

(22) A sample of natural ilimaquinone was obtained by Professor D. John Faulkner (Scripps Institute of Oceanography).