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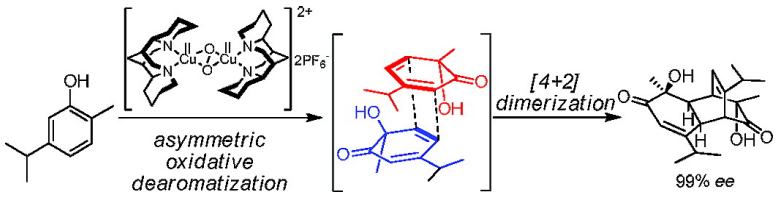
J. Am. Chem. Soc., **2008**, 130 (9), 2738-2739 • DOI: 10.1021/ja711018z



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Enantioselective Synthesis of Bicyclo[2.2.2]octenones Using a Copper-Mediated Oxidative Dearomatization/[4 + 2] Dimerization Cascade[1]

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The bicyclo[2.2.2]octenone skeleton is found in a number of natural products (Figure 1) including homodimers **1**[2] and **2** (aquaticol)[3] and the hetero adduct chamaecypanone C (**3**).[4] Although Diels−Alder cycloaddition of 2,4-cyclohexadienones and *o*-quinols with activated alkenes has frequently been used for the synthesis of bicyclo[2.2.2]octenones, 2,4-cyclohexadienones also have a high propensity to undergo spontaneous [4 + 2] dimerization to homodimeric bicyclo[2.2.2]octenones.[5] Although numerous synthetic efforts utilizing oxidative dearomatization of substituted phenols to construct the bicyclo[2.2.2]octenone core have been developed,[6] the corresponding enantioselective process has not been reported.[7] We have previously reported the highly enantioselective synthesis of azaphilones involving copper-mediated oxidative dearomatization of *o*-alkynylbenzaldehydes.[8] Herein, we report a general protocol for the enantioselective oxidative hydroxylation of phenols (Scheme 1) followed by homodimerization to bicyclo[2.2.2]octenones.

We first investigated oxidation of the 2,5-disubstituted phenol carvacrol (**4**) using conditions previously reported for 2,4-dihydroxybenzaldehyde substrates en route to the azaphilones[8] (Table 1, entry 1). In the event, reaction of **4** with a [(−)-sparteine]$_2$Cu$_2$O$_2$(PF$_6$)$_2$ complex and *N*,*N*-diisopropylethylamine (DIEA) in CH_2Cl_2 at −78 °C (16 h) afforded a mixture of the [4 + 2] dimer (3*S*,10*S*)-**1** in 25% isolated yield (99% ee by chiral HPLC analysis) and biaryl coupling product **5** (23%).[9] The backbone structure and absolute configuration of (3*S*,10*S*)-**1** were determined by comparison to NMR and CD spectral data reported for natural product (3*R*,10*R*)-**1**.[2,10]

Further optimization studies revealed that use of LiHMDS to generate the phenolate in THF as solvent,[11] followed by oxidative dearomatization, cleanly afforded dimer **1** in 58% isolated yield (>99% ee) with a trace amount of biaryl formation (Table 1, entry 2). Use of DIEA as base in THF (entry 3) also led to preferential formation of dimer **1**. This result, along with reactions in propionitrile (entry 4) and acetone (entry 5), revealed a strong solvent effect for the reaction. Solvent and ligand effects reported in the literature[12] have generally been attributed to the equilibrium of binuclear copper-peroxo (**P**, μ-η^2:η^2-peroxodicopper(II)) and copper-oxo (**O**, bis(μ-oxo)dicopper(III)) complex forms.[13,14] In the case at hand, the solvent effects may be rationalized by greater levels of the corresponding radical abstracting[15] [(−)-sparteine]$_2$bis(μ-oxo)dicopper(III) (**O**) complex in CH_2Cl_2 and the electrophilic μ-η^2:η^2-peroxodicopper(II) (**P**) complex in THF. Although evaluation of alternative counterions[16] (e.g. BF_4^-, OTf^-, Cl^-) to favor formation of the corresponding **P** complex did not show substantial improvement over PF_6^-,[10] we found that preformation of the phenolate with LiOH increased conversion and afforded dimer **1** in good yield and high enantioselectivity (>99% ee) (Table 1, entry 6).

To evaluate the scope and limitations of this methodology, a number of phenol substrates were transformed into lithium phenolates and subsequently subjected to copper-mediated oxidative dearomatization (Table 2). Use of 2,5-dimethyl and 2-methyl-5-*tert*-butyl substituted phenols **6** (entry 1) and **7** (entry 2) led to the production of [4 + 2] dimers **8** and **9** in high enantioselectivity,

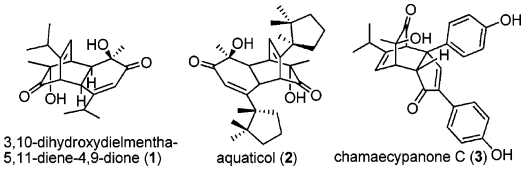


Figure 1. Representative natural products containing the bicyclo [2.2.2]-octenone core.

Scheme 1. Enantioselective Oxidative Dearomatization/[4 + 2] Cycloaddition Cascade

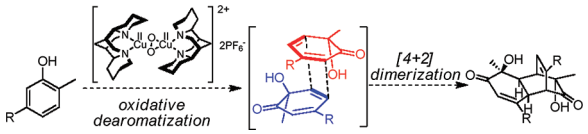
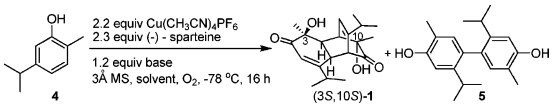


Table 1. Optimization of the Oxidative Dearomatization/Dimerization of Carvacrol (**4**)



entry	solvent	base	conversion[a] (%)	(3*S*,10*S*)-**1**:**5**[c]
1	CH_2Cl_2	DIEA	70 (25)[b]	1:1.5
2	THF	LiHMDS	67 (58)	>40:1
3	THF	DIEA	69 (58)	>40:1
4	CH_3CH_2CN	DIEA	40	1.6:1
5	acetone	DIEA	25	3:1
6[d]	THF	LiOH·H_2O	83 (80)	>40:1

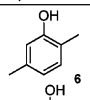
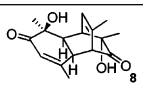
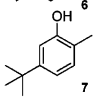
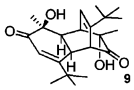
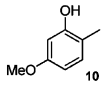
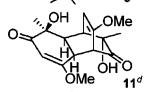
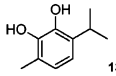
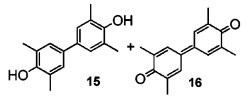
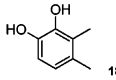
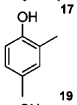
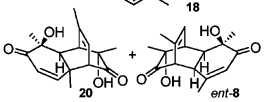
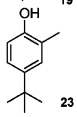
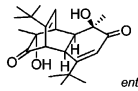
[a] Conversion based on recovered starting materials. [b] Isolated yield of dimer (3*S*,10*S*)-**1** in parenthesis. [c] Ratio was determined by ^{1}H NMR analysis of (3*S*,10*S*)-**1** and **5**. [d] One equivalent of base was used to prepare the lithium phenolate.

with a noticeable lower conversion observed for substrate **6**. Substrate **10** (entry 3) bearing an electron-donating methoxy group at C5 was also successfully converted into dimer **11** after thermolysis of the crude monomer.[10] Attempted oxidation of 2,5-disubstituted phenols with electron-withdrawing groups at C5 gave poor conversion.[10] Phenol **12** bearing a bulky substituent at C2 (entry 4) did not afford a [4 + 2] dimer but instead produced catechol **13**.[11] Attempted oxidation of the lithium phenolate derived from 2,6-dimethylphenol **14** led to the isolation of biaryl **15** and quinone **16** (entry 5) instead of the expected [4 + 2] dimer.[17] Oxidation of 2,3-disubstituted phenol **17** (entry 6) also led to the isolation of the corresponding catechol product **18**, further underscoring the steric control aspects of the oxidation.

Interestingly, oxidation of the substrate 2,4-dimethyl phenol **19** led to the isolation of two dimeric structures **20** and *ent*-**8** (Table 2, entry 7) after column chromatography. Product analysis revealed that the initially formed *o*-quinol **21** (Scheme 2) underwent [4 + 2] dimerization to **20** or stereoselective α-ketol rearrangement[18] to

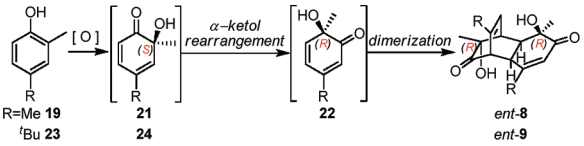
10.1021/ja711018z CCC: $40.75

Table 2. Copper-Mediated Asymmetric Oxidative Dearomatization/[4 + 2] Dimerization[a]

entry	phenol	product	yield[b] (%)	ee (%)
1	 **6**	 **8**	40 (67)[c]	98
2	 **7**	 **9**	82 (92)	99
3	 **10**	 **11**[d]	52 (80)	99
4	 **12**	 **13**	50 (64)	–
5	 **14**	 **15** **16**	40 (53) **15** 12 (16) **16**	–
6	 **17**	 **18**	23 (82)	–
7	 **19**	 **20** *ent*-**8**	25 (37) 7 (10)	99 **20** 99 *ent*-**8**
8	 **23**	 *ent*-**9**[e]	51 (77)	99

[a] Reaction conditions: 1.0 equiv of lithium phenolate, 1.1 equiv of $[(-)\text{-sparteine}]_2Cu_2O_2(PF_6)_2$ complex, 3 Å MS, O_2, THF, −78 °C, 16 h. [b] Isolated yield after chromatography. [c] Yield based on recovered starting materials in parenthesis. [d] Product obtained from thermolysis of the crude oxidation product (neat) at 50 °C (40 min). [e] Product obtained from thermolysis of the crude oxidation product (80 °C, 16 h).

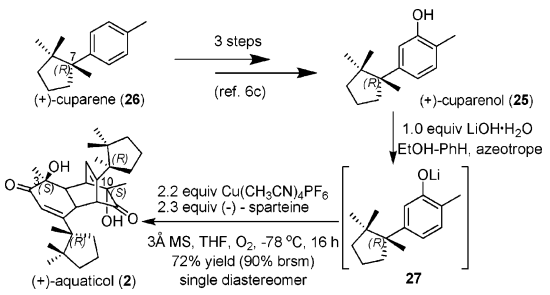
Scheme 2. Rearrangement of 4-Alkyl-2,4-cyclohexadienones



22, which further dimerized to *ent*-**8**. Comparison of the optical rotations of **8** and *ent*-**8** indicates that these two compounds have opposite absolute configurations.[10] To further probe this process, phenol **23** was investigated as an oxidation substrate (entry 8). To our surprise, *o*-quinol **24** did not dimerize at room temperature, and the monomer could be observed by crude NMR analysis.[10] However, attempts to purify this intermediate on silica gel led to decomposition and recovery of only a small amount of dimer *ent*-**9**. Thermolysis of monomer **24** in benzene cleanly afforded dimer *ent*-**9**. On the basis of this information, it is apparent that the α-ketol rearrangement affords an isomeric *o*-quinol possessing an unsubstituted *cis*-alkene moiety that is more reactive in [4 + 2] dimerization.

The copper-mediated asymmetric oxidative dearomatization/dimerization methodology provides a rapid entry to the homochiral dimer (+)-aquaticol (**2**, Scheme 3). Enantiomerically pure (+)-cuparenol (**25**) was prepared from commercially available (+)-cuparene (**26**) following a known procedure.[6c] Asymmetric oxidative dearomatization of the derived lithium phenolate **27** furnished (+)-aquaticol (**2**) ($[\alpha]^{22}_D$ = +46.1, *c* 0.65, $CHCl_3$) as a single diastereomer. X-ray crystal structure analysis of **2** further confirmed its relative stereochemistry and reassignment of the absolute configuration.[6c,10] A control experiment using *N*,*N*-di-*tert*-butylethylenediamine as achiral ligand in the oxidation generated a mixture of **2** and its epimer at C3 and C10 in a 43:57 ratio,[10] which

Scheme 3. Enantioselective Synthesis of (+)-Aquaticol



suggests that use of (−)-sparteine completely overrides the slight chirality induction from the 7-*R* center of (+)-cuparenol (**25**).

In conclusion, we have developed a highly enantioselective approach to bicyclo[2.2.2]octenones involving asymmetric oxidation of substituted phenols to *o*-quinols followed by homochiral dimerization. Our studies have revealed a facile ketol rearrangement/dimerization of *o*-quinols derived from 2,4-disubstituted phenols and have culminated in the enantioselective synthesis of (+)-aquaticol. Further studies, including asymmetric oxidative dearomatization of other substrates and mechanistic experiments, are currently in progress and will be reported in due course.

Acknowledgment. Financial support from the NIH (GM-073855 and P50 GM067041), Wyeth Pharmaceuticals, and Merck Research Laboratories is gratefully acknowledged. We thank Prof. Stéphane Quideau (IECB, ISM UMR-CNRS 5225, University of Bordeaux) for providing a sample of (+)-aquaticol and Dr. Shun Su (Boston University) for helpful discussions.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA711018Z