50.6, 48.7, 46.6, 43.7, 38.9, 34.4, 33.0, 29.7, 26.7, 26.1, 25.4, 21.2, 17.3, 12.2, 9.6; MS (CI, NH_3): 356 [M+1], 373 [M+18]; HR-MS (CI, CH_4) calcd for $C_{20}H_{37}NO_4$ [M+H]: 355.2723, found: 355.2715.

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Keywords: aldol reactions · antifungal agents · asymmetric synthesis · macrocycles · total synthesis

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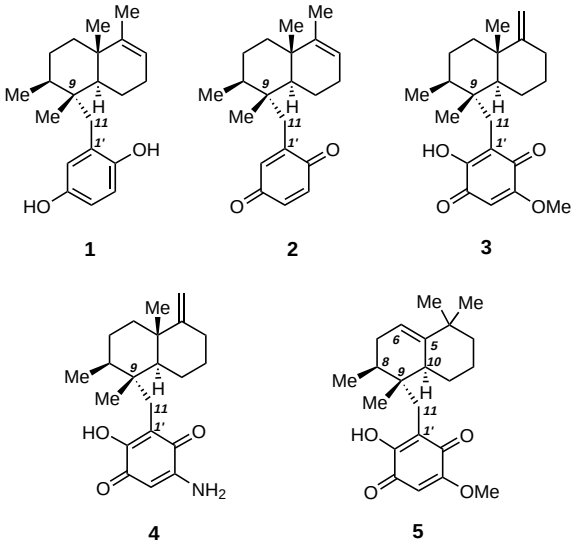
Enantioselective Total Synthesis of Avarol and Avarone**

Taotao Ling, Alan X. Xiang, and Emmanuel A. Theodorakis*

In memory of Sir Derek H. R. Barton

Quinone and hydroquinone subunits are featured in a variety of natural products,[1] including a family of marine metabolites represented by avarol (**1**),[2] avarone (**2**),[2] ilimaquinone (**3**),[3] smenospongine (**4**),[4] and mamanuthaquinone (**5**).[5] Among the exciting and diverse biological properties exhibited by all members of this family, the antimitotic, antileukemic, and antiviral effects reported for **1** and **2** are particularly noteworthy.[6] Although the chemical origins of



these biological properties remain obscure, the redox properties of the hydroquinone – quinone system present in **1** and **2** may be held accountable for such a profile.[7]

The combination of attractive structure and biological activity displayed by the above family has spurred the development of multiple syntheses for some of these compounds.[8, 9] A common element in all reported strategies is the early assembly of the entire skeleton of the natural products

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Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

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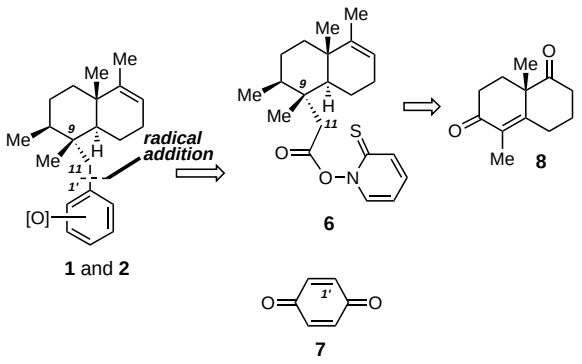
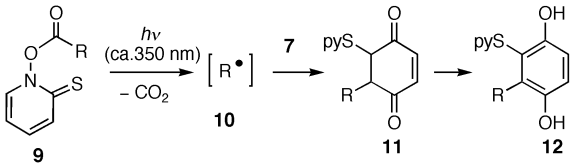
by constructing the C9–C11 bond. This is generally achieved by allowing the C9 enolate (formed by in situ reduction of enone **8**, see Scheme 1) to react with a suitably substituted benzyl bromide.[10] While this regime has allowed the synthesis of the natural products, it consistently suffers from low yields during the final deprotection of the masked quinone.

In considering the above observations, we sought to develop a method for constructing the entire framework by forming the C11–C1′ carbon–carbon bond (Scheme 1). If



Scheme 1. Strategy for the synthesis of avarol (**1**) and avarone (**2**).

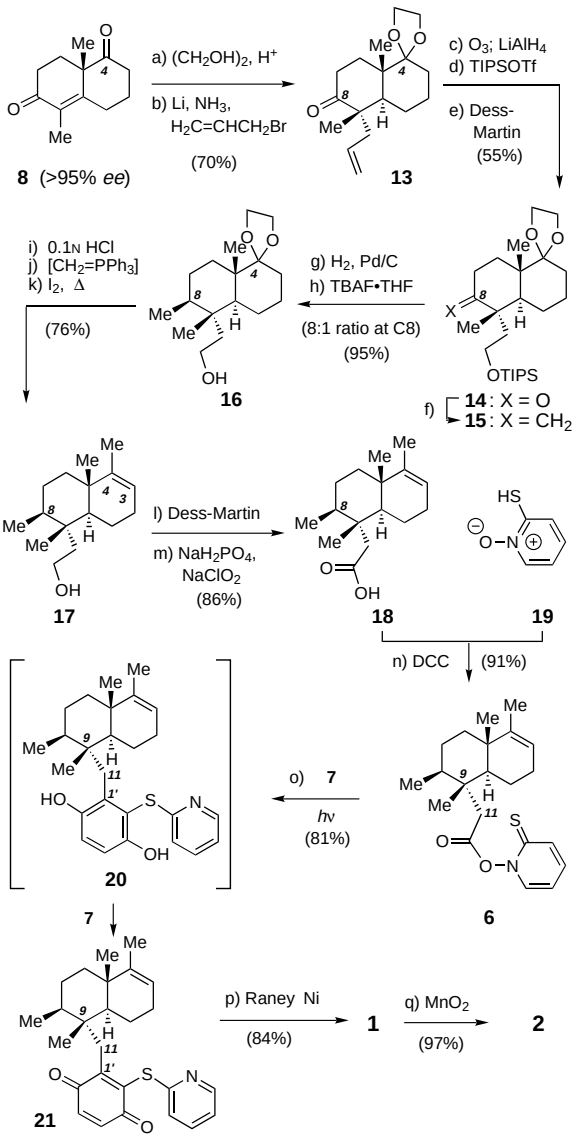
successful, this strategy could allow for the rapid construction of several analogues of **1** and **2** differing only in the quinone moiety, which could be used to address the significance of the redox chemistry of these molecules during a biological event. In addition, this strategy could circumvent the low-yielding deprotection steps toward **1** or **2**. To this end, application of Barton's radical decarboxylation and quinone addition appeared to be the best reaction candidate (Scheme 2).[11]



Scheme 2. Use of Barton's radical decarboxylation and addition to quinones for the synthesis of **12**. py = 2-pyridyl.

Conceptually, this reaction involves photochemical activation of a thiohydroxamic ester **9** and in situ trapping of the generated carbon-centered radical **10** with a quinone radicophile (such as benzoquinone (**7**)).[12] In accordance with a radical chain mechanism, this conjugate-type addition was expected to furnish initially the 1,2 substituted quinone **11**, which could rapidly tautomerize to hydroquinone **12**. Further manipulation of **12** could produce avarol (**1**) and avarone (**2**). Execution of this strategy is shown in Scheme 3.[13]

Our synthetic approach began with optically pure enone **8**, which was readily available through an L-phenylalanine-mediated asymmetric Robinson annulation (60–65% yield, >95% *ee*).[14] Selective protection of the C4 ketone group followed by reductive alkylation with allyl bromide afforded ketone **13** in 70% overall yield. Transformation of alkene **13** to silyl ether **14** was accomplished in 64% combined yield by ozonolysis, reduction, and silylation of the resulting alcohol. The C8 ketone functionality that also suffered reduction



Scheme 3. Synthesis of avarol (**1**) and avarone (**2**). a) $(CH_2OH)_2$ (1.0 equiv), TsOH (0.1 equiv), 80 °C, benzene, 12 h, 90%; b) Li (5.0 equiv), NH_3, $-80 \rightarrow -30$ °C, H_2O (1.0 equiv), $CH_2{=}CHCH_2Br$ (5.0 equiv), $-80 \rightarrow -30$ °C, 5 h, 78%; c) O_3, CH_2Cl_2, -78 °C, then $LiAlH_4$ (3.0 equiv), Et_2O, $0 \rightarrow 25$ °C, 1 h, 65%; d) TIPSOTf (1.0 equiv), 2,6-lutidine (1.3 equiv), CH_2Cl_2, -80 °C, 0.5 h, 98%; e) Dess–Martin periodinane (1.6 equiv), CH_2Cl_2, 1 h, 25 °C, 87%; f) CH_3PPh_3Br (3.0 equiv), NaHMDS (2.5 equiv), THF, 65 °C, 10 h, 89%; g) Pd/C (10%, 0.1 equiv by weight), H_2, CH_3CO_2Et, 25 °C, 12 h, 95%; h) TBAF·THF (1N, 1.3 equiv), THF, 25 °C, 0.5 h, 100%; i) 0.1N HCl, THF, 3 h, 25 °C, 93%; j) CH_3PPh_3Br (3.0 equiv), NaHMDS (2.5 equiv), THF, 65 °C, 10 h, 92%; k) I_2 (0.01 equiv), xylenes, 150 °C, 12 h, 89%; l) Dess–Martin periodinane (1.2 equiv), CH_2Cl_2, 1 h, 25 °C, 96%; m) $NaClO_2$ (2.0 equiv), NaH_2PO_4 (2.0 equiv), $CH_3CH{=}C(CH_3)_2$ (2.0 equiv), *t*BuOH/H_2O (2/1), 25 °C, 1 h, 90%; n) **19** (1.0 equiv), **18** (1.0 equiv), DCC (1.0 equiv), CH_2Cl_2, 12 h, 25 °C, dark, 91%; o) **7** (3.0 equiv), CH_2Cl_2, *hν* (300 W), 2 h, 0 °C, 81%; p) Raney nickel (excess), CH_2Cl_2, 45 °C, 10 min, 84%; q) MnO_2 (5.0 equiv), Et_2O, 25 °C, 0.5 h, 97%. DCC = dicyclohexylcarbodiimide, HMDS = hexamethyldisilylamide, TBAF = tetrabutylammonium fluoride, TIPSOTf = triisopropylsilyl trifluoromethanesulfonate, TsOH = *p*-toluenesulfonic acid.

during the above procedure was subsequently restored upon treatment with Dess–Martin periodinane (87% yield). Manipulation of the C8 stereocenter was attained by Wittig olefination of the C8 ketone followed by a Pd-catalyzed

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hydrogenation of the exocyclic methylene unit. This procedure installed the methyl group at the C8 carbon atom in 85% combined yield, as an unseparable mixture of stereoisomers (8:1 in favor of the desired β epimer). The stereoisomers were easily separated after a fluoride-induced deprotection of the primary silyl ether, and alcohol **16** was furnished in 75% overall yield (starting from **14**). Acid-catalyzed deprotection of the C4 ketal of **16** followed by a second Wittig methylenation provided the *exo*-alkene, which was isomerized to the C3–C4 endocyclic olefin **17** upon treatment with iodine (76% yield over three steps).

The stage was now set for the attachment of the aromatic residue on the avarol core. This was accomplished by a two-step oxidation of primary alcohol **17** to carboxylic acid **18** with Dess–Martin periodinane and sodium chlorite (86% overall yield). DCC-induced esterification of **18** with commercially available 2-sulfanylpyridine *N*-oxide (**19**) furnished the photolabile ester **6** (91% yield).[12] Light-induced decarboxylation (350 nm) of **6** in the presence of benzoquinone (**7**, 3.0 equiv) produced the substituted quinone **21** in 81% yield. The structure of **21** can be mechanistically rationalized by considering an initial formation of the hydroquinone adduct **20**, which is further oxidized in situ with excess **7**.[12, 15, 16] An additional remarkable feature of this radical addition is its efficiency, especially when considering the presumed steric hindrance of the intermediate neopentylic carbon-centered radical at C11.

For the transformation of **21** to **1** a reductive desulfurization procedure was sought. To this end, brief treament of **20** with Raney nickel produced synthetic avarol (**1**) in high yield. Avarone (**2**) was produced from **1** in 97% yield by heterogeneous oxidation with MnO_2.

In conclusion, we have developed an enantioselective synthesis of avarol (**1**) and avarone (**2**) that departs from the readily available Wieland–Miesher-type enone **8** and proceeds in 16 steps and 12% overall yield.[17] Essential to our strategy is the application of Barton's radical decarboxylation and quinone addition reaction employed to install the quinone nucleus during the last steps of the synthesis. Our strategy provides the first application of the above methodology to natural products synthesis and clearly demonstrates its power and versatility. Our strategy also paves the way for the construction of designed analogues of **1** and/or **2** that could be used to address biologically relevant issues.

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