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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] While Diels-Alder cycloaddition of 2,4-cyclohexadienones and *ortho*-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 enroute to the azaphilones[8] (Table 1, entry 1). In the event, reaction of **4** with a $[(-)\text{-sparteine}]_2Cu_2O_2(PF_6)_2$ 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] $[(-)\text{-sparteine}]_2$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 pre-formation of the phenolate with LiOH

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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, with a noticeable lower conversion observed for substrate **6**. Substrate **10** (entry 3) bearing an electrondonating 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 *ortho*-quinol **21** (Scheme 2) underwent [4+2] dimerization to **20** or stereoselective *a*-ketol rearrangement [18] to **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] In order to further probe this process, phenol **23** was investigated as an oxidation substrate (entry 8). To our surprise, *ortho*-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**. Based on this information, it is apparent that the α-ketol rearrangement affords an isomeric *ortho*-quinol possessing an unsubstituted *cis*-alkene moiety which 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**) ($[\alpha]_D^{22}$ = + 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 43:57 ratio,[10] which 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 *ortho*-quinols followed by homochiral dimerization. Our studies have revealed a facile ketol shift/dimerization of *ortho*-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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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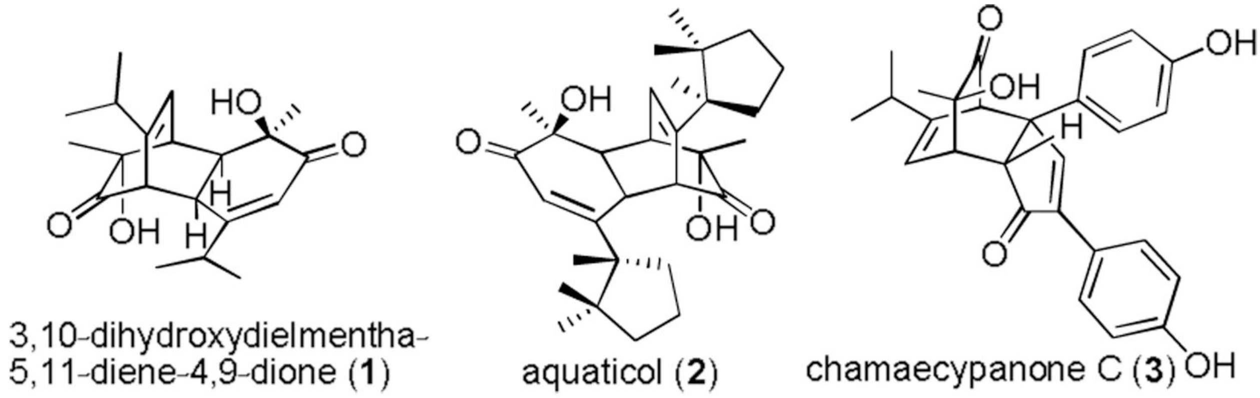
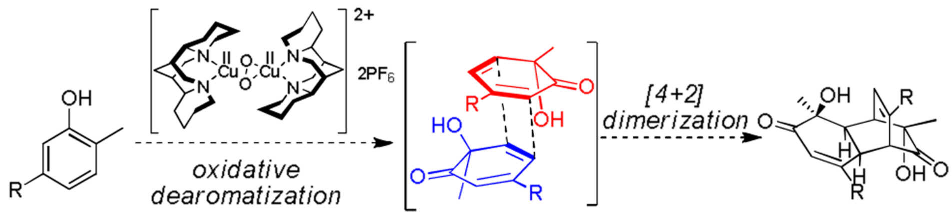
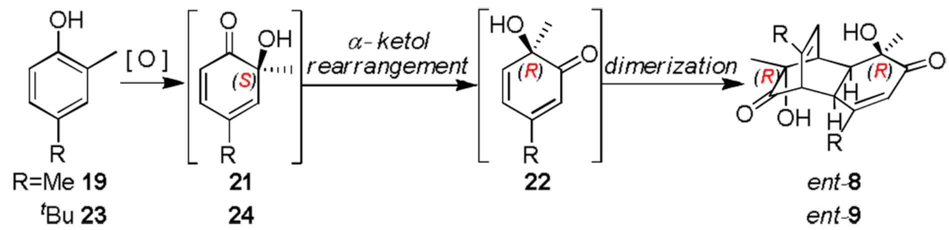


Figure 1.
Representative Bicyclo[2.2.2]octenone-Containing Natural Products

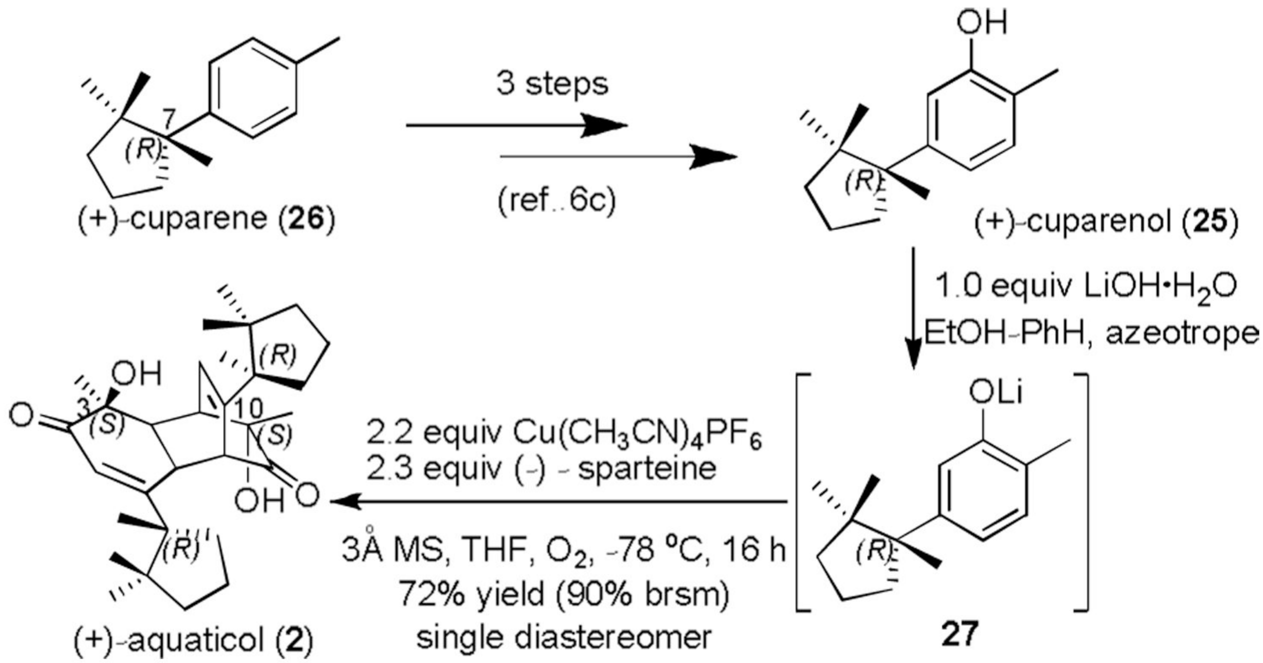


Scheme 1.
Enantioselective Oxidative Dearomatization/[4+2] Cycloaddition Cascade



Scheme 2.

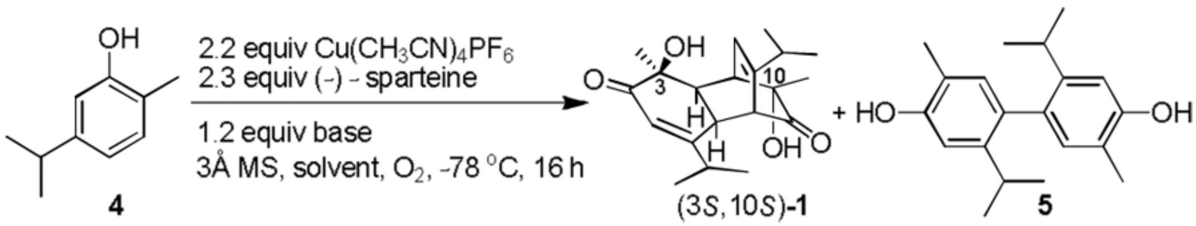
Rearrangement of 4-alkyl-2,4-cyclohexadienones



Scheme 3.
Enantioselective Synthesis of (+)-aquaticol

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	$LiOH{\cdot}H_2O$	83 (80)	> 40 : 1

[a]Conversion based on recovered starting materials.

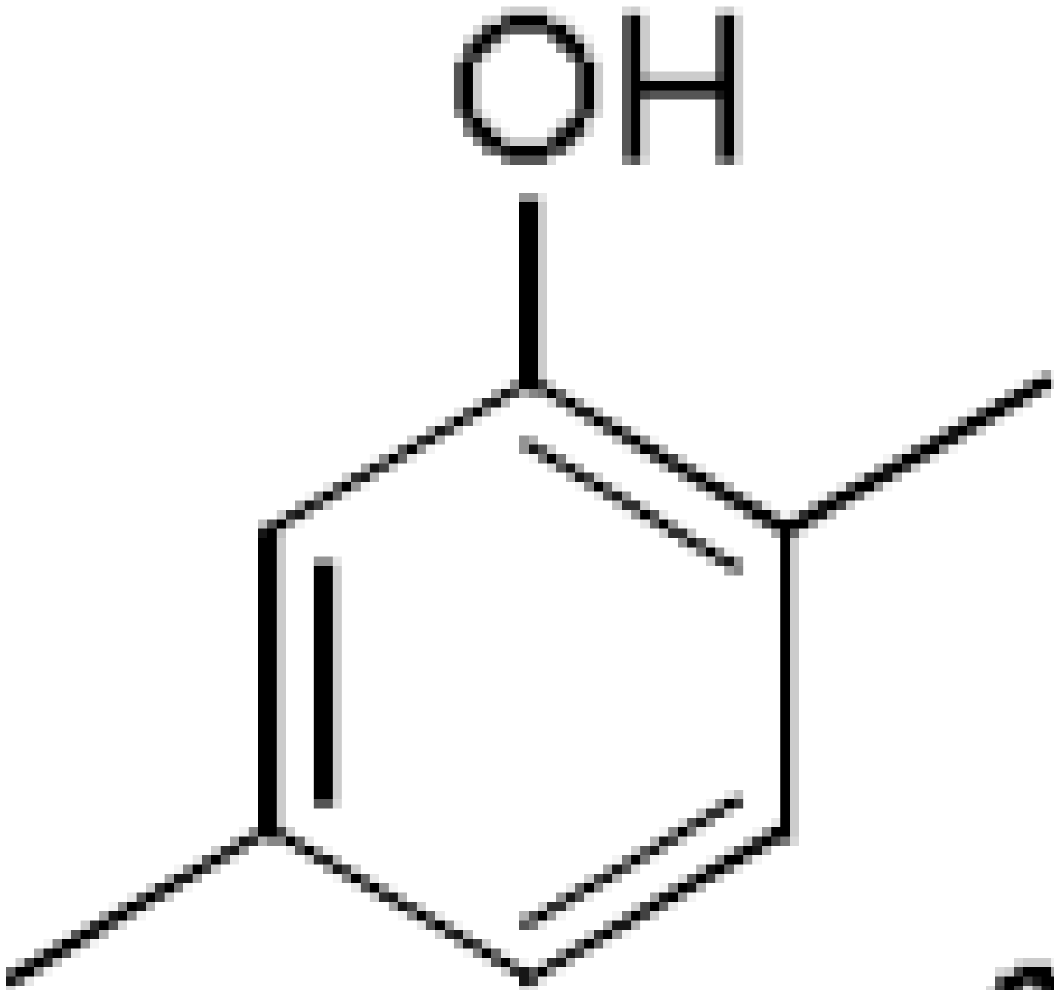
[b]Isolated yield of dimer (3*S*,10*S*)-**1** in parenthesis.

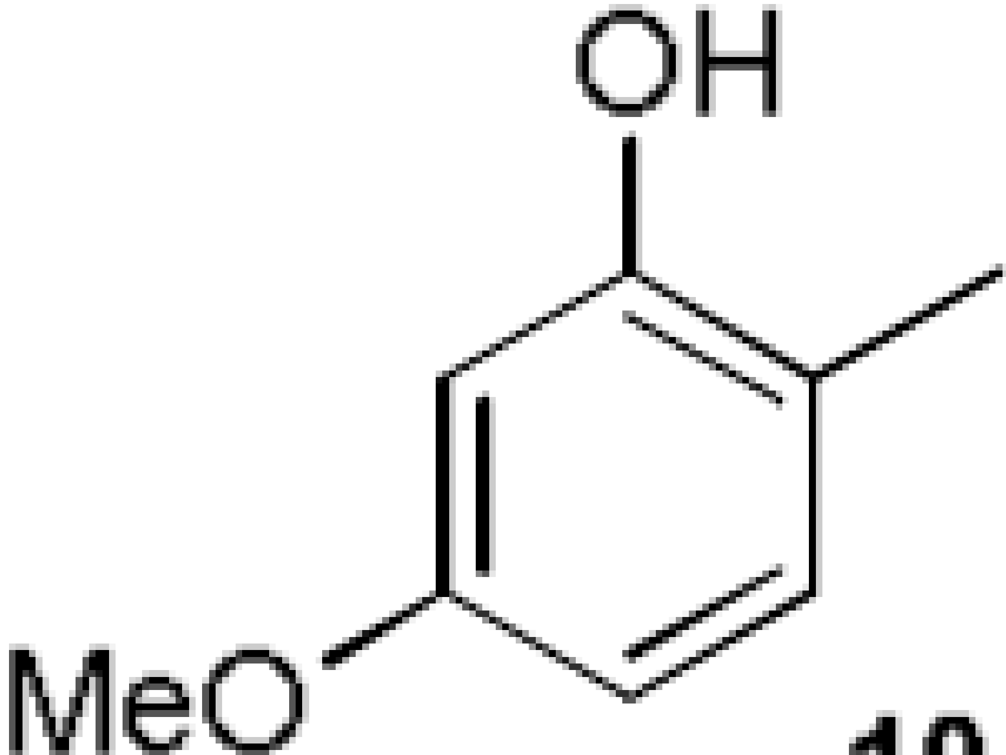
[c]Ratio was determined by ^{1}H NMR analysis of (3*S*,10*S*)-**1** and **5**.

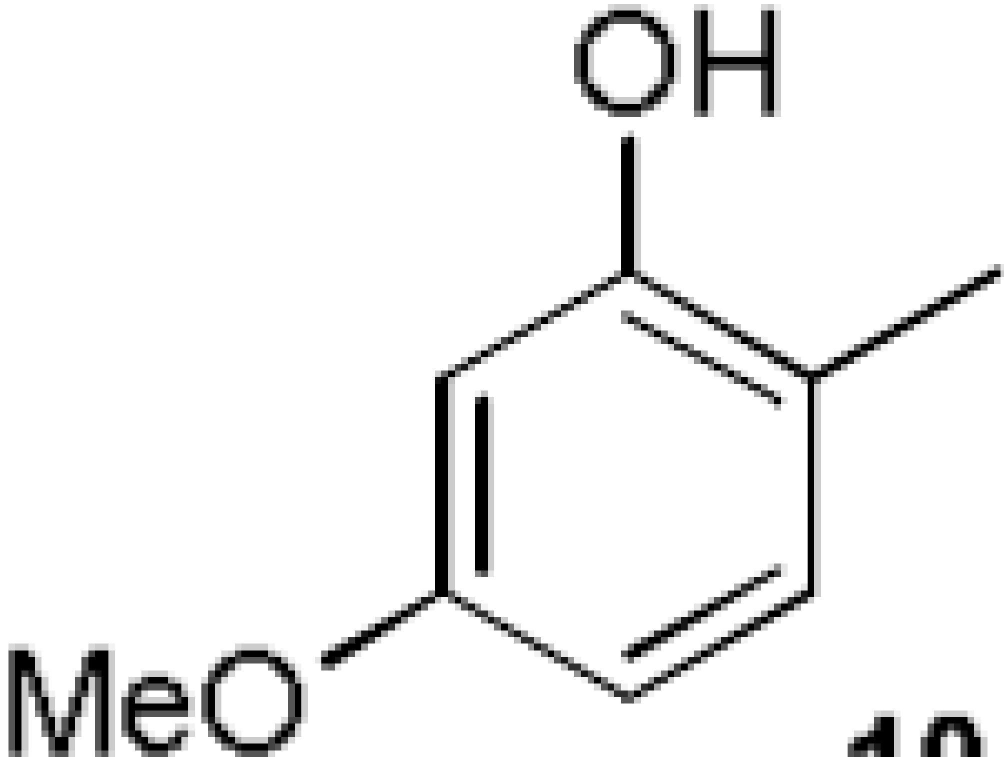
[d]1.0 equiv base was used for preparing the lithium phenolate.

Table 2

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

entry	phenol
1	 **6**

entry	phenol
2	 10

entry	phenol
3	 **10**

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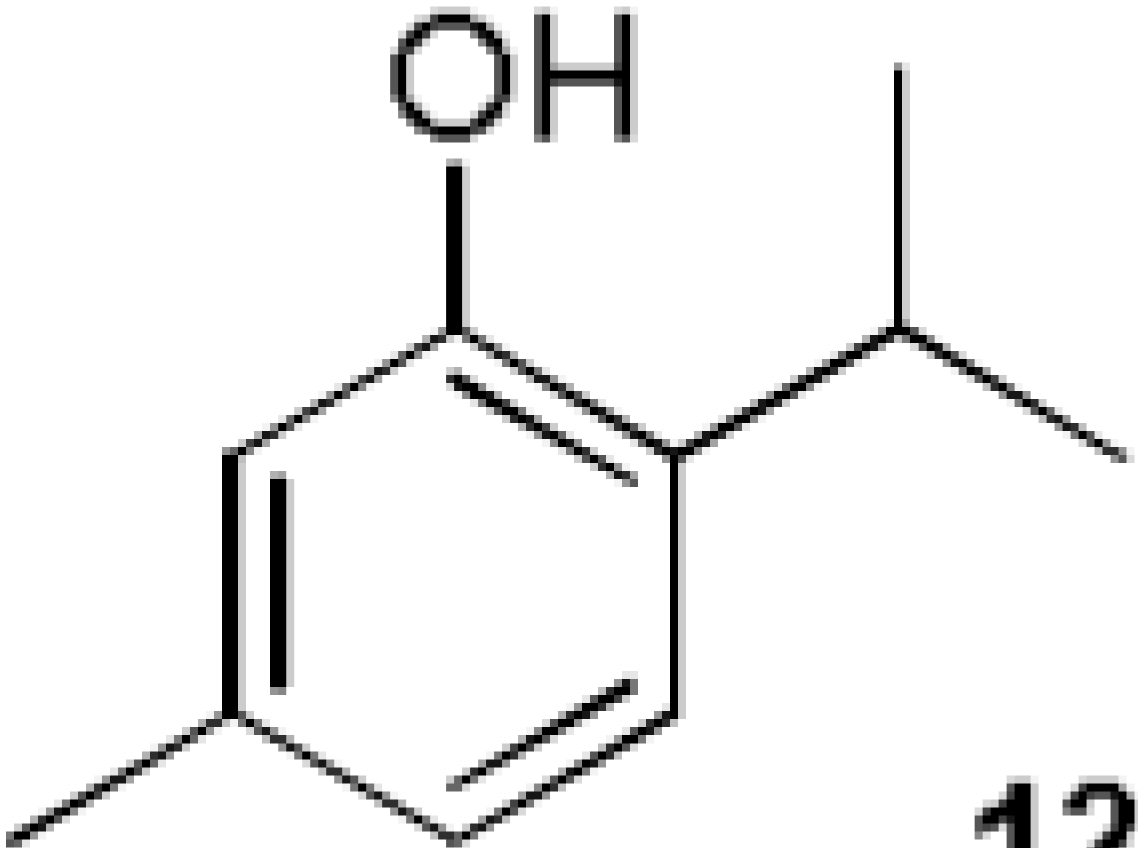
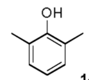
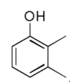
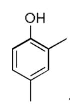
entry	phenol
4	 12

entry	phenol
5	 **14**
6	 **17**
7	 **19**

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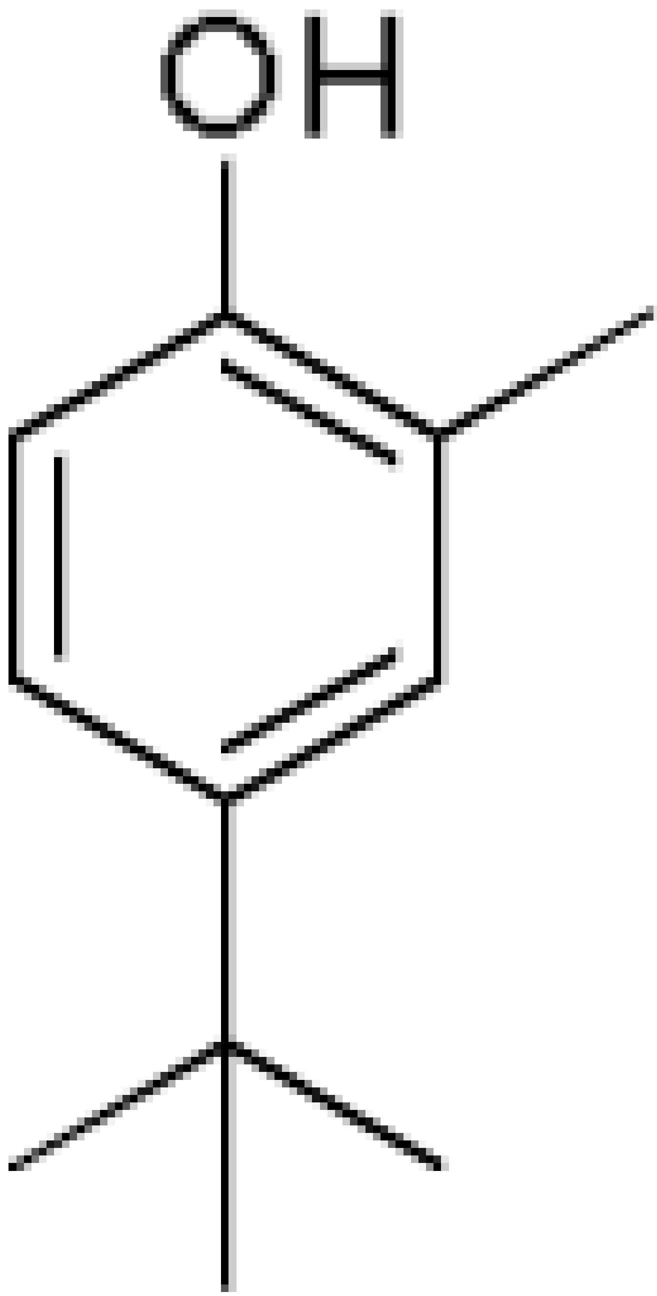
entry	**phenol**
8	 23

[a]Reaction conditions: 1.0 equiv of lithium phenolate, 1.1 equiv of [(−)- sparteine]$_2Cu_2O_2(PF_6)_2$ complex, 3Å 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).

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