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Scalable total synthesis of horsfiequinone A

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ABSTRACT

Starting from two commercially available substrates, methoxyhydroquinone and piperonyl alcohol, a scalable four-step total synthesis of horsfiequinone A was developed. The notable feature of the synthesis is the application of two continuous sequential transformations. Namely, the key aldehyde **9** and horsfiequinone A were prepared *via* scalable Wittig/hydrolysis and Wittig/catalytic hydrogenation/oxidation sequences, respectively. Importantly, the synthetic route required only three recrystallizations and one column chromatography purification step.

Diarylpropanes and their dimers containing a 1,4-*p*-benzoquinone fragment are rare natural products (<30 members) which have been isolated only in some species of *Combretum*,[1] *Horsfieldia*,[2] and *Euonymus*.[3] Despite the small collection, these compounds exhibit intriguing bioactivities, for example, horsfiequinone B (Fig. 1 **2**) shows specific inhibition (IC_{50} = 4.28 μM) against HL-60 in five tested cancer cell lines (HL-60, SMMC-7721, A-549, MCF-7, and SW480),[2] while euonyquinone A (**4**) and combrequinone B (**5**) show potent inhibitory activity against human DOPA decarboxylase (hDDC) with IC_{50} values of 11.5 μM and 21.6 μM, respectively, thus representing promising treatments for Parkinson's (PK) disease.[3]

The unique structure and important bioactivities of the horsfiequinones encouraged us to systematically research *Horsfieldia tetratepala*[4,5] and to propose their biogenetic pathway as well as their chemical synthesis. Biogenetically, an aromatic radical coupling pathway for euonyquinone A (**4**) was proposed by Zhang and co-workers.[3] Due to the different linkage types of the dimeric horsfiequinones, an intramolecular vinylogous aldol pathway was predicted (Scheme 1).[6] The crucial monomer horsfiequinone A (**1**) could be enolized to form its enolate, which could be further coupled with another monomer through a vinylogous aldol reaction to give intermediate **A**. This intermediate is converted to horsfiequinone B (**2**) by reduction and enolization. Compound **2** could be further derivatized to form horsfiequinones C-F. Given the significance of horsfiequinone A for the biosynthesis of dimeric horsfiequinones, it is desirable to develop a scalable and facile route towards this compound. Herein, we report a scalable four-step total synthesis of horsfiequinone A from two commercially available compounds, piperonyl alcohol and methoxyhydroquinone.

Intermolecular aldol reactions of benzaldehydes with acetophenones have been used to prepare diarylpropanes.[7] However, syntheses of diarylpropanes with a 1,4-*p*-benzoquinone framework are barely studied. Retrosynthetic analysis indicated that horsfiequinone A could be produced by the oxidation of compound **6** which could be prepared from olefin **7** by catalytic hydrogenation (Scheme 2). Compound **7** could be synthesized from phosphonium salt **8** and aldehyde **9** *via* a Wittig reaction. Compounds **8** and **9** were easily derived from two commercially available compounds, piperonyl alcohol and methoxyhydroquinone.

Our synthesis started with the preparation of phosphonium salt **8**; piperonyl alcohol was treated with *N*-bromosuccinimide (NBS) and PPh_3 in CH_2Cl_2 at room temperature to give the desired phosphonium salt **8** in quantitative yield (see, ESI for details).[8] The phenol groups of methoxyhydroquinone were benzyl protected using $BnBr/K_2CO_3$ to give dibenzyl protected product **S1** in quantitative yield after recrystallization from petroleum ether/ethyl acetate (PE/EA). Next, Friedel-Crafts formylation (trimethyl orthoformate/$AlCl_3$)[9] was carried out to give aldehyde **10** which was purified by recrystallization from PE/EA in 55% yield. Compound **10** was further converted into aldehyde **9** *via* a continuous Wittig/hydrolysis sequence in 91% yield after recrystallization from PE/EA. Subsequently, compound **8** and **9** were combined using the Wittig reaction to give olefin **7** as a ~2:1 mixture of *Z*/*E* isomers

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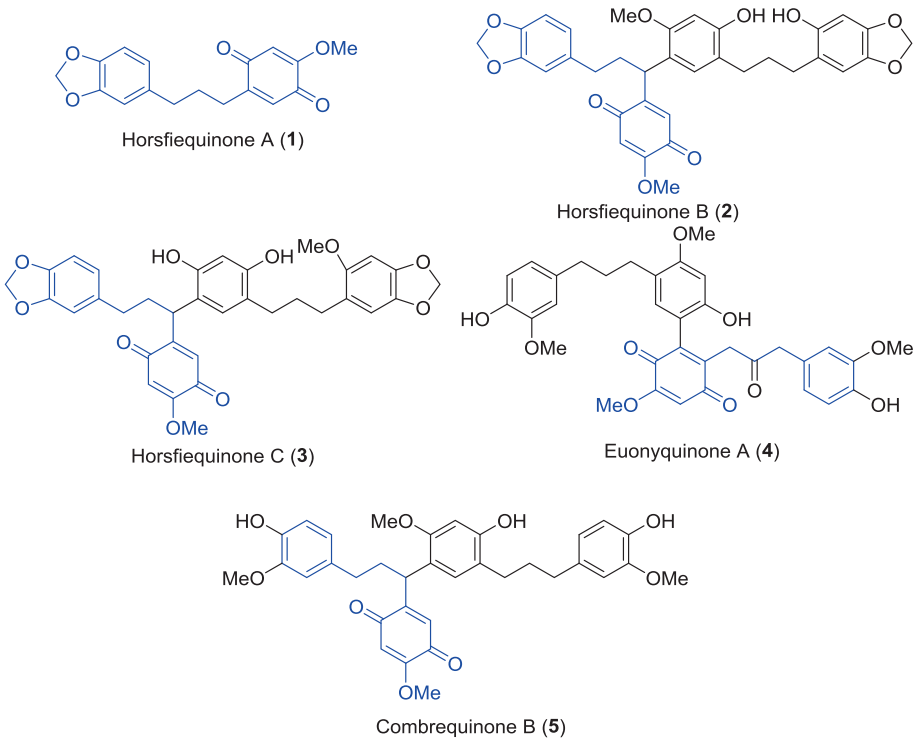
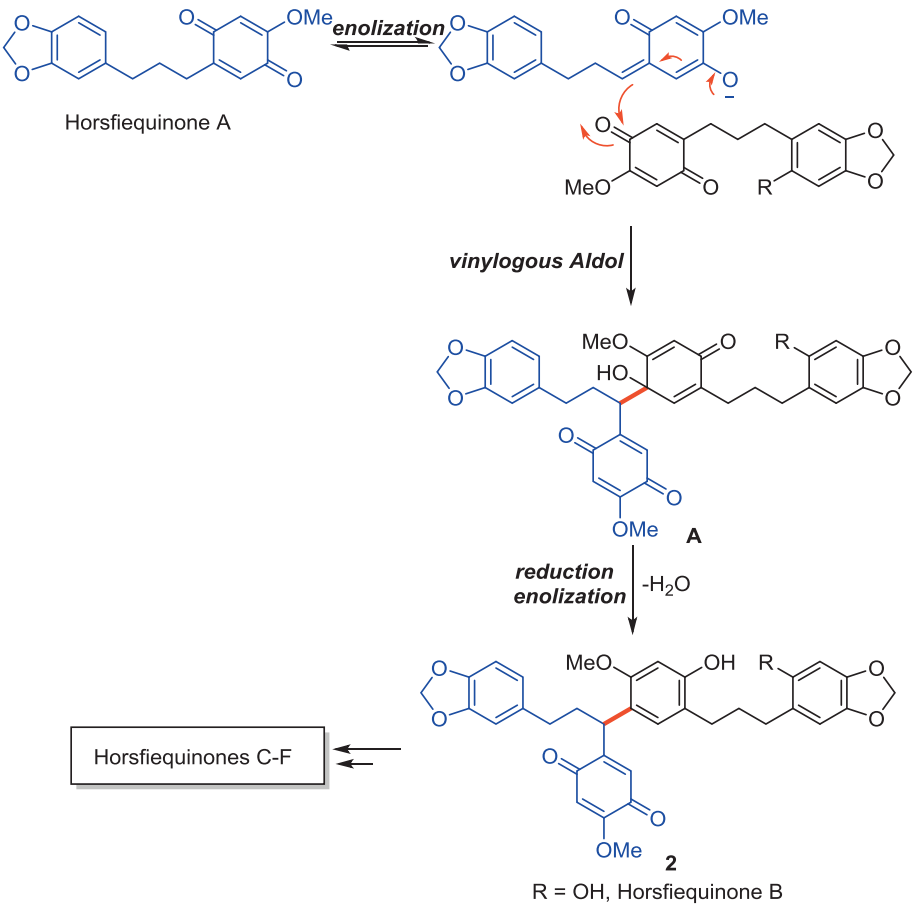


Fig. 1. Structures of selected diarylpropane monomer and dimers.



Scheme 1. Plausible biogenetic pathway of the horsfiequinones.

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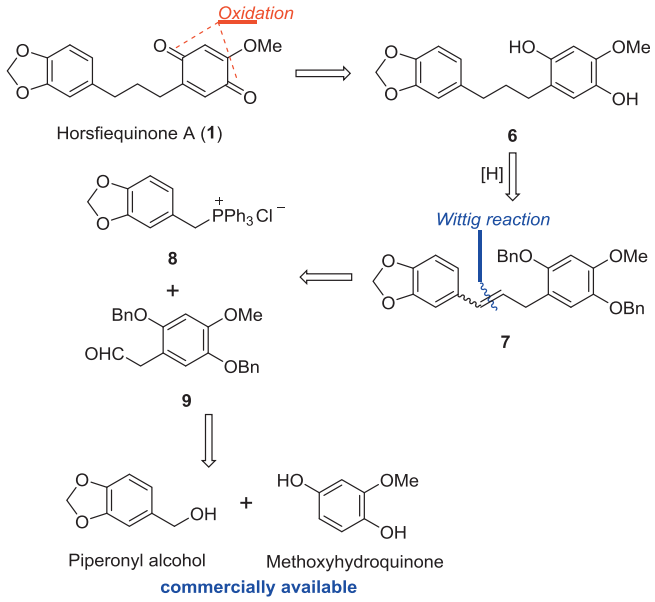


Scheme 2. Retrosynthesis of horsfiequinone A.

Table 1
Oxidation of hydroquinone **6**.

Entry	Conditions	Yield **6** (%)[a]
1	DDQ (2.0 eq.), toluene/CH_2Cl_2 (5:1), 0 °C, 10 min	87
2	Ag_2O (2.0 eq.), Et_2O, RT, 2 h	69
3	$NaIO_4$ (5.0 eq.), MeOH, 0 °C, 1.5 h	90
4	MnO_2 (2.0 eq.), CH_2Cl_2, RT, 4 h	77
5[b]	Silica gel[c], CH_2Cl_2, RT, 12 h	90
6	Silica gel[c], neat, air, 60 °C, 4 h	96

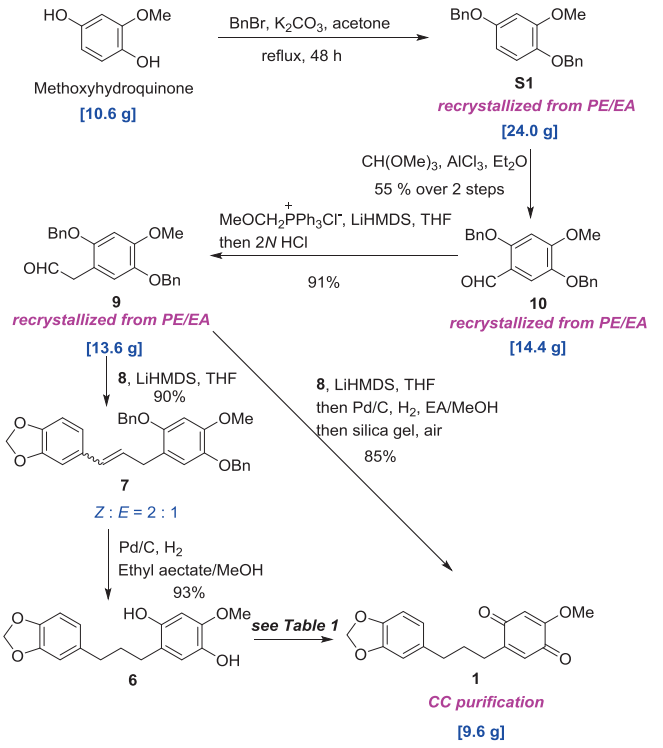
[a] Isolated yield.
[b] BRSM, ~50% starting materials were recovered.
[c] Silica gel was 20-fold (weight) to substrate.

(determined by ^{1}H NMR, ESI) in 90% yield. Catalytic hydrogenation of **7** in EtOAc/MeOH allowed removal of the two benzyl protecting groups to provide hydroquinone **6** in 93% yield.

Although trace amounts of the target product **1** was detected during the work-up and purification process, the autoxidation of **6** was incomplete when it was purified on a silica column. Thus, various oxidative conditions were examined for this transformation (Table 1). All of the tested oxidants (DDQ, Ag_2O, $NaIO_4$, MnO_2, entries 1–4) promoted this transformation, and to our delight, the oxidation also proceeded in the presence of silica gel in CH_2Cl_2 at room temperature in 90% yield BRSM (Entry 5). In order to optimize the reaction, compound **6** was loaded onto silica gel (excess) to form a slightly yellow powder which was heated at 60 °C under air for 4 h to give **1** in 96% yield (Entry 6).

After completion of the synthesis, the synthetic route was simplified using a Wittig/catalytic hydrogenation/oxidation sequence starting from compound **9** (13.6 g). Namely, aldehyde **9** was condensed with phosphonium salt **8** *via* a Wittig reaction, followed by catalytic hydrogenation (Pd/C, H_2) and air mediated oxidation on silica gel to provide the target product **1** (9.6 g) as an orange amorphous solid after purification on a silica column (Scheme 3).

In summary, a facile and scalable total synthesis route to horsfiequinone A (**1**) was achieved within four steps in 43% overall yield. Moreover, three recrystallizations and only one purification using column chromatography were needed in this approach.



Scheme 3. Scalable synthesis of horsfiequinone A.

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A. Supplementary data

Supplementary material including the procedures and ^{1}H and ^{13}C NMR spectra for all compounds. Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.02.082.

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