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# Synthesis of Parvistemin A *via* Biomimetic Oxidative Dimerization

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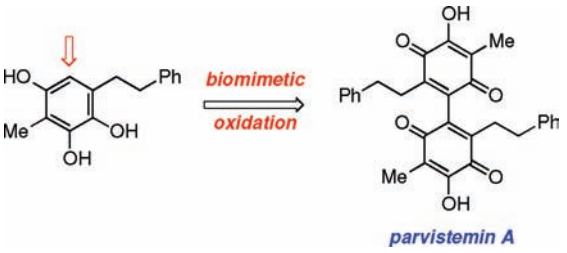
## ABSTRACT




**The first synthesis of the naturally occurring benzoquinone dimer parvistemin A is reported. The key step is the late stage iron(III) mediated dimerization of a 1,2,4-trihydroxyarene to give the natural product in good yield, a phenol oxidative coupling that is believed to be biomimetic. The route proceeds in seven steps from an inexpensive commercially available acetophenone in 14% overall yield.**

The parvistemins **3** (Scheme 1) were isolated from the aerial parts of the flowering plant *Stemona parviflora* Wright in 2007 by Bringmann and co-workers.[1] The roots of this plant have long been used as a substitute for those of *Stemona tuberose*, a popular plant in Chinese medicine for respiratory disorders such as bronchitis and tuberculosis.[2] The *Stemona* genus is well-known for producing the *Stemona* alkaloids, which have been popular targets for the synthetic chemistry community for a number of years,[3−6] but this was the first report of quinonoid metabolites from these plants. Interestingly, these axially chiral compounds were isolated entirely in their racemic forms, and separation of the atrop-enantiomers using HPLC on a chiral stationary phase showed that they did not interconvert at room temperature. This lack of enantioenrichment is not uncommon in naturally occurring axially chiral compounds.[7]

It has been proposed that the parvistemins themselves might arise from the known stilbenoid natural products stilbostemins B−D **1**, isolated from another *Stemona* species in 2002 by Greger and co-workers.[8,9] Oxidation of the resorcinol ring in these compounds would give the corresponding 1,2,4-trihydroxy compounds **2** that could undergo dimerization *via* oxidative phenolic coupling, followed by further oxidation to the parvistemins **3** (Scheme 1), although the intermediates **2** (or the corresponding quinones) have not yet been isolated from the producing organism.

Oxidative phenolic coupling is well established as a powerful method in the synthetic chemist's repertoire,[10,11] and the late stage oxidative dimerization that is apparently employed here by Nature represents the most efficient and aesthetically satisfying approach to these compounds. The oxidative homocoupling of phenolic compounds has proven itself useful as a method for the synthesis of dimeric natural products; recent examples include the kotanins,[12,13]

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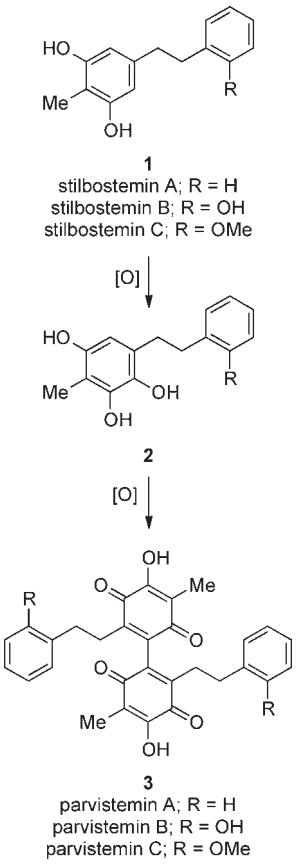
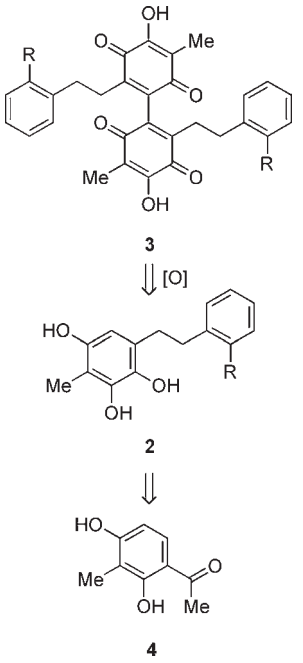
**Scheme 1.** (**a**, R = H; **b**, R = OH; **c**, R = OMe) Parvistemins A–C (**3**) and Their Putative Biosynthesis from Stilbostemins B–D (**1**)




**Scheme 2.** Retrosynthesis of Parvistemins A–C




mastigophorenes A and B,[14,15] and the dimeric core of murrayafoline A.[16] We therefore envisioned a retrosynthesis based on this transformation (Scheme 2). It was decided that the key monomeric building block **2** could be prepared from the commercially available acetophenone **4** using classic aromatic chemistry. Additionally it was planned to introduce the arylethyl moieties shortly before the dimerization by Wittig reaction on a substituted benzaldehyde derived from **4** to impart flexibility to the route, and allow easy access to the other members of the parvistemin family. We now report the successful use of this strategy in the first synthesis of parvistemin A.

The synthesis started with dibenzyl protection of the resorcinol **4** using benzyl bromide and $K_2CO_3$ in DMF (Scheme 3). Baeyer–Villiger oxidation of the acetophenone **5** followed by hydrolysis of the resulting acetate ester gave phenol **6** in good yield. *Ortho*-formylation using Duff conditions (hexamine in refluxing acetic acid)[17] followed by Wittig reaction on the resulting benzaldehyde gave **7**. This olefination reaction required some optimization to obtain a good yield of **7** without recourse to protection of the phenol, with DBU being far superior to alkoxide bases for this step. Thus, using 2 equiv of DBU and benzylphosphonium bromide, stilbene **7** was formed exclusively as the *E*-isomer as evidenced by $^1$H NMR spectroscopy. Simultaneous hydrogenation of the stilbene double bond and hydrogenolysis of the benzyl protecting groups gave the hydroxyquinol **2a**. Careful workup, including filtration and removal of the palladium catalyst under argon, was necessary, as quinol **2a** is rapidly oxidized in the presence of palladium to the monomeric quinone **8**.[18] In the absence of palladium, **2a** is moderately stable to air and can be purified by flash column chromatography if required. Nevertheless, oxidation to the monomeric quinone **8** occurs cleanly in approximately 24 h upon standing in air as a solution in $CH_2Cl_2$ or slightly faster in the presence of silica gel. None of the desired dimer **3a** was observed under these mild conditions.

Although the oxidative dimerization of 1,2,4-trimethoxybenzene is a well-known reaction, facilitated by a number of diverse reagents, only one report exists for the same reaction on the closely related 1,2,4-trimethoxy-benzene system. This was dimerization of 3-neopentylbenzene-1,2,4-triol carried out by Anderson and co-workers in studies toward a biomimetic synthesis of popolohuanone E,[19] using silica supported iron(III) chloride under anhydrous

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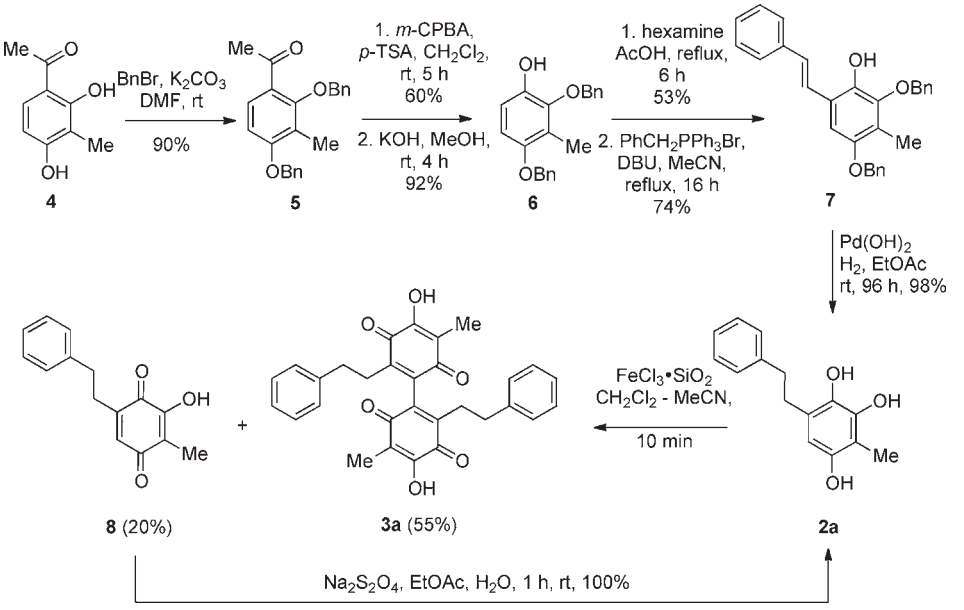
**Scheme 3.** Synthesis of Parvistemin A **3a**




conditions in dichloromethane–acetonitrile.[20,21] We were pleased to find that after some optimization, the application of this reagent to the 1,2,4-trihydroxyarene **2a** gave a reasonable yield of parvistemin A **3a**, whose spectroscopic data closely matched those reported for the natural product (see Supporting Information). In our case the conditions successfully applied by Anderson et al., i.e. slow addition of the monomer to a stirred suspension of the oxidant, only returned the undesired monomeric quinone **8** regardless of the number of equivalents used. It was found that portionwise addition of the oxidant to a solution of **2a** favored the formation of **3a** and that freshly prepared (and rigorously dry) $FeCl_3$•$SiO_2$ was required to ensure reproducibility. The dimer **3a** was accompanied by a small amount of monomeric quinone **8**, which could be readily recycled by reduction back to **2a** using sodium dithionite in essentially quantitative yield.

In conclusion, the first total synthesis of parvistemin A **3a** has been achieved using a biomimetic oxidative dimerization of a 1,2,4-trihydroxybenzene derivative as the key step. This is the first time this powerful transformation, used to form the otherwise challenging biaryl bond, has been applied to the synthesis of a natural product. It was found that dimerization did not occur spontaneously upon oxidation in air, thus implying that some enzymatic assistance is involved in Nature's synthesis of these compounds, despite the fact that natural parvistemin A is a racemate. The route delineated above is high yielding and, by varying the phosphonium salt used in the Wittig reaction, could easily be adapted to the synthesis of other members of this class of natural products.

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**Supporting Information Available.** Full experimental procedures, characterization data, and copies of $^1H$ and $^{13}C$ NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.