JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
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Cascade Polyketide and Polyene Cyclizations: Biomimetic Total Synthesis of Hongoquercin B

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Supporting Information

ABSTRACT: The total synthesis of hongoquercin B was carried out in 9 steps from *trans,trans*-farnesyl acetate using a palladium catalyzed decarboxylative π-farnesyl rearrangement of a diketo-dioxinone ester, aromatization and cationic diene-epoxide cyclization as key steps. This cascade tetracyclization simplifies the synthesis of terpenoid resorcylate natural products.

The hongoquercins (**1**), which were isolated from extracts of an unidentified terrestrial fungus, exhibit antibiotic activity against vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus*.[1] They belong to a group of natural products known as the meroterpenoids—hybrid natural products composed of both terpenoid and polyketide-derived substructures.[2,3] Meroterpenoids containing the drimane-phenol ring system (such as **1**) are known to exhibit antifungal, antiviral, and antitumor activities (Figure 1).[4]

Several total syntheses of these meroterpenoids and the hongoquercins have been reported,[5,6] and many have relied upon the coupling of a protected aromatic unit (**7**) with a cyclic terpenoid entity (**6**) derived from commercially available cyclic enantiopure natural products (Scheme 1). Herein we report a new biomimetic strategy for the synthesis of hongoquercin B, which utilizes total biomimetic cyclization reactions to construct both the resorcylate and tricyclic terpenoid substructures from an acylic precursor.

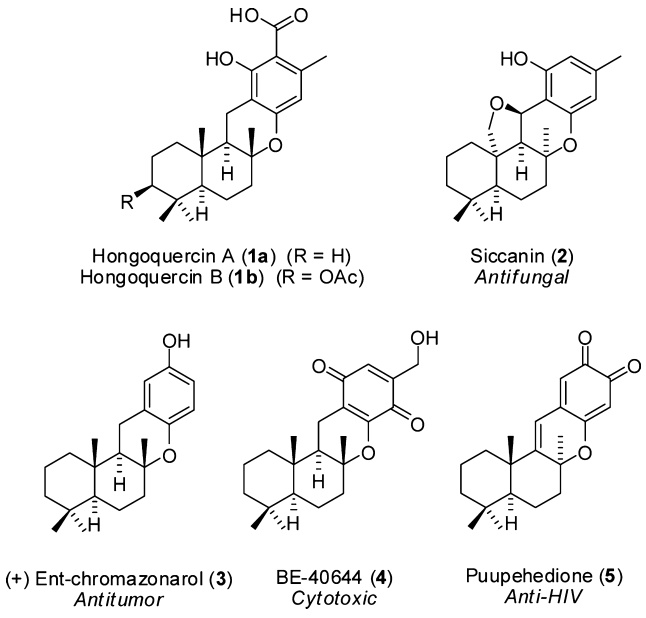
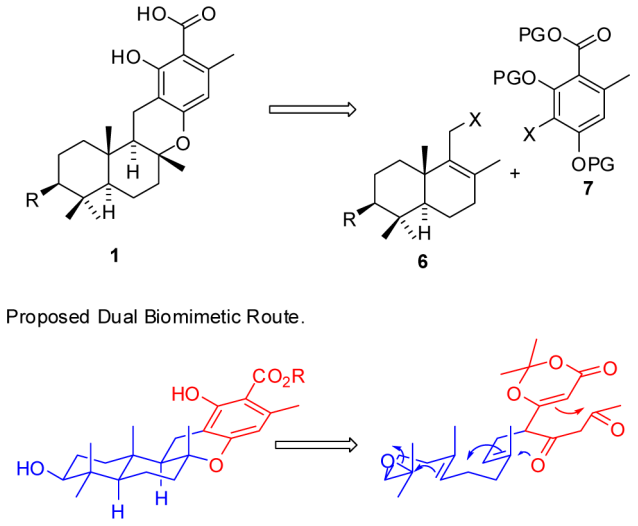


Figure 1. Meroterpenoids containing drimane-phenol ring system.

Scheme 1. Synthetic Strategies to Hongoquercins (1)



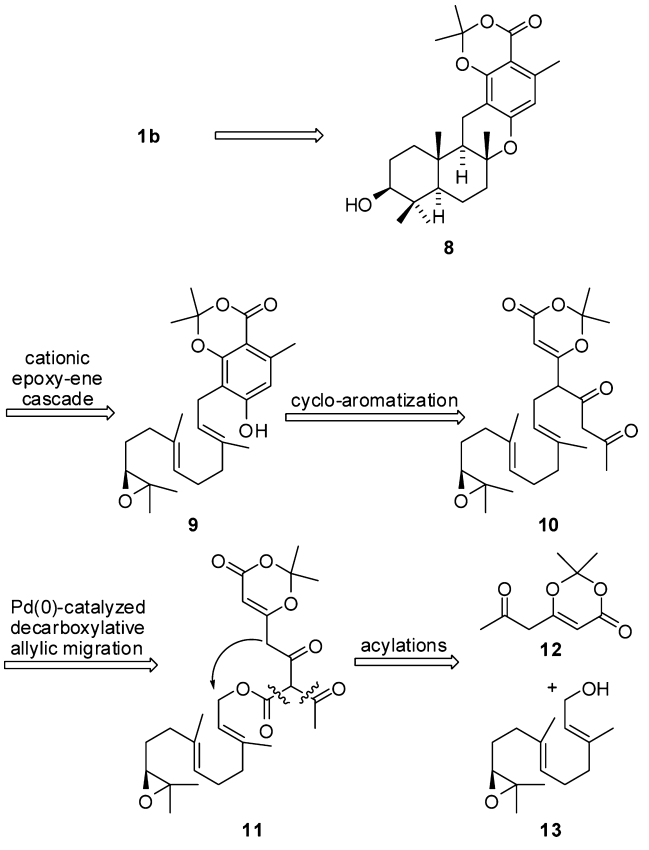
Recently, we have developed a flexible biomimetic strategy for the synthesis of several polyketide resorcylate natural products using late-stage aromatization from diketo-dioxinone precursors.[7,8] Inspired by the work of Stork, Eschenmoser and Johnson on terpenoid polyene cyclization reactions,[9−11] we considered that hongoquercin B (**1b**) should be available via a dual biomimetic approach where polyketide cyclo-aromatization is directly followed by a stereocontrolled diene epoxide cyclization to generate the tetracyclic core of the natural product (Scheme 1). The retrosynthetic analysis is outlined in Scheme 2 in which the drimane-phenol ring system should be available via a cationic epoxy-ene tricyclization terminated by the phenol nucleophile of terpene resorcylate **9**. Smith and coworkers showed that a similar epoxy-ene cascade preferentially gave rise to the desired chair−chair tetracycle rather than the chair-boat isomer.[12] This cascade with dioxinone chemistry should allow for the control of 5 stereocenters in the natural product from a single stereocenter installed in the first step.

Resorcylate **9** should be available through base-mediated cyclo-aromatization of diketo-dioxinone **10** available from regioselective palladium(0)-catalyzed decarboxylative farnesyl

Received: November 10, 2014
Published: November 25, 2014

   dx.doi.org/10.1021/ja511534x | J. Am. Chem. Soc. 2014, 136, 17013−17015

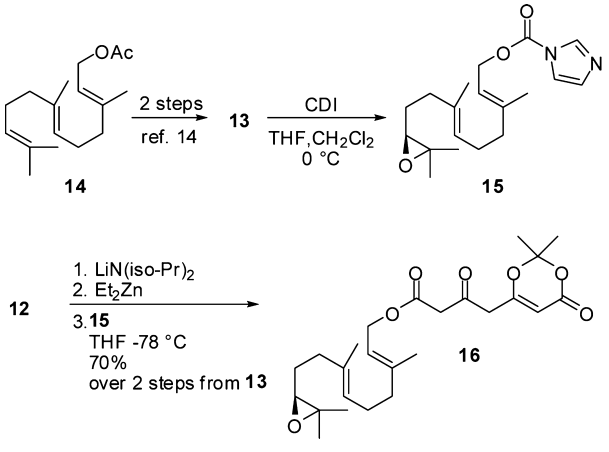
Scheme 2. Retrosynthesis for Hongoquercin B (1b)



migration of dioxinone diketo ester **11** as developed within our group for other systems.[7,13] Diketo-dioxinone ester **11** should be available through double C-acylation of keto-dioxinone **12** with an activated carbonate ester derived from the known 10,11-(*S*)-epoxyfarnesol (**13**) and acetyl chloride.

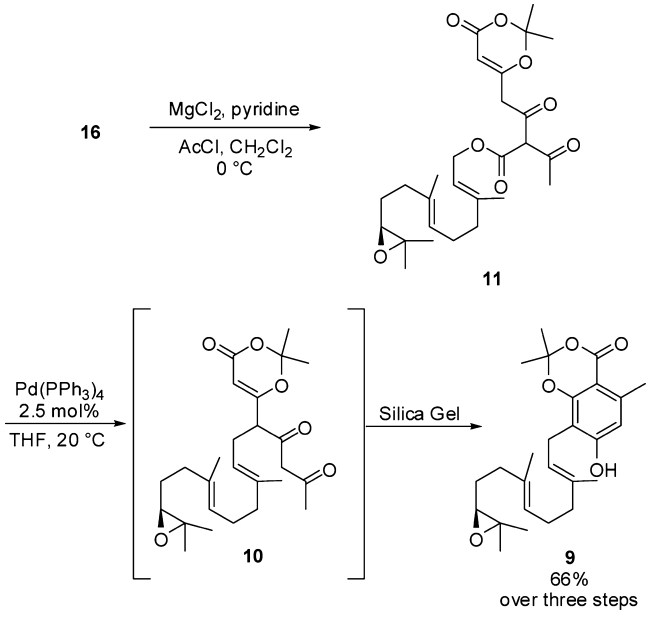
10,11-(*S*)-Epoxyfarnesol (**13**) was prepared from *trans,trans*-farnesyl acetate (**14**) via enantioselective Sharpless dihydroxylation and epoxide formation.[14] Reaction of alcohol **13** with excess of carbonyl diimidazole (CDI) at 0 °C gave the imidazolecarboxylate **15** which was directly allowed to react with the zinc dienolate from keto-dioxinone **12** to give keto-ester **16** (Scheme 3) in a 70% yield over two steps from **13**.

Scheme 3. Synthesis of Dioxinone Keto-ester 16



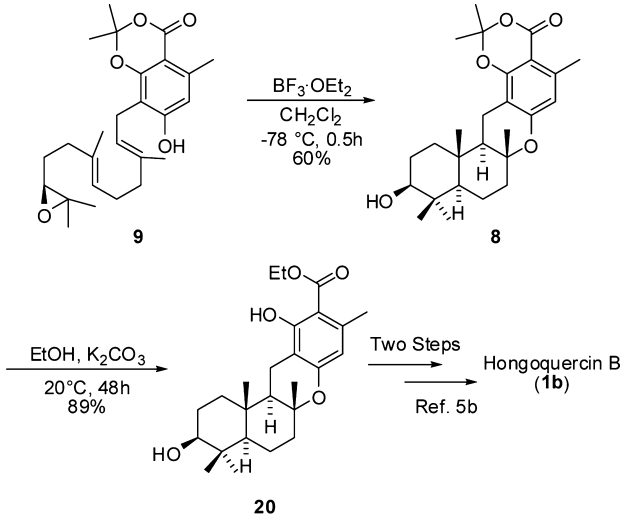
Magnesium chloride and pyridine mediated regioselective acetylation of keto-ester **10** gave the key intermediate diketo-ester **11**. Treatment of ester **11** with $Pd(PPh_3)_4$ at room temperature gave diketo-dioxinone **10**, which was readily aromatized over silica gel to give the resorcylate **9** (Scheme 4) in 66% yield over 3 steps. It is important to note that only the desired linear *E,E*-isomer was observed in this sequence.

Scheme 4. Synthesis of β-Resorcylate 9



With the open chain epoxy-terpenoid resorcylate **9** in hand, studies on the use of both Lewis and Brønsted acids to induce the desired cascade cyclization were examined (Scheme 5).

Scheme 5. Cationic Epoxy-diene Cascade



Gratifyingly reaction of epoxide **9** with boron trifluoride etherate in dichloromethane gave the tetracyclic resorcylate **8** (60%), which was isolated as a single diastereoisomer. The stereochemistry of the product was confirmed from subsequent transformations.

Transesterification of resorcylate **8** with ethanol and potassium carbonate gave hongoquercin B as its known ethyl

dx.doi.org/10.1021/ja511534x | J. Am. Chem. Soc. 2014, 136, 17013−17015

ester **20**. At this stage the stereochemistry of ester **20** was confirmed by comparison of the ^{1}H NMR, ^{13}C NMR, HRMS and $[\alpha]_D$ with data reported together and NOE correlations in the ^{1}H NMR spectrum between various hydrogens of ester **20**.[5b]

In summary, the total synthesis of hongoquercin B (**1b**) has been completed in 9 steps from *trans,trans*-farnesyl acetate (**14**) using a double biomimetic strategy, a palladium(0) catalyzed regioselective decarboxylative farnesyl migration, cycloaromatization to produce the resorcylate and cationic epoxy-diene cyclization. The single epoxy-farnesyl stereocenter was used to control all the remaining 4 stereocenters of the tetracyclic core. Further applications of this dual biomimetic strategy for the syntheses of other bioactive meroterpenoids will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures, characterization of new compounds and comparison of ^{1}H NMR, ^{13}C NMR, IR, HRMS and $[\alpha]_D$ of hongoquercin B ethyl ester 20 with published data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank GlaxoSmithKline for a generous endowment to A.G.M.B and the European Research Council for an Advanced Grant (267281).

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