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ortho-Quinone Methide Cyclizations Inspired by the Busseihydroquinone Family of Natural Products

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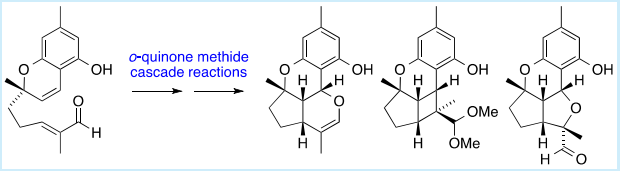
Supporting Information

ABSTRACT: A series of cascade reactions of *o*-quinone methides have been developed based on the proposed biosynthesis of busseihydroquinone and parvinaphthol meroterpenoid natural products. The polycyclic framework of the most complex family members, busseihydroquinone E and parvinaphthol C, was assembled by an intramolecular [4 + 2] cycloaddition of an electron-rich chromene substrate. The resultant cyclic enol ether underwent rearrangements under acidic or oxidative conditions, which led to a new total synthesis of rhodonoid D.



Flowering plants of the genus *Pentas* are widely found in East Africa, where they are often used in traditional medicine for the treatment of malaria and other ailments.[1] These plants are a rich source of complex meroterpenoid natural products, such as busseihydroquinones A–F[2] and parvinaphthols A–C,[3] which make up a family of polycyclic meroterpenoids and polyketides isolated from *Pentas bussei* and *Pentas parvifola*, respectively. As part of our research into the biosynthesis of meroterpenoids via the oxidative cyclization of polyhydroxynaphthalene derivatives,[4] we became interested in the biogenetic relationships between busseihydroquinones C–E (**1**–**3**) and parvinaphthol C (**4**) (Figure 1). The structures

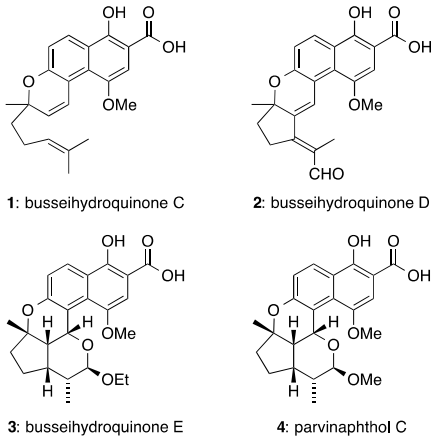


Figure 1. Busseihydroquinones C–E and parvinaphthol C.

of **3** and **4** are particularly intriguing, with six contiguous stereocenters embedded within a pentacyclic ring system. The relative and absolute configurations of **3** and **4** were determined using X-ray crystallography.

Our proposed biosynthetic pathway linking busseihydroquinones C–E and parvinaphthol C is outlined in Scheme 1. First, the chromene ring of busseihydroquinone C (**1**) could be derived from the oxidation and oxa-6π-electrocyclization of a C-5 geranylated naphthalene precursor. The allylic oxidation of **1** to give the reactive enal **5**, followed by an intramolecular hetero-Diels–Alder reaction with the chromene dienophile via an endo transition state, would give cyclic enol ether **6**. A similar all-carbon intramolecular Diels–Alder reaction of a chromene was used in our recent total synthesis of verrubenzospirolactone.[5] We propose that cyclic enol ether **6** could be an undiscovered natural product and that busseihydroquinone E (**3**) and parvinaphthol C (**4**) could be artifacts of the isolation process formed by the addition of either EtOH or MeOH, respectively, to **6**.[6] Both the *Pentas bussei* and *Pentas parvifola* plant materials were exposed to MeOH, EtOAc, and oxalic-acid-impregnated silica gel in the isolation procedures. It is plausible under these conditions that **6** could be protonated on its convex face to give oxonium ion **7**, followed by the nucleophilic addition of MeOH or EtOH (again on the convex face) to give **3** and **4**. The sequence consisting of the intramolecular Diels–Alder reaction of **5** followed by the addition of MeOH/EtOH to **6** would set five stereocenters relative to the sole existing stereocenter at C-3′ in a highly diastereoselective manner, which was attractive to us from a synthetic viewpoint. Furthermore, we propose that cyclic enol ether **6** could be the biosynthetic precursor of busseihydroquinone D (**2**) via diastereoselective epoxidation on its convex face to give epoxide **8**. Ring opening of the epoxide could then give α-hydroxyaldehyde **9**, followed by stereospecific dehydration to give **2**.

The synthesis of enal **12** was first targeted as a simplified version of the busseihydroquinone enal **5** (Scheme 2). Chromene **10** was formed via the condensation of orcinol with citral according to a known procedure.[7] The oxidation of

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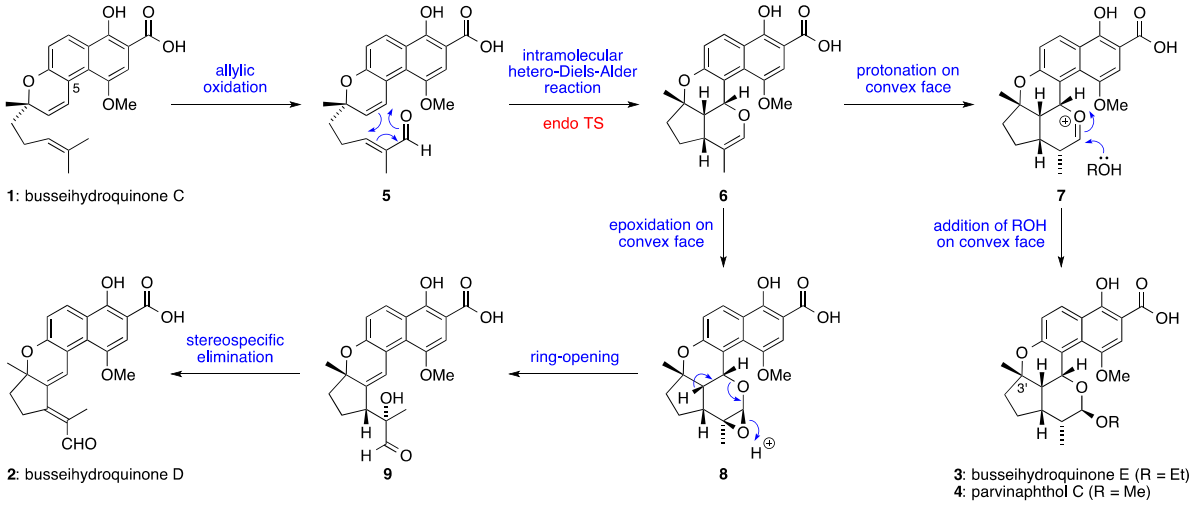
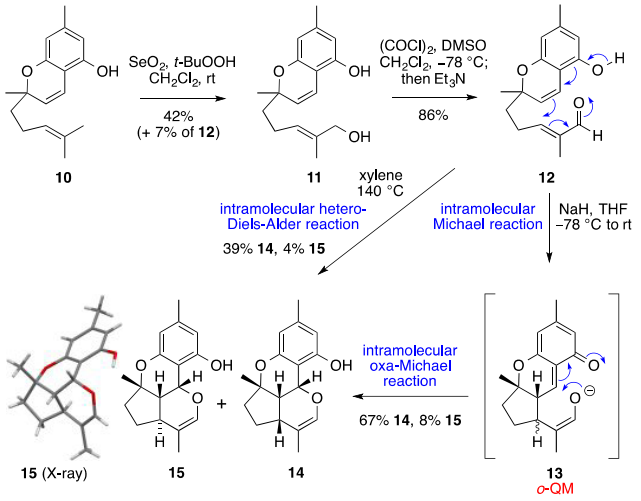
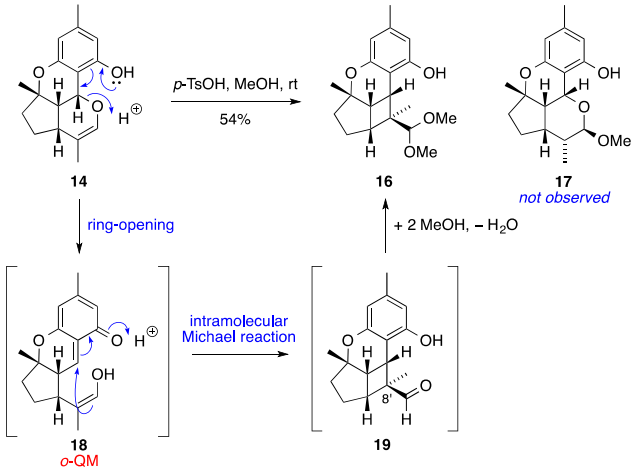
Scheme 1. Proposed Biosynthesis of Busseihydroquinones D–E and Parvinaphthol C from Busseihydroquinone C



Scheme 2. Synthesis of the Busseihydroquinone E Ring System via a [4 + 2] Cycloaddition



Scheme 3. Ring Contraction of the Busseihydroquinone E Ring System under Acidic Conditions



10 using catalytic SeO_2 and *t*-BuOOH gave allylic alcohol **11**, which was converted into enal **12** via a Swern oxidation. Heating **12** to 140 °C in xylenes then gave the desired endo Diels–Alder product **14** in 39% yield, alongside 4% of the exo product **15**. The structure of **14** was determined using 2D nuclear magnetic resonance (NMR) studies,[8] whereas the structure of **15** was secured via single-crystal X-ray crystallography. Alternatively, the exposure of **12** to basic conditions formed **14** and **15** in higher yield, perhaps via a stepwise pathway involving an intramolecular Michael reaction to give the *o*-quinone methide[9] enolate **13** as a mixture of diastereomers, followed by an intramolecular oxa-Michael reaction.

It was anticipated that the exposure of **14** to acidic MeOH would result in the stereoselective addition of MeOH across the enol ether to give the parvinaphthol C analogue **17** (Scheme 3). However, we instead observed a ring contraction of **14** to give cyclobutane **16**. This transformation presumably occurs via the acid-catalyzed ring opening of **14** by a retro-oxa-Michael reaction to generate *o*-quinone methide enol **18**, followed by an intramolecular Michael reaction with an attack by the enol at C-8′ to give aldehyde **19**. The acid-catalyzed addition of MeOH to **19** then formed the dimethyl acetal of **16**. Structurally related cyclobutane meroterpenoids are more commonly synthesized by intramolecular [2 + 2] cycloadditions of chromenes.[10]

Next, we epoxidized cyclic enol ether **14** in the hope of forming **24**, an analogue of busseihydroquinone D (**2**), via ring opening of the epoxide and pyran ring systems (Scheme 4). The epoxidation of **14** presumably occurred on the less hindered, convex face to give epoxide **20**, which ring-opened to give *o*-quinone methide **21**, followed by an intramolecular oxa-Michael reaction to give the tetracyclic aldehyde **22**. Attempts to dehydrate **22** to give **24** were unsuccessful. The relative configuration of **22** was determined by 2D nuclear Overhauser enhancement spectroscopy (NOESY) studies. Aldehyde **22** contains the same ring system as the meroterpenoid rhodonoid D (**23**);[11] indeed, **22** was converted into **23** via the reduction of an intermediate, 1,3-dithiane.

We thought that the unexpected transformations of **14** into **16** (under acidic conditions) and **22** (under oxidative conditions) could be due to the ease of formation of the *o*-quinone methide intermediates. Naphthalene enol ether **26** was therefore synthesized as a closer analogue of the proposed biosynthetic intermediate **6** (Scheme 5). The two-step allylic oxidation of chromene **25**[12] gave an α,β-unsaturated aldehyde,

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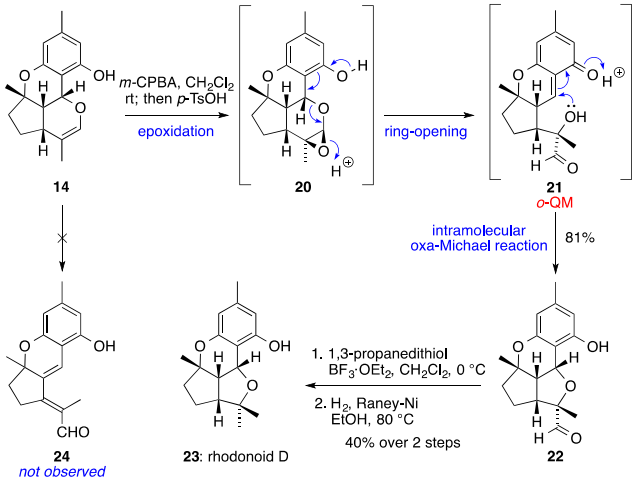
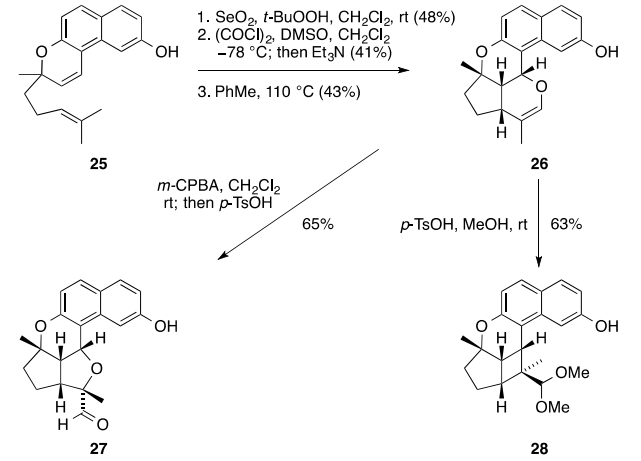
Scheme 4. Ring Contraction of the Busseihydroquinone E Ring System via Epoxidation and the Synthesis of Rhodonoid D



Scheme 5. Rearrangements of Naphthalene Enol Ether 26



which underwent a hetero-Diels–Alder reaction under thermal conditions to give **26**. We hoped that **26** would undergo the facile addition of alcohols to give analogues of **3** and **4** and an oxidative ring opening to give an analogue of **2**. However, the treatment of **26** with acidic MeOH gave the cyclobutane **28**, whereas the epoxidation and acidification gave aldehyde **27**. Clearly, the same cascades occur in this naphthalene system, perhaps via naphthoquinone methide intermediates.

In summary, we have shown that the polycyclic framework of busseihydroquinone E and parvinaphthol C can be formed via a diastereoselective, intramolecular hetero-Diels–Alder reaction of a chromene intermediate under thermal or basic conditions. The resultant cyclic enol ether underwent acid-catalyzed and oxidative cascade reactions via *o*-quinone methide intermediates to form ring-contracted products, one of which was efficiently converted into rhodonoid D. Future work will focus on the synthesis of the proposed biosynthetic intermediate **6**. We anticipate that this less electron-rich aromatic system could be converted into the natural products **2**, **3**, and **4** via reactions that avoid *o*-quinone methide intermediates, as outlined in Scheme 1.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03060.

Experimental procedures and analytical and crystallographic data for all new compounds (PDF)

Accession Codes

CCDC 1944007 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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