Communication

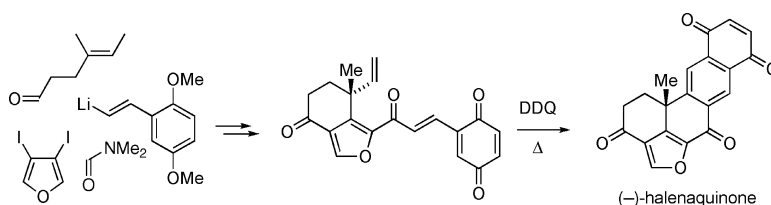# Vinyl Quinones as Diels#Alder Dienes: Concise Synthesis of (#)-Halenaquinone

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Vinyl Quinones as Diels−Alder Dienes: Concise Synthesis of (−)-Halenaquinone

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Eight decades after its discovery, the synthetic appeal of the Diels−Alder reaction has not diminished, and new modes continue to be discovered. The versatility of the reaction and the ease with which its components can be modified is indeed remarkable. Quinones, for instance, are classical electron-deficient dienophiles, yet relatively little is known about their role in neutral or inverse-electron-demand Diels−Alder reactions. With appropriate substitution, however, they can be part of an electron-deficient diene system that can readily engage in cycloadditions. Indeed, vinyl-*p*-quinones are known to dimerize thermally to yield hydrophenanthrenes with excellent regio- and chemoselectivity (**1**→**2**; Scheme 1).[1,2] Additionally, Noland and Kedrowski have shown that extremely electron-deficient vinyl nitroquinones undergo facile cycloadditions to electron-rich furans and indoles (e.g., **3**→**4**).[3]

Although these modes of reactivity provide rapid access to highly functionalized ring systems, they appear to have never been exploited in total synthesis.[4] We now report a concise, asymmetric synthesis of (−)-halenaquinone, which is based on an intramolecular inverse-electron-demand Diels−Alder reaction involving a vinyl quinone.

Scheme 1. Diels−Alder Reactions of Vinyl-*p*-quinones
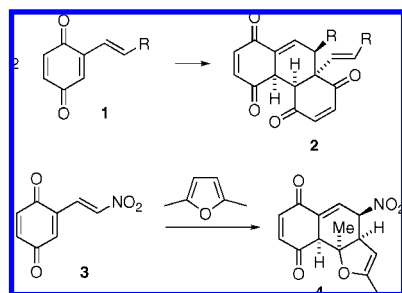
(+)-Halenaquinone (**5**), the natural enantiomer, is a pentacyclic natural product that has attracted considerable interest in the synthetic and medicinal chemistry communities due its unusual structure and multifaceted bioactivity.[5,6] To date, two asymmetric syntheses of the molecule have been reported by Shibasaki[7] and Harada,[8] whereas a total synthesis of the racemic natural product was achieved by Rodrigo et al.[9] A thiophene derivative of (±)-halenaquinone (**6**) was recently synthesized by Wipf et al. to study the contribution of the diacyl furan system to the bioactivity of the natural product.[10]

Our total synthesis of (−)-halenaquinone starts with iodofuran **9** (Scheme 2), which was previously developed for our synthesis of guanacastepene E and heptemerone B.[11] Enantiomerically enriched **9** can be obtained in three simple steps from diiodofuran **7** and the unsaturated aldehyde **8**. Protection of **9** as a silyl ether was then followed by a regioselective deprotonation and formylation to afford iodofurfural **10** in excellent yield.
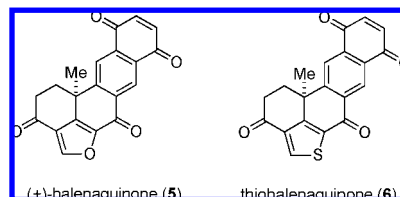
In one of the key steps of our synthesis, the quaternary stereocenter of (−)-halenaquinone was formed through an intramolecular Heck cyclization.[12] This reaction proceeded with high diastereoselectivity to afford furanocyclohexanol **11** as the major isomer (dr = 7:1). Interestingly, in the absence of the 2-formyl group, the reaction proceeded with opposite (and lower) diastereoselectivity.[11a] This observation points to a role of the formyl group as a coordinating ligand in a palladium(II) intermediate. The relative configuration of the furanocyclohexanol **11** could not be determined directly but was ultimately proven by its conversion to (−)-halenaquinone, whose absolute stereochemistry is known.[8]

Addition of an organolithium compound derived from the vinyl stannane **12** to aldehyde **11** afforded the acid-sensitive vinyl furyl carbinol **13** in excellent yield.[13] Subsequent desilylation of **13**, followed by oxidation of both secondary alcohols, gave hydroquinone ether **14**. This intermediate was converted into the key vinyl quinone **15** by oxidative demethylation with silver(II) oxide and nitric acid.

With vinyl quinone **15** in hand, we explored the inverse-electron-demand Diels−Alder reaction under various conditions. We found that the reaction proceeded even at room temperature in dichloromethane solution, albeit slowly, to afford the sparingly soluble pentacyclic hydroquinone **17**. Higher temperatures or the addition of Lewis acids, such as Sc(OTf)₃, increased reaction rates but had little effect on the yields. High-pressure conditions, however, gave the most satisfactory results; subjecting **15** to 10 kbar of pressure at room temperature afforded **17** in 78% yield. In all cases investigated, vinyl hydroquinone **17** was the only isolated isomer.

In the final step of our synthesis, **17** was oxidized and aromatized to afford (−)-halenaquinone (*ent*-**5**).[3a,14] This oxidative endgame could be combined with the cycloaddition in a single operation: heating of quinone **15** with DDQ afforded halenaquinone directly, albeit in low yield.

Synthetic (−)-halenaquinone was identical in all respects to the natural product, with the exception of its optical rotation, which had the opposite sign but a similar absolute value ([α]²⁵_D −22.7°, *c* 0.25, CH₂Cl₂; [α]^Lit._D +22.2°, *c* 0.124, CH₂Cl₂).[5]

The key Diels−Alder step of our synthesis warrants further analysis in terms of its simple and induced diastereoselectivity. The latter can be inferred from the relative stereochemistry of **17**, which was elucidated by detailed NMR studies (see Supporting Information).
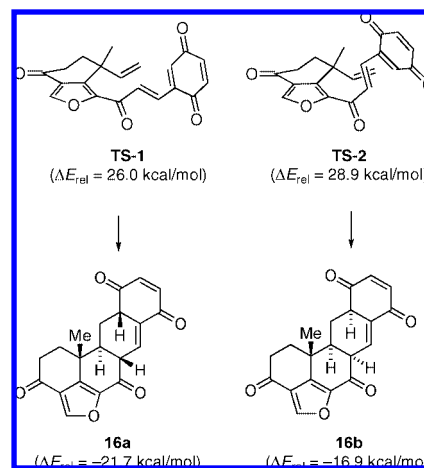
Scheme 2. Total Synthesis of (−)-Halenaquinone[a]

Scheme 3. Transition States of the Key Diels−Alder Reaction
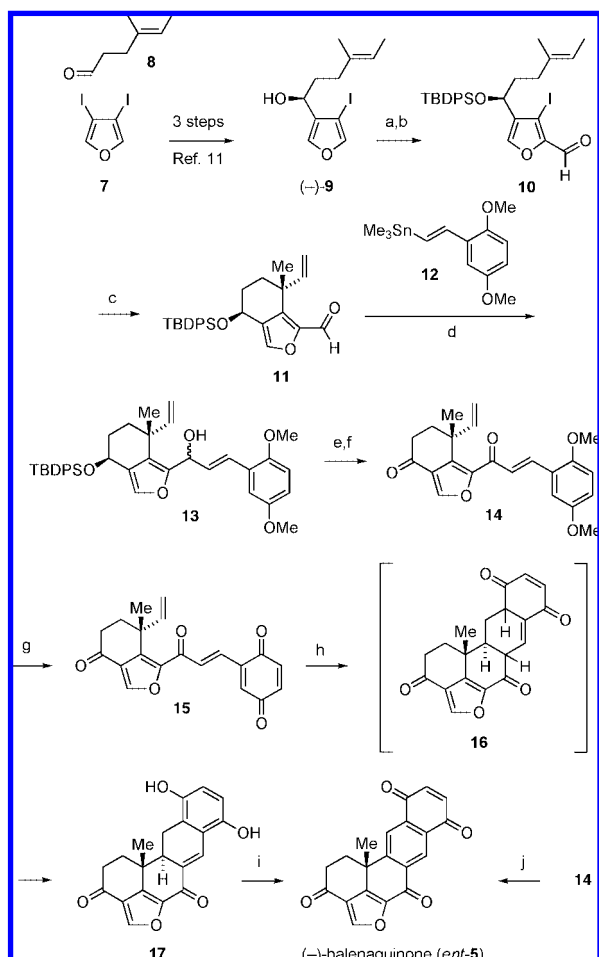
[a] Reagents and conditions: (a) TBDPSCl, imidazole, DMAP, DMF (93%); (b) n-BuLi, DMF, THF (94%); (c) Pd(OAc)$_2$, TBAB, Et$_3$N, MeCN (95%); (d) **12**, n-BuLi, THF, then **11** (92%); (e) TBAF, THF (85%); (f) TPAP, NMO, (64%); (g) AgO, HNO$_3$, dioxane (65%); (h) DCM, 10 kbar (78% from **14**); (i) MnO$_2$, PhH (60%); (j) AgO, HNO$_3$, dioxane; then DDQ, dioxane (12%).

In contrast to the examples shown in Scheme 1, the initial cycloaddition product (e.g., **16**) could not be isolated because it underwent rapid tautomerization to vinyl hydroquinone **17** under all conditions tested. Therefore, the simple diastereoselectivity (*exo/endo* selectivity) of the reaction could not be determined directly.

Density functional theory (DFT) calculations at the B3LYP/6-31G** level were able to locate both the *exo* transition state (**TS-1**) and the *endo* transition state (**TS-2**) of the reaction (Scheme 3).[15] According to these calculations, **TS-1**, which yields diastereomer **16a**, is 26.0 kcal/mol higher in energy than the lowest-energy conformer of **15**. The more congested **TS-2**, which could be relevant at high pressures and leads to **16b**, is energetically less favorable (ΔE_{rel} = 28.9 kcal/mol). Both transition states are marked by essentially synchronous bond formations and fall well within the regime of classical Diels−Alder reactions. Thermodynamically, the reaction was found to be highly exothermic and essentially irreversible (cf. Scheme 3).

In summary, we have achieved a concise asymmetric synthesis of (−)-halenaquinone that hinges on a previously unexploited mode

of the Diels−Alder reaction. The viability of vinyl quinones as dienes in intramolecular versions of this reaction has been demonstrated, and potential transition states have been explored with DFT calculations. Other notable features of our convergent synthesis include the regioselective lithiation and formylation of a 3-iodofuran enabling a highly diastereoselective intramolecular Heck cyclization. The further application of vinyl quinone cycloadditions in total synthesis is under investigation in our laboratories.

Supporting Information Available: Experimental procedures and compound characterization data. B3LYP coordinates and electronic energies of TSs and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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