Diels–Alder Cycloaddition

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Total Synthesis of (+)-Aquaticol by Biomimetic Phenol Dearomatization: Double Diastereofacial Differentiation in the Diels–Alder Dimerization of Orthoquinols with a C_2-Symmetric Transition State**

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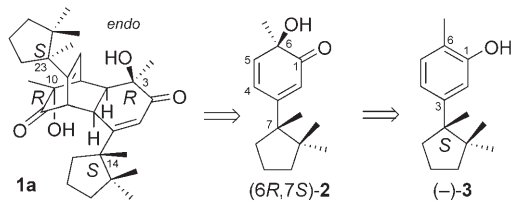
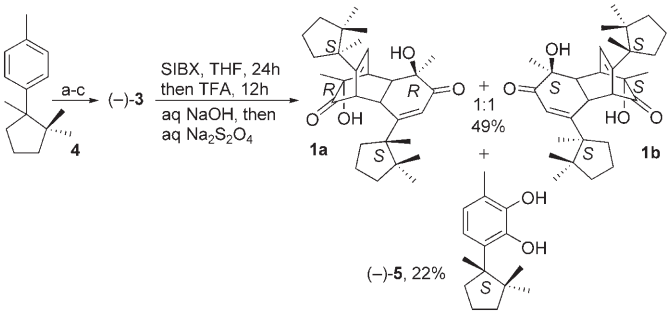
(+)-Aquaticol (**1a**) is a bissesquiterpene that was isolated from *Veronica anagallis-aquatica*, a plant used in traditional Chinese medicine.[1] Retrosynthetic analysis of its structure quickly revealed that it should be accessible through a Diels–Alder dimerization of the orthoquinol (6*R*,7*S*)-**2**,[2] which could itself be derived from natural (−)-hydroxycuparene ((−)-**3**) by hydroxylation accompanied by dearomatization (Scheme 1).[3] Although biosynthetic evidence is still lacking, there is little doubt that this disconnection pathway relates directly to the route by which **1a** is produced naturally.



Scheme 1. Biomimetic retrosynthesis of (+)-aquaticol (**1a**)

In fact, **1a** is just one example of several natural products[4] that can be derived from orthoquinol derivatives (that is, 6-alkyl 6-hydroxycyclohexa-2,4-dienones) by a [4+2] cyclodimerization. These intermediates would be generated in vivo by a stereoselective dearomatizing *ortho* hydroxylation of phenolic monomers. Examples of such a hydroxylation/Diels–Alder sequence can be found in the chemistry of the natural phenols curcuphenol,[4a] ferruginol,[4b] and sorbicillin.[4c] All of these cycloadditions occur with *endo* selectivity, and the orthoquinol that acts as the dienophile always reacts through its Δ-4,5 bond in a site-selective manner. Most remarkably, the two orthoquinols approach one another with their hydroxy groups oriented towards each other. No sound rationale for this double diastereofacial selectivity has yet been proposed, despite the cornucopia of experimental data that has been gathered during the last fifty years.[2,5] The synthesis of **1a** gave us the opportunity to investigate further these intriguing aspects of orthoquinol dimerization. We report herein the first orthoquinol-based biomimetic synthesis of (+)-aquaticol (**1a**), and discuss the structural features that underlie the extraordinary level of diastereofacial selectivity observed in this Diels–Alder dimerization process.

Hydroxycuparene (**3**) was prepared as the racemate from (±)-cuparene (**4**) (Scheme 2).[6] The nitration of **4**[7] was followed by conversion of the resulting nitrocuparene into an acetate through the elegant two-step one-pot procedure described by Glatzhofer et al.[8] Alkaline hydrolysis of this acetate then furnished **3** in 57% yield from **4** (see the Supporting Information). This racemate was then resolved by HPLC on a chiral phase, and each enantiomer was submitted at room temperature to the dearomatizing *ortho*-selective



Scheme 2. Synthesis of (+)-aquaticol (**1a**) from (−)-hydroxycuparene ((−)-**3**): a) HNO_3/AcOH, Ac_2O, 57%; b) 1) H_2 (4.5 bar), 10% Pd/C (80% w/w), Ac_2O/AcOH (2:1); 2) Pd/C filtration; 3) $NaNO_2$ (4 equiv), 100%; c) 1) KOH, MeOH/H_2O, 100%; 2) separation by HPLC on a chiral phase. TFA = trifluoroacetic acid.

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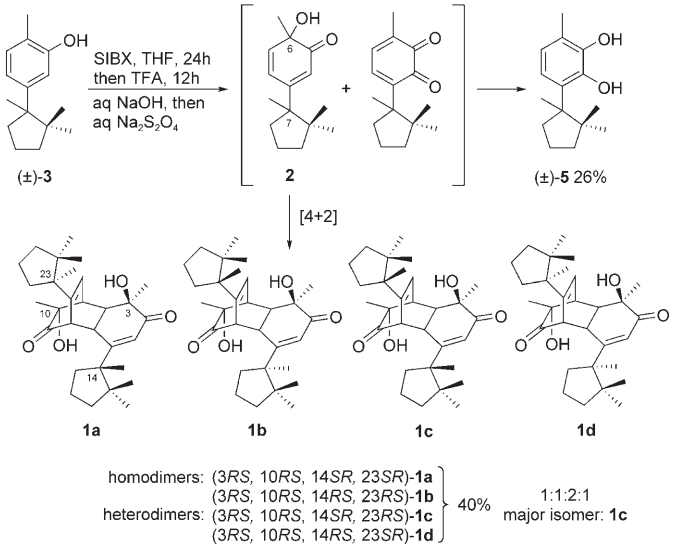
Supporting information for this article (including experimental procedures, characterization data for all new compounds, ORTEP diagrams of X-ray structures, and optimized transition-state geometries) is available on the WWW under http://www.angewandte.org or from the author.

hydroxylation conditions that we developed previously with the λ^5-iodane SIBX (stabilized IBX), a stabilized (that is, nonexplosive) version of *o*-iodoxybenzoic acid (IBX).[9] Following treatment with TFA and workup with aqueous solutions of NaOH and $Na_2S_2O_4$, reversed-phase HPLC of the reaction mixture generated from (−)-**3** furnished pure **1a**[1] in 6% yield from **4** along with the all-*S* dimer **1b**. 1,2-Dihydroxycuparene ((−)-**5**) was also formed as a result of unavoidable hydroxylation at the unsubstituted position *ortho* to the hydroxy group in (−)-**3**.

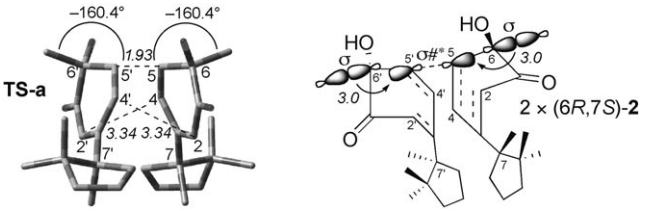
This one-pot dearomatizing hydroxylation/Diels–Alder transformation of (−)-**3** led to only two of eight possible *endo* cyclodimers. Of course, no stereocontrol was imposed during the SIBX-mediated hydroxylation at the C6 center of (−)-**3**, but the two diastereomeric orthoquinol intermediates (6*R*,7*S*)-**2** and (6*S*,7*S*)-**2** thus produced recognized each other and reacted to furnish the cyclodimers (+)-**1a** and (−)-**1b**, which were expected on the basis of the regioselectivity, site selectivity, and diastereofacial selectivity observed previously with many related orthoquinol models.[2,5] When (±)-**3** was submitted to the same reaction conditions, the four possible stereoisomers of **2** were formed, and again only those with the same configuration at their stereogenic C6 center combined with each other to furnish the expected racemic mixture of the four *endo* cyclodimers **1a**–**d** (Scheme 3 and Supporting Information).



Scheme 3. SIBX-mediated oxidation of (±)-**3**. One enantiomer of each of the racemic homo- and heterodimers is shown; the configurations of all of them are given at the bottom.

It can be deduced from the above results that the steric bulk and the chirality of the cyclopentyl unit have no apparent influence on the observed diastereofacial selectivity. To convince ourselves further of this observation, we carried out the same SIBX-mediated reaction on a series of phenols with different substituents, such as a hydrogen atom, or a methyl, isopropyl, or *tert*-butyl group, replacing the cyclopentyl group. All cyclodimeric products, which were isolated in yields ranging from 30 to 96%, were formed with the same facial selectivity as those derived from **3** (see the Supporting Information). It is unlikely that any hydrogen bonding between the hydroxy groups at the two C6 centers of the analogues of **2** has anything to do with this facial selectivity, for the replacement of the hydroxy group with a fluorine atom in analogous cases of dimerization led to the same facial selectivity.[5c] The difference in steric bulk between the methyl and hydroxy groups at C6 has also been used as an argument for the fact that the bulkier methyl groups end up oriented away from each other.[5c] However, this simple rationale is again not fully satisfying, as the dimers we prepared initially by using SIBX still had even bulkier IBX-derived λ^3-iodanyl iodosylbenzoic acid units bonded to the C6 oxygen atom.[10] The reaction mixture is treated with TFA to induce the cleavage of these units in situ. Furthermore, when the hydroxy groups were replaced with bulkier acetate groups in analogous systems, the methyl groups were still oriented *anti* to each other in the cyclodimers formed kinetically.[5b]

We then decided to use computational chemistry to gather further insight into this facial selectivity. Thus, we carried out a search at the B3LYP/6-31G(d) level of all transition states (TSs) that lead experimentally to cyclodimers from the orthoquinols **2**. A natural bond orbital (NBO) analysis[11] was also carried out to obtain additional details on the electronic structure of these TSs. These calculations indicated that the TSs have similar energies and are asynchronous with an initial formation of the C5–C5′ bond, the length of which ranges from 1.92 to 1.95 Å (see the Supporting Information). Most remarkably, the **TS-a** structure, which leads to the natural dimer **1a**, has a twofold axis of symmetry (Scheme 4),



Scheme 4. Structure of **TS-a**, which leads to (+)-aquaticol (**1a**), with dihedral angles and interatomic distances (Å), and schematic view of "Cieplak–Fallis" interactions (in kcal mol^{-1}).

so that it is not possible to differentiate the diene from the dienophile in this TS.[12] A structure analogous to **TS-a**, but with opposite configurations at the two C6 centers, was also calculated to examine any perturbation brought about by this stereochemical change. This **TS-a′** structure was found to be 9.9 kcal mol^{-1} higher in energy than **TS-a** (see the Supporting Information). This large energy difference can be explained, at least in part, in terms of hyperconjugative effects, which can also serve as a basis for rationalizing the facial selectivity.[13] In all TSs that lead to observed dimers, the Δ-4,5 bond of one orthoquinol follows an approach *anti* to the $\sigma_{C,C}$ bond of the allylic methyl substituent at C6 of the other orthoquinol unit. This approach could benefit from Cieplak hyperconjugation, first discussed by Macaulay and Fallis,[14] since the aforementioned $\sigma_{C6,Me}$ orbital is suitably aligned with the σ#* orbital of the incipient C5–C5′ bond, as in **TS-a** (Scheme 4). The

relevant dihedral angles $\sphericalangle C_{Me}$-C6-C5-C5′ closely reflect the ideal antiperiplanar atom positioning required for optimal hyperconjugation (see the Supporting Information).

Our NBO analysis indicated that Cieplak $\sigma_{C6,Me} \rightarrow \sigma\#^*$ interactions amount to approximately 3.0 kcal mol^{-1}, and apply mutually to both reaction partners (see the Supporting Information). Felkin–Anh interactions between the incipient σ# bond and the electron-withdrawing σ^*_{CO} orbitals of the C6-linked OH groups also occur, but to a much smaller extent (ca. 1.1 kcal mol^{-1}).[15] However, Felkin–Anh-type interactions that involve instead the more electron donating but better aligned $\sigma^*_{C6\text{-}Me}$ bond amount to approximately 2.6 kcal mol^{-1}. We then wondered whether or not these last interactions stabilize these TSs. In this regard, the NBO analysis of **TS-a′** was highly informative and revealed that a change in the configuration at C6 of one reaction partner does, as expected from geometrical considerations, reinforce its Felkin–Anh $\sigma\# \rightarrow \sigma^*_{CO}$ interaction (4.4 kcal mol^{-1}). However, the higher-energy **TS-a′** structure, which exhibits a significantly longer C5–C5′ bond (1.99 Å), does not lead to any cyclodimer under the kinetic conditions used.

Other factors, such as electrostatic and steric effects induced by the allylic substituents and shown to control single facial selectivity in some [4+2] cycloaddition systems,[16] might also contribute to the double diastereofacial selectivity observed in the [4+2] cyclodimerization described herein. However, our analysis shows that a double "Cieplak–Fallis" hyperconjugation appears to be the determining factor in this stereoselectivity, which was also observed in all cases reported to date of the kinetically controlled [4+2] dimerization of chiral orthoquinols.[2,4,5] Finally, we emphasize that we have described the first example of the construction of a natural product on the basis of theoretical bispericyclic cycloaddition models, represented in our case by the C_2-symmetric **TS-a**.[12]

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