Total Synthesis of (−)-Ilimaquinone

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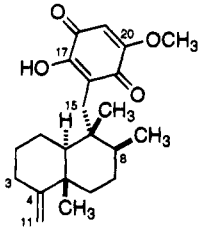
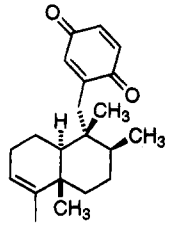
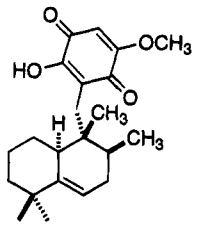
Natural products have often served as effective probes of cellular processes.[2] Within this context, the sesquiterpene quinones,[3] with their wide range of biological activities,[4] may be useful in developing a better understanding of the molecular basis of specific biological events. In this family of quinones, the cellular effects reported for ilimaquinone are especially noteworthy. We now report the first synthesis of (−)-ilimaquinone (**1**).[5]



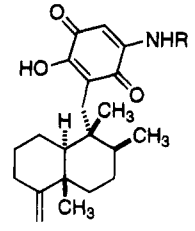
ilimaquinone (**1**)



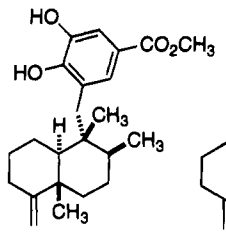
avarone



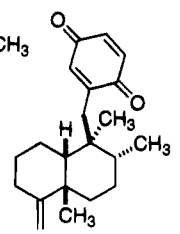
mamanuthaquinone



smenospongine R=H; smenospongidine R=CH_2CH_2Ph



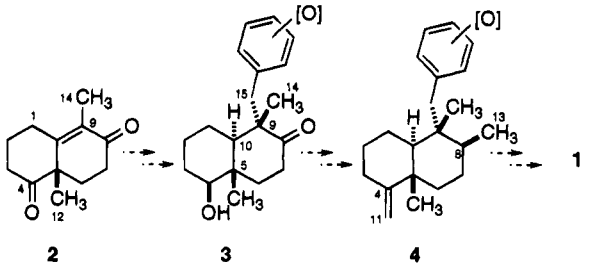
smenospondiol



arenarone

Originally isolated from *Hippiospongia metachromia*,[6] ilimaquinone is reported to have antimicrobial, anti-HIV,[7] antiinflammatory, antimitotic,[8] and antisecretory[9] activity. Although the molecular basis for this broad range of activity is unknown, it is plausible that ilimaquinone's antimitotic, antiinflammatory, and antisecretory activities are due to interactions with cytoskeletal elements, particularly when avarone's ability to influence microtubule functions is considered.[10] In this regard, we plan to use ilimaquinone analogs to study the endosomal and cytoskeletal components affected by this compound.

Scheme 1



2 **3** **4**

Isolation of an intracellular target for ilimaquinone will require an active analog that carries a tethered reporter group. Construction of such an analog demands a flexible, asymmetric synthesis, where numerous modifications can be made on the ilimaquinone structure. In light of these requirements, we herein report the first step in our program aimed at deciphering the mechanism of action of this natural product.

Our strategy for the synthesis of ilimaquinone is summarized in Scheme 1. With compound **2** as the starting point, a masked quinone could be introduced and the decalin ring fusion stereochemistry established by a reductive alkylation (→**3**).[11] After the completion of the remaining decalin functionality (→**4**), the masked quinone moiety could be unveiled to yield **1**.

Diketone **2** is readily available in 60% yield and 75–90% ee through an L-phenylalanine-mediated enantioselective Robinson annulation.[12] Recrystallization from Et_2O/hexanes provides material with >99% ee.[13] As shown in Scheme 2, diketone **2** is reduced to alcohol **5** ($NaBH_4$, 95%)[14] which is then treated with lithium/ammonia. The resulting lithium enolate is quenched with 2-chloro-3,5-dimethoxybenzyl bromide (**6**)[15] to give compound **7** in a 75% yield.[16] These first transformations thus establish the ring system and three of the four contiguous stereocenters found in the decalin portion of ilimaquinone.

The remaining stereocenter (C-8) is established through a Wittig olefination of ketone **7**, followed by a platinum-

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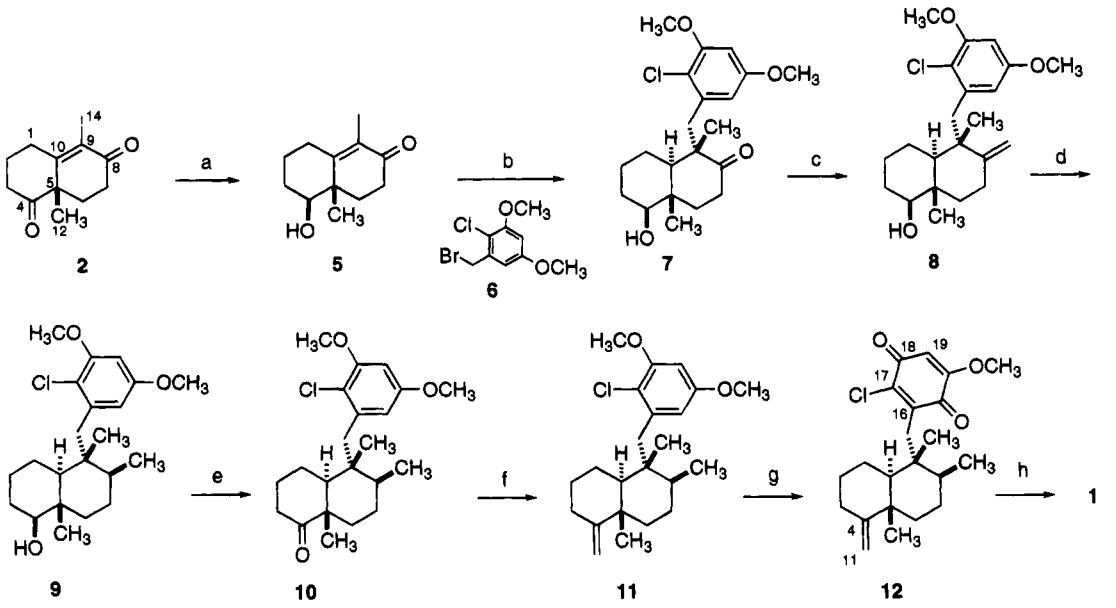
Scheme 2[a]



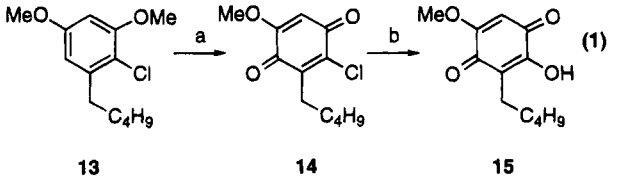
[a] Key: (a) $NaBH_4$, EtOH (95%); (b) Li, NH_3, **6** (75%); (c) $Ph_3P{=}CH_2$, DMSO (71%); (d) H_2, PtO_2, CH_2Cl_2 (60%); (e) PCC, CH_2Cl_2 (95%); (f) $Ph_3P{=}CH_2$, DMSO (82%); (g) CAN, CH_3CN, H_2O (72%); (h) $Pd(Ph_3P)_4$, THF, H_2O, $NaHCO_3$ (33%).

catalyzed hydrogenation of the resulting exo-olefin. This sequence introduces the C-13 methyl group as a mixture of diastereoisomers favoring compound **9** (3:1 ratio). Oxidation of the alcohol functionality of **9**, followed by a Wittig olefination of the resulting ketone, produces alkene **11** in 78% overall yield. With the completion of the lower portion of ilimaquinone, we next turned our attention to the quinone portion of the molecule.

A survey of the literature presented several possible strategies for the construction of the quinone ring found in **1**.[17] Our original plan was to assemble the target moiety by oxidizing a dimethoxyaryl group to a methoxyquinone. A Thiele–Winter acetoxylation[18] followed by treatment of the resulting triacetoxyaryl moiety with LAH and mild oxidation of the aryl system would then be employed to yield the desired quinone functionality.[19] Unfortunately, in practice the acetoxylation was met with a nonproductive consumption of starting material which involved the loss of the $\Delta^{4,11}$ olefin.[20]

After examining alternate solutions and considerable experimentation, we found that oxidation of a chlorodimethoxyarene will produce a chloromethoxyquinone in a reasonable yield (*cf.*, eq 1, Scheme 3). Furthermore, the chloromethoxyquinone can be converted to the desired quinone functionality found in **1** by a palladium-mediated exchange of the chloride for a hydroxyl group.[21]

Scheme 3[a]



[a] Key: (a) CrO_3, AcOH, H_2O (68%); (b) $Pd(Ph_3P)_4$, $NaHCO_3$, THF, H_2O (50%).

Application of this chemistry to the completion of the total synthesis is illustrated in Scheme 2. Oxidation of **11** to the chloromethoxyquinone **12** proceeds in 72% yield with cerium ammonium nitrate.[22] In the final step, treatment of chloroquinone **12** with palladium(0) in basic aqueous THF delivers (−)-ilimaquinone in 33% yield.

This total synthesis of (−)-ilimaquinone requires 10 steps and proceeds in 3% overall yield from commercially available starting materials. Of special interest is the oxidation strategy developed to establish the natural product's sensitive quinone functionality. Moreover, the synthesis route offers numerous opportunities for the preparation of analogs that will serve to identify interactions responsible for ilimaquinone's wide range of biological activities.

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Supplementary Material Available: Detailed experimental procedures and characterization data for compounds **1**, **5**, and **7**–**12** (6 pages).

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