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Total Synthesis of Wasabidienones B_1 and B_0 via SIBX-Mediated Hydroxylative Phenol Dearomatization

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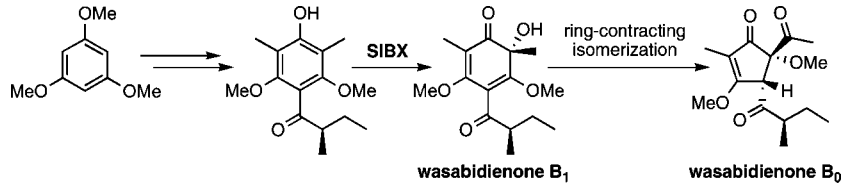
ABSTRACT



The first total synthesis of the natural nondimerizing *o*-quinol (+)-wasabidienone B_1 was achieved from commercially available 1,3,5-trimethoxybenzene. The key dearomatizing transformation was efficiently accomplished via a hydroxylative phenol dearomatization reaction using the stabilized λ^5-iodane reagent IBX (SIBX). (+)-Wasabidienone B_1 was then converted into its congener (−)-wasabidienone B_0 via an improved thermally induced ring-contracting isomerization reaction.

o-Quinols (i.e., 6-alkyl-6-hydroxycyclohexa-2,4-dienone derivatives) are seldom found as constituting motifs of natural products because of their high intrinsic reactivity and, notably, their propensity toward dimerization via Diels−Alder processes.[1] Among the very few examples of nondimerizing *o*-quinols are the hop constituents called humulones[2] and a series of fungal metabolites referred to as wasabidienones **1a**−**c** and **2a**,**b** (Figure 1). These fungal polyketides were isolated in the 1980s by Soga and co-workers from a potato culture of *Phoma wasabiae* Yokogi,[3] a fungus responsible for the blackleg disease causing widespread destruction among cruciferous crops such as rape, cabbage, and wasabi (Japanese horseradish). Some of these metabolites were also later isolated from *Phoma lingam*[4a] and *Aspergillus viridinutans*[4b] cultures. *Aspergillus parasiticus* and *P. lingam* were also reported to produce, respectively, aspersitin (**2c**), i.e., the C-8 epimer of wasabidienone B_2 (**2b**),[4c] and phomaligin A (**2d**).[4a] These fungal metabolites all feature an *o*-quinol-type cyclohexa-2,4-dienone core. They differ from one

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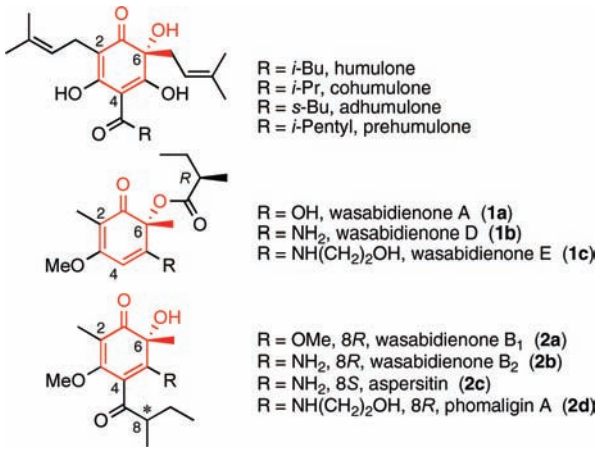

Figure 1. Examples of natural nondimerizing *o*-quinols.

another by the nature of their C-5 substituent and the positioning of their 2-methylbutanoyl side chain. In wasabidienones A (**1a**),[3a−d] D (**1b**),[3a] and E (**1c**),[3e] this chiral unit acylates the tertiary alcohol function of the *o*-quinol moiety, while in wasabidienones B_1 (**2a**)[3a,4b] and B_2 (**2b**),[3a,4a] aspersitin (**2c**),[4c] and phomaligin A (**2d**),[4a] it is connected to the C-4 position of the cyclohexa-2,4-dienone core (Figure 1).

Efforts in the total synthesis of these naturally occurring *o*-quinols have, to the best of our knowledge, only resulted in that of wasabidienone A (**1a**)[5a] and in that of (+)-aspersitin (**2c**).[5b] In both cases, installation of the 2-methylbutanoyl moiety was achieved by Friedel−Crafts acylation using racemic 2-methylbutanoic acid. Sato and co-workers next developed an acyl rearrangement reaction from carbon to oxygen for the synthesis of **1a**, which was achieved in eight steps in ca. 4% overall yield from 1,2,3,5-tetrahydroxybenzene.[5a] In their six-step synthesis of (+)-**2c** obtained in ca. 5% overall yield from dimethylphloroglucinol, Büchi and co-workers relied on a dearomatizing Wessely oxidative acetoxylation (i.e., lead tetraacetate in acetic acid) of a phenolic intermediate to install the required oxygen atom at C-6.[5b]

Oxygenating phenol dearomatization methods indeed stand out among the most straightforward tactics to access *o*-quinols, as long as they can efficiently target the desired *o*-carbon center. Besides the Wessely oxidation, several other oxygenative dearomatizing reagents have been examined over the last 50 years to generate these systems from 2-alkylphenols.[1a,6] More recently, the λ^5-iodane 2-iodoxybenzoic acid (IBX) and its stabilized nonexplosive version (SIBX)[7] were revealed as particularly appropriate reagents to promote hydroxylative phenol dearomatization (HPD) in a strictly ortho-selective manner.[1b,8] For example, we previously applied the SIBX-mediated HPD reaction to the synthesis of natural *o*-quinol-derived [4 + 2] cyclodimers [e.g., (±)-biscarvacrol,[1b,8a] (±)-grandifloracin,[8a] and (+)-aquaticol[8b]] in one step from phenolic precusors. Herein, we report the first application of this HPD reaction to the synthesis of the natural nondimerizing *o*-quinol (+)-wasabidienone B_1 (**2a**), followed by its conversion into (−)-wasabidienone B_0 (**14**).

Our choice of performing this HPD reaction on a phenolic substrate to access the title compounds may find some biomimetic justification in view of investigations on the biosynthetic origin of the C-6 oxygen atom in other *o*-quinol-based natural products such as the humulones[9a,b] and dimerizing sorbicillinoids.[9c,d] The synthesis began with the multigram-scale preparation of the known symmetric phenol **4**[10a] in four steps in 52% overall yield from commercially available 1,3,5-trimethoxybenzene (**3**) (Scheme 1, see the Supporting Information). Installation of the butyryl side chain was next envisioned through nucleophilic addition of a C-4 lithiated derivative of **4** on 2-methylbutanal (**8**). Unfortunately, lithiation conditions applied to a *O*-silylated derivative[10b] of **4** failed to generate the desired C-4 carbanion. We then relied on a standard halogen−metal exchange protocol and prepared bromobenzenes **7a**,**b** in high yields from **4** via either bromination and silylation or benzylation and bromination (Scheme 1). Coupling of these bromides with commercially available aldehyde (±)-**8** or its (*S*)-enantiomer, efficiently prepared by oxidation of commercial (*S*)-2-methylbutan-1-ol,[11] was achieved upon treatment with *tert*-butyllithium in pentane at low temperature, which led to 1.5:1 diastereomeric mixtures (unassigned) of benzylic alcohols **9**. Of particular note is that these coupling conditions were nonepimerizing when using (*S*)-**8**. Debrominated benzene byproducts were successfully recycled in the preparation of **7a**,**b** (see the Supporting Information).

Benzylic alcohols (±)-**9a** and (*S*)-**9a**,**b** were next cleanly oxidized in excellent yields into their corresponding ketones (±)-**10a** and (*S*)-**10a**,**b**. This oxidation was performed in a 9:1 (v/v) mixture of THF/DMSO at room temperature for 1.5 h using SIBX, which we previously also unveiled as a

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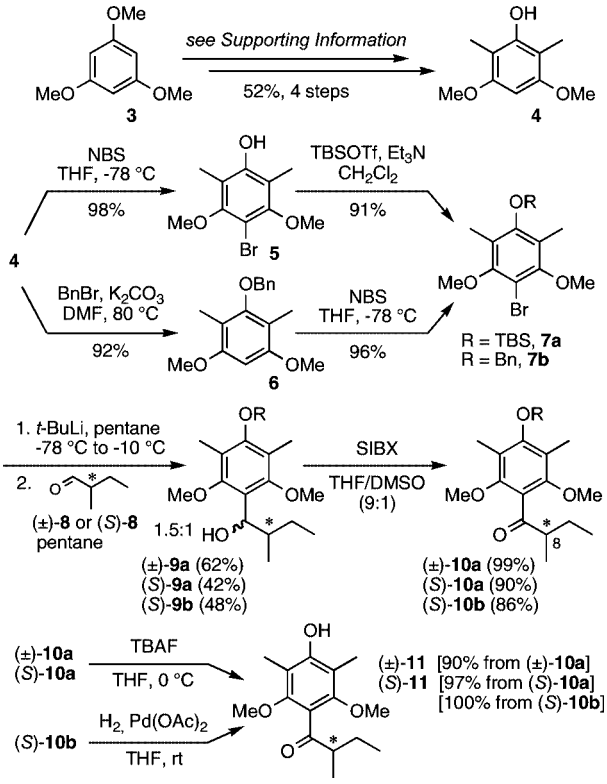
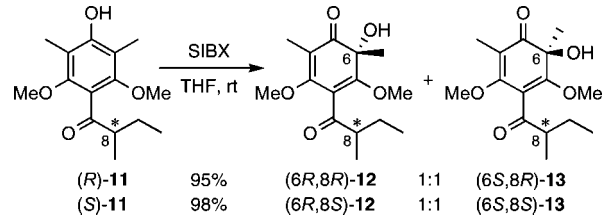
Scheme 1. Synthesis of Phenols (*R*)- and (*S*)-**11**



safe and efficient alternative to the use of IBX or the Dess−Martin reagent.[7a] Again, no epimerization at the C-8 carbon center was observed under these conditions. Phenol (±)-**11**[5b] was then obtained in a 90% yield through TBAF-mediated desilylation of ketone (±)-**10a**; subsequent chiral HPLC resolution furnished both pure enantiomers (*R*)- and (*S*)-**11** (see the Supporting Information). Phenol (*S*)-**11** was also prepared in nearly quantitative yield via either desilylation of (*S*)-**10a** or hydrogenolytic debenzylation of (*S*)-**10b** (Scheme 1).

The key HPD reaction was next performed individually on (*R*)- and (*S*)-**11** in THF at room temperature by adding SIBX (2.25 equiv, i.e., 1.10 equiv of IBX). The resulting suspension was stirred for 15 h, after which time a simple filtration, followed by an aqueous basic workup, afforded clean 1:1 diastereomeric mixtures of the corresponding *o*-quinols in 95% and 98% yields (Scheme 2). Separation by semipreparative HPLC furnished pure (6*R*,8*R*)-**12** and (6*S*,8*R*)-**13** on the one hand and (6*R*,8*S*)-**12** and (6*S*,8*S*)-**13** on the other hand (see the Supporting Information). NMR analyses and optical rotation measurements of all four *o*-quinols led to the unambiguous identification of (6*R*,8*R*)-**12** as the targeted (+)-wasabidienone B_1 (**2a**, $[\alpha]^{20}_D$ +122.2).[4b] The (6*S*,8*R*)-**13**, (6*R*,8*S*)-**12**, and (6*S*,8*S*)-**13** stereoisomers were respectively identified as the non-natural (−)-6-*epi*-, (+)-8-*epi*-, and (−)-*ent*-wasabidienone B_1. These nondimerizing *o*-quinols could be stored as dry oils for several days at −20 °C without any noticeable degradation. However, they were found much less stable in solution, as

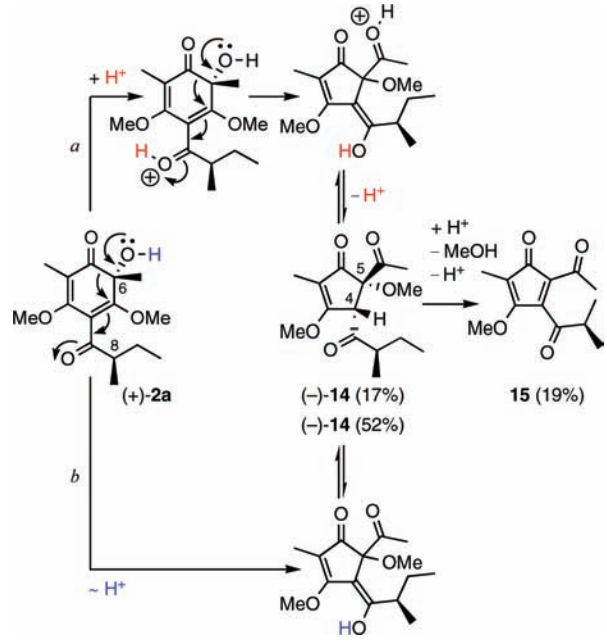
Scheme 2. SIBX-Mediated Hydroxylative Phenol Dearomatization



observed during ^{13}C NMR analysis in $CDCl_3$ over several hours (vide infra). This instability was more pronounced for the 8*S*- than for the 8*R*-compounds and could explain the loss of material observed during the HPLC purification of the 8*S*-stereoisomers (see the Supporting Information).

We were satisfied with these results but yet intrigued by the instability of the synthetic wasabidienone B_1 (**2a**) and its stereoisomers. As alluded to above, (+)-**2a** indeed began to evolve slowly but noticeably into some other species in solution in $CDCl_3$ (ca. 0.08 M). After standing 10 days at room temperature, purification of the resulting mixture by standard silica gel chromatography afforded two compounds in 17 and 19% yield, respectively. Full characterization of the faster-eluting compound led to the identification of wasabidienone B_0 (**14**, $[\alpha]^{20}_D$ −296.7),[12] the naturally occurring ring-contracted isomer of **2a**.[12,4b] ^1H NMR and mass analyses of the second compound indicated the cyclopentadienone structure **15**, resulting from methanol elimina-

Scheme 3. Isomerization of Wasabidienone B_1 (**2a**) into Wasabidienone B_0 (**14**)[a]



[a] Key: (a) $CDCl_3$, rt, 10 days, then SiO_2 column; (b) benzene, 80 °C, 5 days, then HPLC (OJ-H column).

tion from **14** (Scheme 3, path *a*). These data led us to reassess some earlier observations made by Soga and co-workers on the slow conversion over 20 h in refluxing benzene of (+)-**2a** into (−)-**14** (33% yield).[12] We observed that wasabidienone B_1 (**2a**) is stable in freshly distilled benzene (ca. 0.02 M), even heated up to 60 °C, as evidenced by ^{1}H NMR monitoring in C_6D_6. Heating at refluxing temperature (80 °C) for 5 days is necessary to reach nearly complete conversion of **2a** into **14** (Scheme 3, path *b*), which was purified in 52% on a cellulose-based chromatographic support (Chiralcel OJ-H column, see the Supporting Information). No elimination of methanol was observed under these conditions. It is probably the presence of some residual acidity in $CDCl_3$ that had previously promoted the formation of **15** (Scheme 3, path *a*).

In summary, the ortho-selective SIBX-mediated hydroxylative phenol dearomatization (HPD) reaction was successfully applied as a key (and biomimetic) step in the synthesis of the nondimerizing *o*-quinols (+)-wasabidienone B_1 (**2a**) and its three non-natural stereoisomers. The total synthesis of the fungal metabolite (+)-**2a** was thus achieved for the first time in 10 steps and ca. 5% overall yield from 1,3,5-trimethoxybenzene. The conversion of (+)-**2a** into (−)-wasabidienone B_0 (**14**) was performed by a thermally induced ring-contracting isomerization in an improved yield of 52%.

This work demonstrates the applicability of this HPD reaction in the synthesis of *o*-quinolic natural products. The next challenge will consist in setting up an asymmetric version of this regioselective reaction. Our initial efforts in this avenue relied on substrate-controlled accesses to *o*-quinols in nonracemic forms.[13] The convenient use and efficacy of SIBX described therein for mediating the HPD reaction have since prompted us to focus on the development of a reagent-controlled reaction using chiral iodanes. Results will be reported in due course.

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Supporting Information Available: Experimental procedures, NMR spectra, and HPLC traces for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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