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Total Synthesis of Mevashuntin

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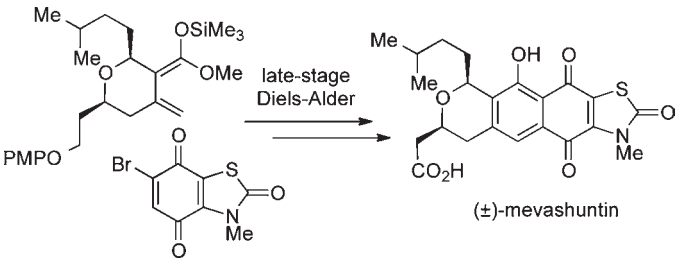
ABSTRACT



The total synthesis of (±)-mevashuntin, a structurally unique naturally occurring pyrano-naphthoquinone-thiazolone, is described. The route is centered upon a late stage regioselective Diels–Alder reaction between two highly functionalized components, as well as an improved protocol for the one pot synthesis of benzothiazolones from *ortho*-bromoaryl isothiocyanates. The strategy results in a highly convergent route, providing access to the natural product in 11 steps from 3-(4-methoxyphenoxy)propanol and confirming its relative stereochemistry.

The Diels–Alder reaction employing quinones as dienophiles has been an important tactic in the total synthesis of natural products for some 60 years, since Woodward's early work on cholesterol,[1] and has subsequently been applied in the construction of an impressive range of alkaloids, steroids and polyketides. Well known examples include reserpine,[2,3] ibogamine,[4] tetrodotoxin,[5,6] giberellic acid,[7,8] and myrocin C.[9] In particular, the reaction is uniquely suited to the construction of naphthoquinone containing natural products, of which many commercially and biologically important examples exist.[10] Surprisingly, the majority of naphthoquinone syntheses based around this Diels–Alder strategy have employed relatively simple dienes and benzoquinones. However, for more complex targets, this typically necessitates a large number of steps after the cycloaddition reaction, and often reduction and protection of the sensitive quinone, making the routes to these compounds linear and lengthy. For this reason, a much more appealing strategy for polycyclic naphthoquinone containing natural products would be a convergent, late-stage Diels–Alder reaction involving diene and quinone components containing as much functionality as possible.[11–13]

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Recently, as part of our ongoing studies on the synthesis of naturally occurring quinones,[14−20] we became interested in the structurally unique pyranonaphthoquinone mevashuntin, reported in 2005 by Shin-ya and co-workers (Figure 1).[21] The highly unusual benzothiazolonequinone motif of **1** was appealing both as an unsolved problem in heterocyclic chemistry and as a novel synthetic target.

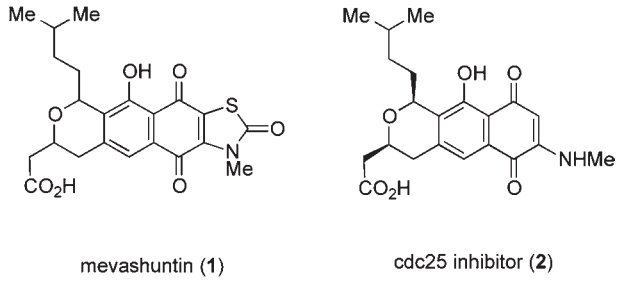
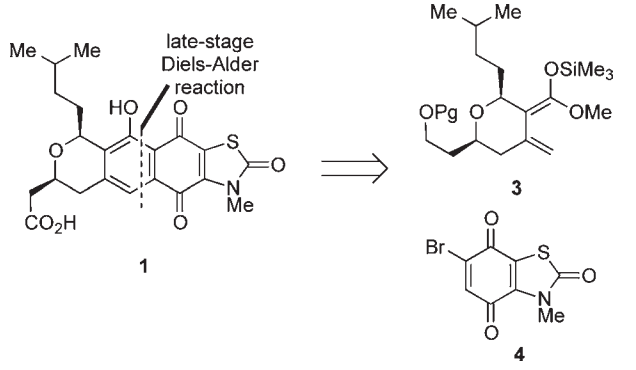


Figure 1. Mevashuntin **1** and the structurally related cdc25 inhibitor **2**.

However, the unknown relative and absolute stereochemistry of the pyran substituents in mevashuntin, and uncertainty in the relative position of the sulfur and nitrogen atoms, as the structure was assigned predominantly by NMR methods, demanded the use of a flexible approach in which both halves of the molecule could be easily varied. This, in addition to the benefits outlined above, suggested the use of a late-stage Diels−Alder strategy. Comparison of the NMR data reported for **1** with those available for the structurally related cdc25 inhibitor **2**,[22] the *cis*-arrangement of pyran substituents being confirmed by NOE experiments (such experiments were not carried out on the natural product **1**), led us to target the *cis*-diastereomer of the natural product. Thus, application of the Diels−Alder disconnection to *cis*-**1** gave the pyran-containing silyl ketene acetal **3** and the bromobenzoquinone thiazolone **4** as the diene and dienophile components respectively (Scheme 1).

Scheme 1. Late Stage Diels−Alder Disconnection



The pyran **3** was chosen as a suitable diene, containing a protected alcohol in place of the acid found in the natural product. It was anticipated, in accordance with pioneering work by Brassard,[23−26] as well as related literature precedent,[27,28] that the bromine atom present in **4** would confer high levels of regioselectivity in the Diels−Alder reaction, as well as aid in aromatization of the initial cycloadduct. Although we have recently reported the use of protected aminobenzoquinones in Diels−Alder reactions toward aminonaphthoquinone natural products,[29] model studies on the construction of thiazolones from such precursors were unpromising, and the use of this tactic would result in a more linear sequence.

For the preparation of the benzothiazolonequinone, a modified form of the copper catalyzed cyclization of *ortho*-bromoaryl thiocarbamates, generated *in situ* from the corresponding isothiocyanates, reported by Patel was used.[30] The substrate for this reaction was prepared by bromination of 2,5-dimethoxyaniline, followed by conversion into the isothiocyanate **6** by heating with thiocarbonyldiimidazole (TCDI) (Scheme 2). In the original procedure, after initial cyclization to the 2-ethoxybenzothiazole had occurred, trifluoroacetic acid was added to the reaction mixture to effect hydrolysis to the desired benzothiazolone **7** in 56−68% yield. During optimization of this step it was found that once the starting isothiocyanate had been consumed, concentration of the reaction mixture, followed by addition of 6 M hydrochloric acid to the residue and heating gave the desired product **7** in almost quantitative yield. Furthermore, under these conditions the product could be isolated by simple filtration and did not require additional purification. *N*-Methylation and oxidation to the quinone were then carried out to give the required dienophile **4** in excellent yield. Although the overall yield from dimethoxyaniline is depressed by the poor yield obtained in the initial bromination step, the inexpensive nature of the starting material meant that batches of more than 10 g of the benzoquinonethiazolone could be routinely obtained, requiring only two purification steps over the entire sequence.

For the preparation of the diene component, the route began from the known 3-(4-methoxyphenoxy)propanol **9**.[31] This was converted directly into the α,β-unsaturated

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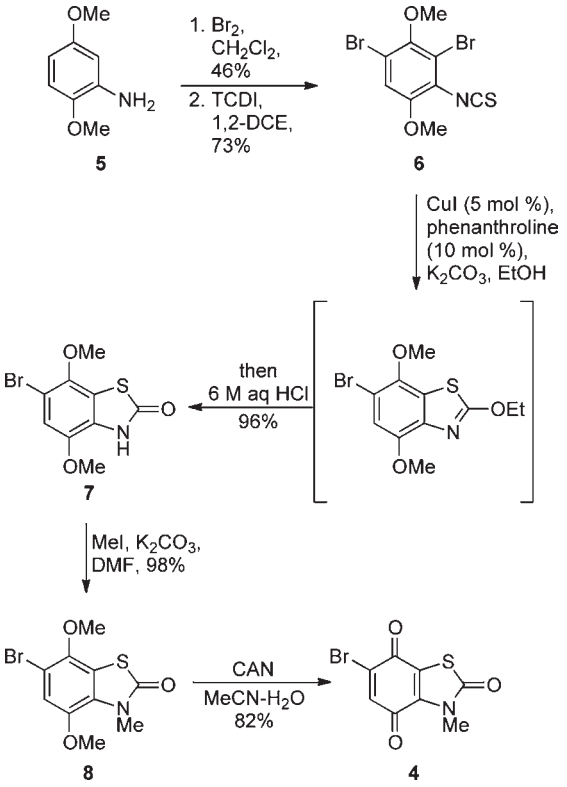
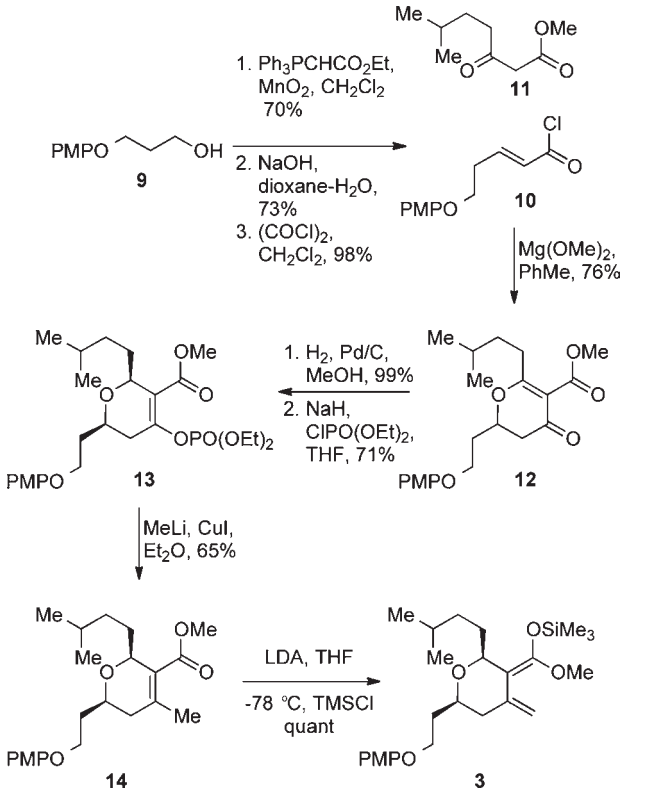
Scheme 2. Preparation of the Dienophile Component **4**



Scheme 3. Preparation of the Diene **3**



ester using the one pot tandem oxidative process reported by Taylor.[32,33] Hydrolysis of the ethyl ester gave the corresponding acid in good yield, which was subsequently converted into the acid chloride **10** and used directly for pyranone formation with the β-ketoester **11**, readily prepared by alkylation of the dianion of methyl acetoacetate.[34] Pyranone **12** was then subjected to hydrogenation at 200 psi over palladium-on-carbon to give the expected saturated compound. Conversion of the β-ketoester into the required acrylate was then carried out according to a literature procedure.[35] Thus, the ketone was first converted into the enol phosphate **13** using diethyl chlorophosphate and sodium hydride, and this was then displaced by treatment with excess lithium dimethylcuprate in ether to give **14** in good yield. At this point, the *syn* stereochemistry of the two pyran substituents, a consequence of the hydrogenation, was confirmed by NOESY experiments. Finally, acrylate **14** was treated with TMSCl and LDA to give the required diene component **3** (Scheme 3).

With both diene and dienophile now in hand it was time to explore the crucial Diels–Alder reaction to unite them. It was found that simply stirring quinone **4** (1 equiv) with a slight excess of diene **3** and triethylamine (1 equiv) in dichloromethane at 0 °C gave a good yield of the desired tetracycle **15** as a single regioisomer. Deprotection of the PMP ether using standard conditions (CAN in various solvents) gave only traces of the desired product, despite the fact that deprotection of the diene precursor **14** could be carried out in excellent yield. Eventually, it was found that treatment of **15** with excess AgO and HNO_3 in dioxane effected rapid deprotection in excellent yield.[36] Although these conditions have been extensively used in the preparation of quinones from hydroquinone ethers, we believe this is the first report of their application to the removal of oxidatively labile protecting groups. Finally, oxidation directly to the acid using Jones' reagent in acetone gave **1** in good yield (Scheme 4).

Interestingly, during characterization of the synthetic material it was found that the NMR spectroscopic data (both ^1H and ^{13}C) was highly concentration dependent and this made comparison with the reported data for the natural product difficult. This effect is believed to originate from the two different modes of hydrogen bonding available to **1** as well as the intermolecular dimeric hydrogen bonding typically displayed by carboxylic acids, intramolecular hydrogen bonding between the acid and pyran oxygen is also possible. Presumably, the former predominates in more concentrated solutions where as the latter mode is more

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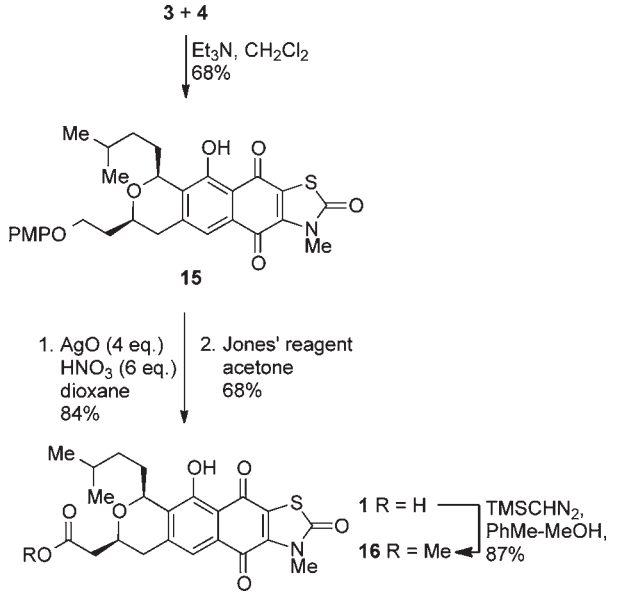
Scheme 4. Diels–Alder Reaction and Completion of the Synthesis of (±)-Mevashuntin **1**



favorable in very dilute solutions. Fortunately, during the structural elucidation of **1** the corresponding methyl ester was also prepared and characterized, and in order to facilitate comparison, methylation of the synthetic acid was carried out. Thus, treatment with excess trimethylsilyldiazomethane gave the methyl ester **16** in excellent yield, and the data obtained were found to match very closely those reported (see Supporting Information). The *syn* nature of the pyran substituents in **16** was confirmed though the use of NOESY NMR experiments that showed a strong interaction between the two methine signals confirming, for the first time, the relative stereochemistry of the natural product.

In conclusion, we have developed a convergent and scalable route to mevashuntin. Key steps include the copper-catalyzed formation of a benzothiazolone and the successful implementation of a late-stage regioselective Diels–Alder strategy to unite two highly functionalized fragments. This allowed construction of the natural product with minimal use of protecting group chemistry and without recourse to reduction and protection of the quinone moiety. The synthesis confirms both the highly unusual structure of the natural product and its relative stereochemistry.

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Supporting Information Available. Full experimental details and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.