

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

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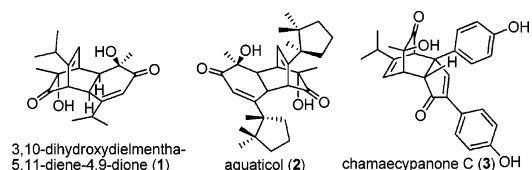
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The bicyclo[2.2.2]octenone skeleton is found in a number of natural products (Figure 1) including homodimers **1**<sup>2</sup> and **2** (aquaticol)<sup>3</sup> and the hetero adduct chamaecyanone C (**3**).<sup>4</sup> Although Diels–Alder cycloaddition 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.<sup>5</sup> Although numerous synthetic efforts utilizing oxidative dearomatization of substituted phenols to construct the bicyclo[2.2.2]octenone core have been developed,<sup>6</sup> the corresponding enantioselective process has not been reported.<sup>7</sup> We have previously reported the highly enantioselective synthesis of azaphilones involving copper-mediated oxidative dearomatization of *o*-alkynylbenzaldehydes.<sup>8</sup> Herein, we report a general protocol for the enantioselective oxidative hydroxylation of phenols (Scheme 1) followed by homodimerization to bicyclo[2.2.2]octenones.

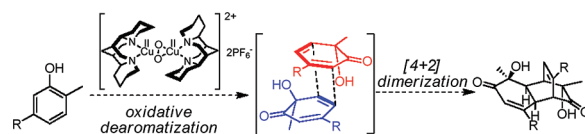
We first investigated oxidation of the 2,5-disubstituted phenol carvacrol (**4**) using conditions previously reported for 2,4-dihydroxybenzaldehyde substrates en route to the azaphilones<sup>8</sup> (Table 1, entry 1). In the event, reaction of **4** with a [(–)-sparteine]<sub>2</sub>Cu<sub>2</sub>O<sub>2</sub>·(PF<sub>6</sub>)<sub>2</sub> complex and *N,N*-diisopropylethylamine (DIEA) in CH<sub>2</sub>Cl<sub>2</sub> 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%).<sup>9</sup> 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**.<sup>2,10</sup>

Further optimization studies revealed that use of LiHMDS to generate the phenolate in THF as solvent,<sup>11</sup> 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<sup>12</sup> have generally been attributed to the equilibrium of binuclear copper-peroxo (**P**,  $\mu$ - $\eta^2$ : $\eta^2$ -peroxodicopper(II)) and copper-oxo (**O**, bis( $\mu$ -oxo)dycopper(III)) complex forms.<sup>13,14</sup> In the case at hand, the solvent effects may be rationalized by greater levels of the corresponding radical abstracting<sup>15</sup> [(–)-sparteine]<sub>2</sub>bis( $\mu$ -oxo)dycopper(III) (**O**) complex in CH<sub>2</sub>Cl<sub>2</sub> and the electrophilic  $\mu$ - $\eta^2$ : $\eta^2$ -peroxodicopper(II) (**P**) complex in THF. Although evaluation of alternative counterions<sup>16</sup> (e.g. BF<sub>4</sub><sup>–</sup>, OTf<sup>–</sup>, Cl<sup>–</sup>) to favor formation of the corresponding **P** complex did not show substantial improvement over PF<sub>6</sub><sup>–</sup>,<sup>10</sup> 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 <sup>a</sup> (%)	(3 <i>S</i> ,10 <i>S</i> )- <b>1</b> : <b>5</b> <sup>c</sup>
1	CH <sub>2</sub> Cl <sub>2</sub>	DIEA	70 (25) <sup>b</sup>	1:1.5
2	THF	LiHMDS	67 (58)	>40:1
3	THF	DIEA	69 (58)	>40:1
4	CH <sub>3</sub> CH <sub>2</sub> CN	DIEA	40	1.6:1
5	acetone	DIEA	25	3:1
6 <sup>d</sup>	THF	LiOH·H <sub>2</sub> O	83 (80)	>40:1

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

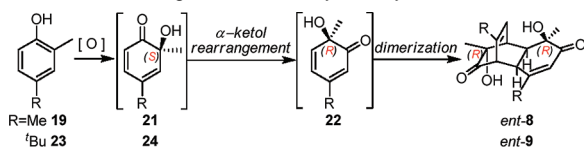
with a noticeable lower conversion observed for substrate **6**. Substrate **10** (entry 3) bearing an electron-donating methoxy group at C5 was also successfully converted into dimer **11** after thermolysis of the crude monomer.<sup>10</sup> Attempted oxidation of 2,5-disubstituted phenols with electron-withdrawing groups at C5 gave poor conversion.<sup>10</sup> Phenol **12** bearing a bulky substituent at C2 (entry 4) did not afford a [4 + 2] dimer but instead produced catechol **13**.<sup>11</sup> 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.<sup>17</sup> 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  $\alpha$ -ketol rearrangement<sup>18</sup> to

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

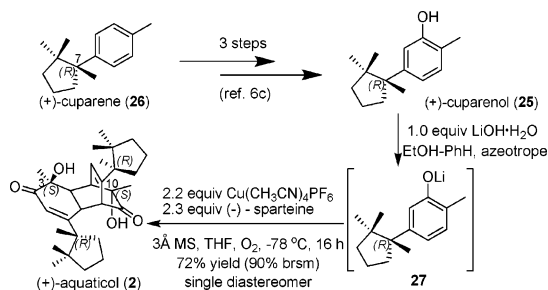
entry	phenol	product	yield <sup>b</sup> (%)	ee (%)
1			40 (67) <sup>c</sup>	98
2			82 (92)	99
3			52 (80)	99
4			50 (64)	—
5			40 (53) 15 12 (16) 16	—
6			23 (82)	—
7			25 (37) 7 (10)	99 20 99 ent-8
8			51 (77)	99

<sup>a</sup> Reaction conditions: 1.0 equiv of lithium phenolate, 1.1 equiv of [(−)-sparteine]<sub>2</sub>Cu<sub>2</sub>O<sub>2</sub>(PF<sub>6</sub>)<sub>2</sub> complex, 3 Å MS, O<sub>2</sub>, THF, −78 °C, 16 h. <sup>b</sup> Isolated yield after chromatography. <sup>c</sup> Yield based on recovered starting materials in parenthesis. <sup>d</sup> Product obtained from thermolysis of the crude oxidation product (neat) at 50 °C (40 min). <sup>e</sup> 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.<sup>10</sup> 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.<sup>10</sup> 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  $\alpha$ -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 (+)-aqualic (**2**, Scheme 3). Enantiomerically pure (+)-cuparenol (**25**) was prepared from commercially available (+)-cuparene (**26**) following a known procedure.<sup>6c</sup> Asymmetric oxidative dearomatization of the derived lithium phenolate **27** furnished (+)-aqualic (**2**) ([ $\alpha$ ]<sub>D</sub><sup>25</sup> = +46.1, *c* 0.65, CHCl<sub>3</sub>) as a single diastereomer. X-ray crystal structure analysis of **2** further confirmed its relative stereochemistry and reassignment of the absolute configuration.<sup>6c,10</sup> 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,<sup>10</sup> which

**Scheme 3.** Enantioselective Synthesis of (+)-Aqualic

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 (+)-aqualic. Further studies, including asymmetric oxidative dearomatization of other substrates and mechanistic experiments, are currently in progress and will be reported in due course.

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**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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- See Supporting Information for complete experimental details.
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