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Intramolecular Vinyl Quinone Diels–Alder Reactions: Asymmetric Entry to the Cordiachrome Core and Synthesis of (–)-Isoglaziovianol

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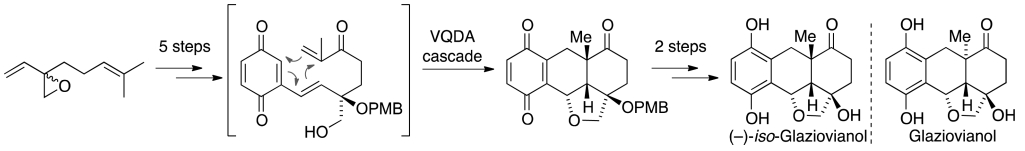
ABSTRACT



A short and asymmetric entry to the core structure of the cordiachromes has been developed, allowing access to (–)-isoglaziovianol in seven steps. Our synthesis includes a Trost asymmetric allylic alkylation and a reaction cascade triggered by a vinyl quinone Diels–Alder reaction and followed by intramolecular nucleophilic interception.

The cordiachromes are an unusual class of meroterpenoids that have been isolated either in the quinone or quinol form. They all feature a hydroanthracene skeleton that is further oxidized to varying degrees (Figure 1).[1,2] Most of them possess a *cis*-fused decalin moiety with one remarkable exception: glaziovianol **1**, which is the only member of the family known to date that features a *trans*-fused decalin. This natural product was isolated from the trunk heartwood of Auxemma glazioviana, a tree endemic in the region of northeastern Brazil.[3] The wood of this tree is resistant to fungi and termite attacks and thus often used for civil construction.[3] In folk medicine, cuts and wounds are treated with the trunk bark.[4]

The intriguing tetracyclic structure of glaziovianol includes four contiguous stereocenters, one of which is quaternary, thus rendering it a challenging target for total synthesis. To date only cordiachrome B **2** has been synthesized, albeit in racemic form.[5] To the best of our knowledge, no asymmetric entry to this class of natural products has been reported.

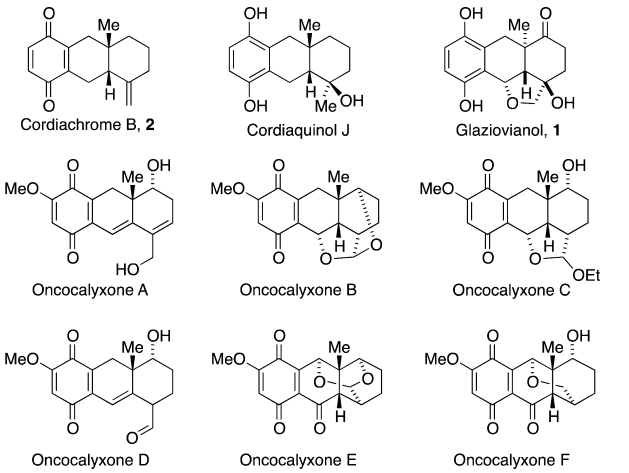


Figure 1. The cordiachrome family of natural products (shown with arbitrary absolute configuration).

(1) Moir, B. M.; Thomson, R. H. *J. Chem. Soc., Chem. Commun.* **1972**, *14*, 363–364.
(2) Moir, B. M.; Aberdeen, O. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1556–1561.
(3) Da Costa, G. M.; De Lemos, T. L.; Pessoa, O. D. L.; Monte, F. J. Q.; Braz-Filho, R. *J. Nat. Prod.* **1999**, *62*, 1044–1045.
(4) Braga, R. *Plantas do Nordeste, Especialmente do Ceara*, 2nd ed.; Imprensa Oficial: Fortaleza, Ceara, Brasil, 1960.
(5) Watabe, T.; Hosoda, Y.; Okada, K.; Oda, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3801–3802.

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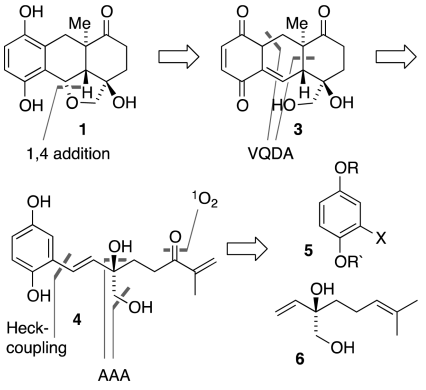
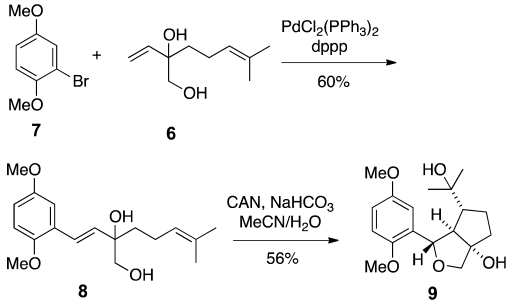
Our retrosynthetic analysis of glaziovianol **1** (Scheme 1) was based on biosynthetic consideration and commences with the disconnection of the tetrahydrofuran ring at the benzylic position, which would result in isoquinone methide **3**. Intermediate **3** bears the retron of an intramolecular vinyl quinone Diels–Alder (VQDA)[6,7] reaction with neutral electron demand, the implementation of which yields alkenyl hydroquinone **4**. According to our synthetic plan, the enone functionality in **4** would be introduced through a singlet oxygen ene reaction in the side chain, while the alkenyl hydroquinone moiety would be assembled from aryl halide **5** with tertiary allylic alcohol **6**.

Scheme 1. Retrosynthetic Analysis of Glaziovianol, **1**



Our synthetic studies commenced with a model system shown in Scheme 2. Heck-coupling of myrcene-derived diol **6**[8] with bromo hydroquinonedimethyl ether **7** gave tertiary allylic alcohol **8** (Scheme 2). This compound turned out to be very sensitive toward acid, complicating our efforts to oxidize it to the corresponding vinyl quinone. Interestingly, when subjecting methoxyether **8** to radical oxidation conditions such as buffered CAN or DDQ, compound **9** was observed as the only isolable product. The relative configuration of compound **9** was established through NOE measurements (see Supporting Information).

Scheme 2. Formation of Unexpected Cyclization Product **9**



This unusual cyclization presumably involves the initial formation of a stabilized benzylic radical cation, which undergoes stereoselective cyclization to yield a benzylic cation and a tertiary radical. The benzylic cation is quenched by the internal nucleophile, whereas the tertiary radical is further oxidized to a cation and then intercepted by water.

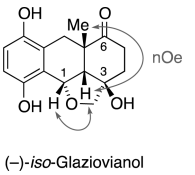


Figure 2. Relative configuration of (−)-**21**.

Our second generation, asymmetric approach, which drew from lessons learned in the racemic series, is shown in Scheme 3. It commenced with a Trost asymmetric alkylation of *para*-methoxybenzyl alcohol **10** with the known racemic vinyl epoxide **11**. Employing the *S*,*S*-DACH phenyl ligand, we obtained tertiary allylic ether **12** with high regio- and enantioselectivity (85% isolated yield and 93% *ee*).[9] Heck-coupling of **12** with protected *ortho*-bromohydroquinone **13** then gave alkenyl hydroquinone **14**.[10] A TPP sensitized singlet-oxygen ene reaction of **14**, followed by acetylation and elimination, gave the desired α,β-unsaturated ketone **15**.[11] It should be noted that this reaction mode could also occur in the biosynthesis of the cordiachromes.

In the key sequence of our synthesis, the acetyl protecting groups were removed under Zemplén deacetylation conditions, and the resulting phenol was oxidized to the corresponding quinone **16** under mild conditions.[12] This vinyl quinone, however, could not be isolated since it rapidly underwent VQDA reaction at room temperature, presumably via the endo transition state **17**, followed by nucleophilic interception of the resulting isoquinone methide **18**.

Further oxidation of the resulting hydroquinone **19** upon workup afforded the tetracyclic quinone **20** in 39% overall yield. Oxidative removal of the PMB group and reduction then gave hydroquinone **21**, which bears the constitution of glaziovianol.

Unfortunately, **21** turned out to be an isomer of the natural product glaziovianol with respect to the decalin junction, which is *cis*-fused instead of *trans*-fused. The stereochemistry of (−)-**21** was elucidated through detailed NOE measurements. We were able to observe NOE signals beteween the methine protons at C1 and C2, as well as signals between C2 and the angular methyl group (Figure 2).

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(10) Trost, B. M.; Andersen, N. G. *J. Am. Chem. Soc.* **2002**, *124*, 14320–14321.
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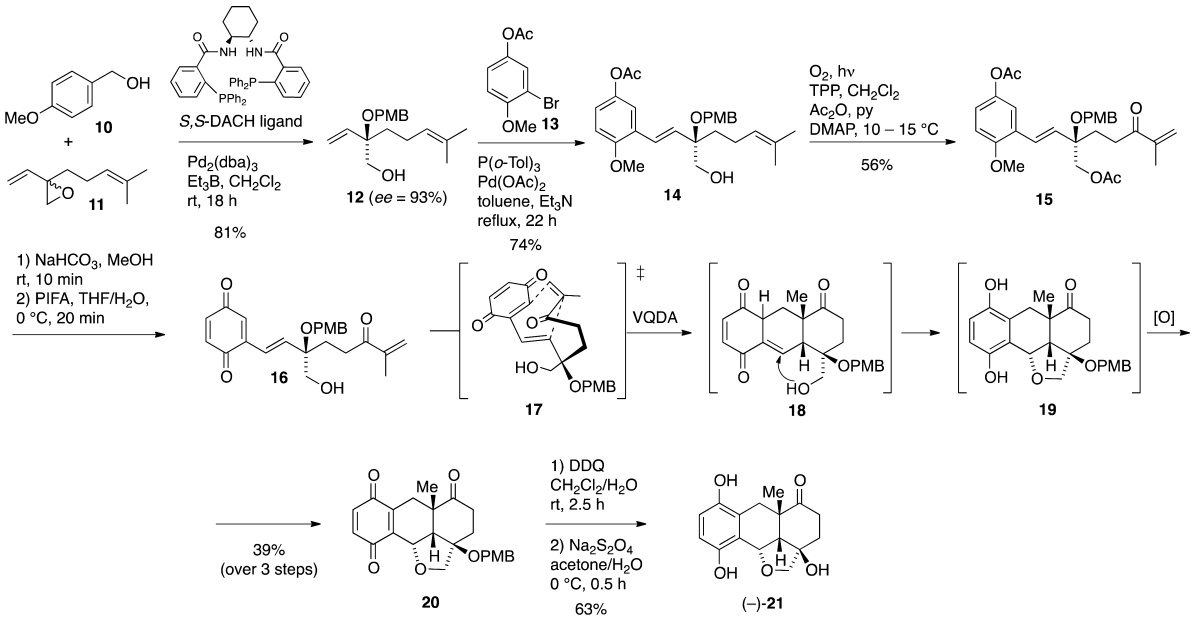
Scheme 3. Synthesis of Isoglaziovianol through a VQDA Cascade Reaction



In addition, the chemical shift of the methyl group in **21**, which we propose to call isoglaziovianol, is in better agreement with the *cis*-fused "regular" cordiachromes than with *trans*-fused glaziovianol (1.27 ppm vs 0.94 ppm).[3] Attempts to overcome the undesired diastereoselectivity of the Diels–Alder reaction and favor an *exo*-transition state, e.g. by employing catalysts or using an allylic alcohol instead of an enone as the dienophile, proved fruitless.

In conclusion we have developed an asymmetric synthesis of (−)-isoglaziovianol that emphasizes the uniqueness of glaziovianol in the cordiachrome series. Our short synthesis raises interesting biosynthetic questions, since an uncatalyzed VQDA reaction does not appear to be involved, indicating that an enzyme might be required for the formation of the *trans*-decalin moiety. Alternatively, it is conceivable that isoglaziovianol is indeed a natural product, which is epimerized at its quaternary sterocenter to glaziovianol via a photochemical reaction, similar to the epimerization of estrone to lumiestrone.[13]

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Supporting Information Available. Detailed experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.