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ortho-Quinone Methides from *para*-Quinones: Total Synthesis of Rubioncolin B

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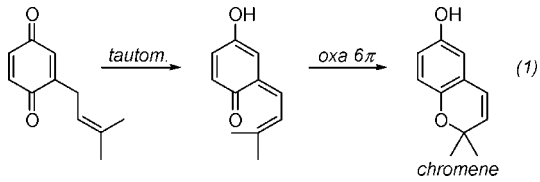
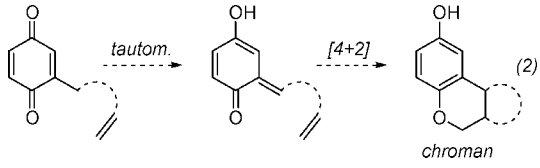
ortho-Quinone methides have proven to be remarkably versatile reactive intermediates, and many methodologies, generally relying on benzylic activation of *ortho*-substituted phenols, have been developed to access them.[1] In Nature, *ortho*-quinone methides appear to be often formed via tautomerization of alkyl-substituted *para*-quinones (eqs 1 and 2).[2] This surprisingly facile tautomerization can be a powerful tool in total synthesis as well. Recently, we reported the tautomerization/electrocyclization of prenylated *para*-quinones as a strategy for the synthesis of chromene natural products (eq 1).[3] Herein, we show that this method can be modified to include intramolecular Diels−Alder (IMDA) cycloadditions (eq 2).[4] These efforts have resulted in a concise total synthesis of the complex naphthohydroquinone dimer rubioncolin B (**1**).

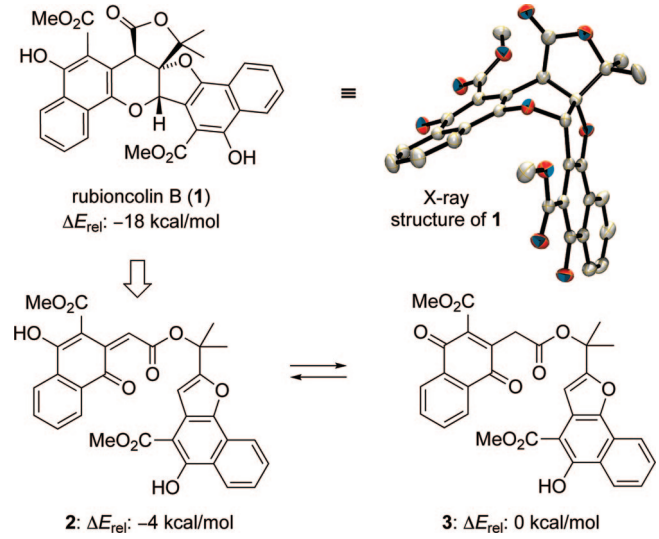




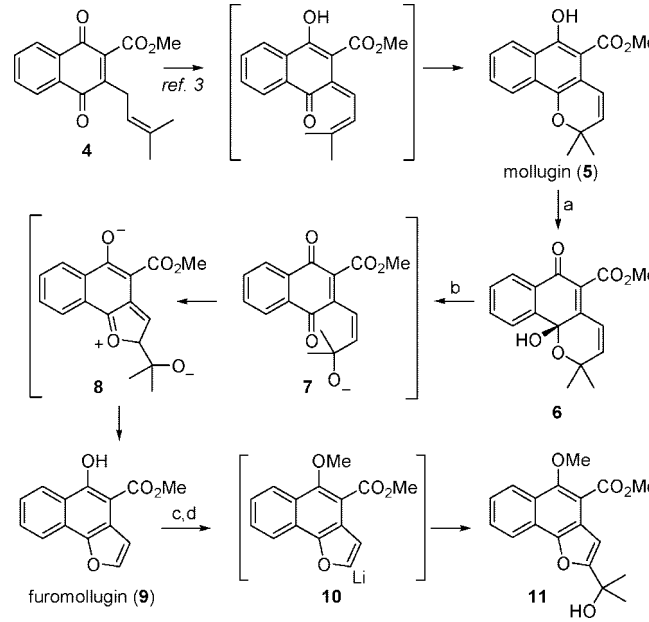
Rubioncolin B (**1**) belongs to a class of unusual naphthohydroquinones isolated from the roots of *Rubia oncotricha* and *R. cordifolia*.[5] The genus *Rubia* is well-known as a prolific source of biologically active anthraquinones and naphthoquinones that are administered in traditional Chinese and Ayurvedic medicine.[6] Of these, the 6-hydroxy-2*H*-chromene mollugin (**5**) is perhaps the most widely studied. Interestingly, only a handful of dimeric natural products have been isolated from *Rubia*, and each of these is found in racemic form.[7]

We reasoned that the complex molecular architecture of **1** could be rapidly assembled via an intramolecular Diels−Alder reaction involving an *ortho*-quinone methide as the diene and a naphthofuran as the dieneophile (Scheme 1). Retrosynthetically, this disconnection would provide **2**, which would be in equilibrium with its *para*-quinone tautomer **3**. In line with our hypothesis, density functional theory (DFT) calculations, performed at the B3LYP/6-31G** level of theory, indicate that the electronic energy (*E*) of the ground-state conformer of **2** is favored over **3** by 4 kcal/mol. In addition, **1** is energetically favored over **3** by 18 kcal/mol.[8] In light of these calculations, we were confident that a synthesis of **3** would readily provide the necessary *ortho*-quinone methide for the formation of rubioncolin B. However, the feasibility of the Diels−Alder reaction remained uncertain, as few examples of benzo- or naphthofurans serving as dienophiles have been reported.[9] Our key intermediate **3** could be formed via oxidation of a hydroquinone precursor, whose synthesis would hinge on the esterification of a tertiary alcohol and a benzylic carboxylic acid.

Scheme 1. Retrosynthetic Analysis of Rubioncolin B



Scheme 2. Synthesis of the Tertiary Alcohol[a]



[a] Reagents and conditions: (a) CAN (2 equiv), H_2O/CH_3CN (1:1), 0 °C, 15 min, 99%; (b) K_2CO_3 (5 equiv), DMF, 100 °C, 1 h, 70%; (c) Me_2SO_4, K_2CO_3, $(CH_3)_2CO$, 23 °C, 12 h, 90%; (d) LDA (1.1 equiv), THF, −78 °C, 1 h; $(CH_3)_2CO$ (15 equiv), −78 to 0 °C, 1 h; NH_4Cl, 0 °C, 84%.

Synthesis of the requisite tertiary alcohol began from the natural product mollugin (**5**), whose biomimetic synthesis from **4** has been reported (Scheme 2).[3] Oxidation of **5** afforded **6**, which was converted to furomollugin (**9**)[5] under basic conditions. This transformation presumably involves cyclization of *para*-quinone **7** to provide **8**, followed

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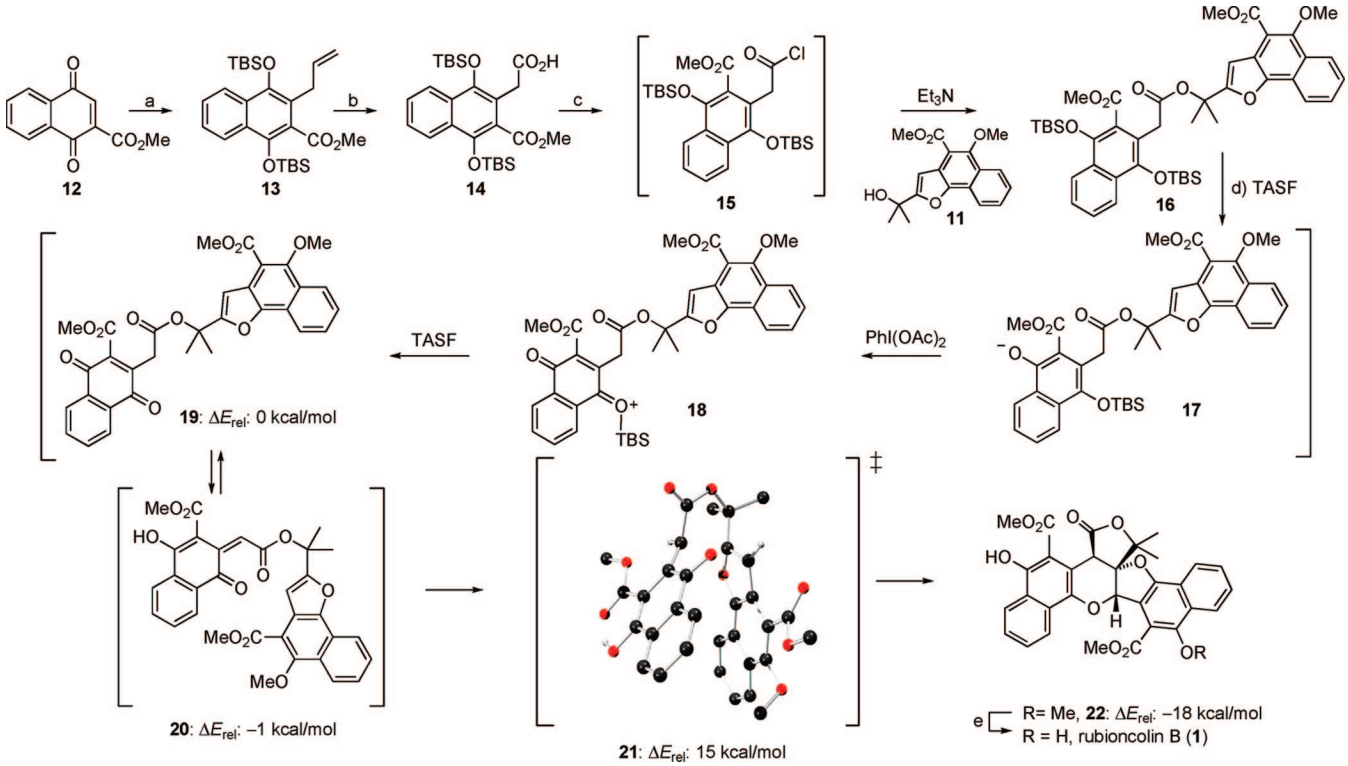
Scheme 3. Synthesis of Rubioncolin B via An Oxidation/Tautomerization/Diels–Alder Cycloaddition Cascade[a]



[a] Reagents and conditions: (a) allyltributyltin (1.1 equiv), $BF_3 \cdot Et_2O$ (1.1 equiv), CH_2Cl_2, −78 °C, 90 min; H_2O, 0 °C; TBSOTf (3 equiv), 2,6-lutidine (5 equiv), CH_2Cl_2, 0 °C, 2 h, 35%; (b) K_2OsO_4 (0.01 equiv), $NaIO_4$ (5 equiv), 1,4-dioxane, H_2O, 23 °C, 12 h; $NaClO_2$ (9 equiv), NaH_2PO_4 (7 equiv), 2-methyl-2-butene, *tert*-butanol, 23 °C, 3 h, 45%; (c) i. $(COCl)_2$ (1.5 equiv), DMF (1 drop), CH_2Cl_2, 2 h, 23 °C, then concentrate in vacuo; ii. **11** (1.2 equiv), Et_3N (5 equiv), CH_2Cl_2, 23 °C, 12 h, 70%; (d) $PhI(OAc)_2$ (1.1 equiv), TASF (2.1 equiv), CH_3CN/H_2O (20:1), 23 °C, 2 h, 60%; (e) BBr_3 (1.1 equiv), CH_2Cl_2, −78 °C, 15 min, 95%. TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate.

by expulsion of acetone to afford **9**. Methylation, followed by lithiation (→**10**) and addition to acetone afforded the tertiary alcohol **11**.

Coupling partner **14** was synthesized in two straightforward steps from the known naphthoquinone **12**[10] (Scheme 3; see Supporting Information for details). The key esterification was accomplished by conversion of **14** to the acid chloride **15**, followed by exposure to **11** in the presence of triethylamine to provide hydroquinone bis-TBS ether **16** in 70% yield.

Initial attempts to elaborate **16** to the *para*-quinone were met with difficulties as both acidic and basic conditions resulted in cleavage of the benzylic ester. However, *exposure of* **16** to 2 equiv of TASF in the presence of $PhI(OAc)_2$ *directly provided rubioncolin B methyl ether* (**22**) in 60% isolated yield. Deprotection of **22** in the presence of BBr_3 afforded synthetic rubioncolin B (**1**), whose structure was confirmed by X-ray analysis (Scheme 1; see Supporting Information for details).

Presumably, this oxidation/tautomerization/Diels–Alder cascade begins by TASF-mediated desilylation to provide a phenoxide **17**. Oxidation with $PhI(OAc)_2$ then provides oxonium ion **18**, which is readily desilylated by a second equivalent of TASF, yielding quinone **19**. As anticipated, **19** is in equilibrium with its *ortho*-quinone methide tautomer **20**. Endo transition state **21** was located at the B3LYP/6-31G** level and *is merely 15 kcal/mol higher in energy than the ground-state conformation of* **20**. Therefore, once formed, **20** should undergo a facile cycloaddition to afford rubioncolin B methyl ether (**22**).

We believe that our synthesis sheds light onto the biosynthetic origin of rubioncolin B. The spontaneous conversion of **19** into **22** provides further evidence that *ortho*-quinone methides can be formed in Nature via facile tautomerization of *para*-quinone precursors. This process does not necessitate enzymatic assistance and, as a result, provides a reasonable explanation for the isolation of **1** as a racemate.

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Supporting Information Available: Detailed synthetic and computational protocols. This material is available free of charge via the Internet at http://pubs.acs.org.

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