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Asymmetric Syntheses of (−)-Mitorubrin and Related Azaphilone Natural Products

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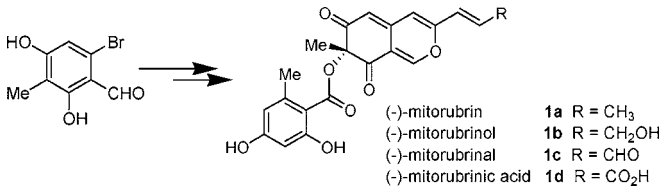
ABSTRACT



Asymmetric syntheses of (−)-mitorubrin and related azaphilone natural products are reported. Key steps involve copper-mediated, enantioselective oxidative dearomatization to prepare the azaphilone core and olefin cross-metathesis for side-chain installation.

The azaphilones are a structurally diverse family of natural products containing a highly oxygenated, bicyclic core and a chiral quaternary center (cf. **1a**−**d**, **2**, Figure 1). Mitorubrin and related natural products are a subclass of azaphilones including (−)-mitorubrin **1a**,[1] (−)-mitorubrinol **1b**,[1] (−)-mitorubrinal **1c**,[1c] (−)-mitorubrinic acid **1d**,[1b,c,2] and the [4+2] dimer (−)-diazaphilonic acid (**2**).[3] In addition, (+)-mitorubrin, (+)-mitorubrinol, (+)-mitorubrinol acetate, (+)-mitorubrinic acid, and their derivatives have also been isolated from a variety of sources.[4] (−)- and (+)- Mitorubrin and related molecules have (*R*)- and (*S*)-configurations at C-7, respectively. The relative and absolute stereochemistry of diazaphilonic acid has not been determined. (−)-Lunatoic acid A, an azaphilone related to **1d** bearing an aliphatic ester side chain, has also been reported.[5] (−)-Mitorubrin and related molecules display diverse biological activities. For example, (−)-mitorubrin and (−)-lunatoic acid A show moderate inhibition of geranylgeranyltransferase I (GGTase I).[4c] (−)-Mitorubrinic acid (**1d**) has been shown to induce formation of chlamydospore-like cells in fungi and also to

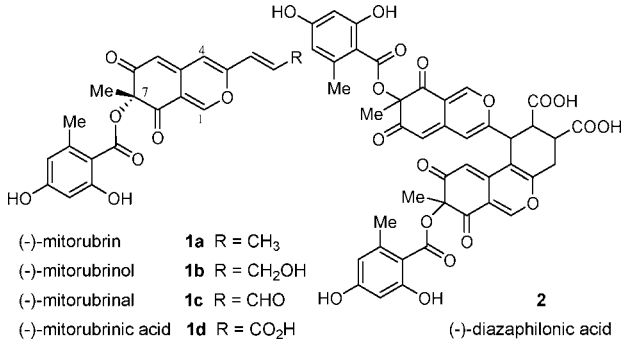


Figure 1. (−)-Mitorubrin and related azaphilone natural products.

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inhibit trypsin (IC_{50} = 41 μM).[2b] The dimeric azaphilone diazaphilonic acid (**2**) inhibits Tth DNA polymerase (IC_{50} = 2.6 μg/mL) and MTI (human leukemia) telomerase (complete inhibition at 50 μM).[3a]

Because of the interesting structural features and biological properties of mitorubrin and related azaphilones, a number of synthetic studies have been disclosed. In the early 1970s, Whalley and co-workers reported a synthesis of (±)-mitorubrin (**1a**).[6] Recently, a synthesis of (±)-mitorubrinic acid was reported by Pettus and co-workers.[7] As part of our synthetic studies toward the azaphilones, our laboratory has developed a racemic route employing gold(III)-mediated cycloisomerization of alkynylbenzaldehydes.[8] More recently, we reported an asymmetric synthesis of the azaphilone core involving copper-mediated oxidative dearomatization.[9] In this Communication, we describe syntheses of (−)-mitorubrin and related natural products employing enantioselective oxidative dearomatization methodology to rapidly assemble the azaphilone core and olefin cross-metathesis to install the requisite side chains from a common intermediate.

Our retrosynthesis of (−)-mitorubrin and related natural products is outlined in Figure 2. Natural products varying

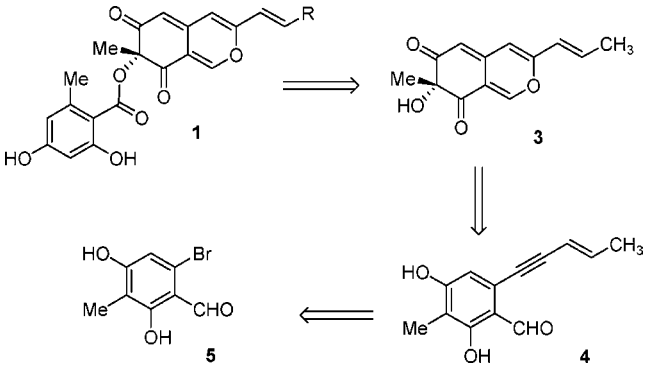
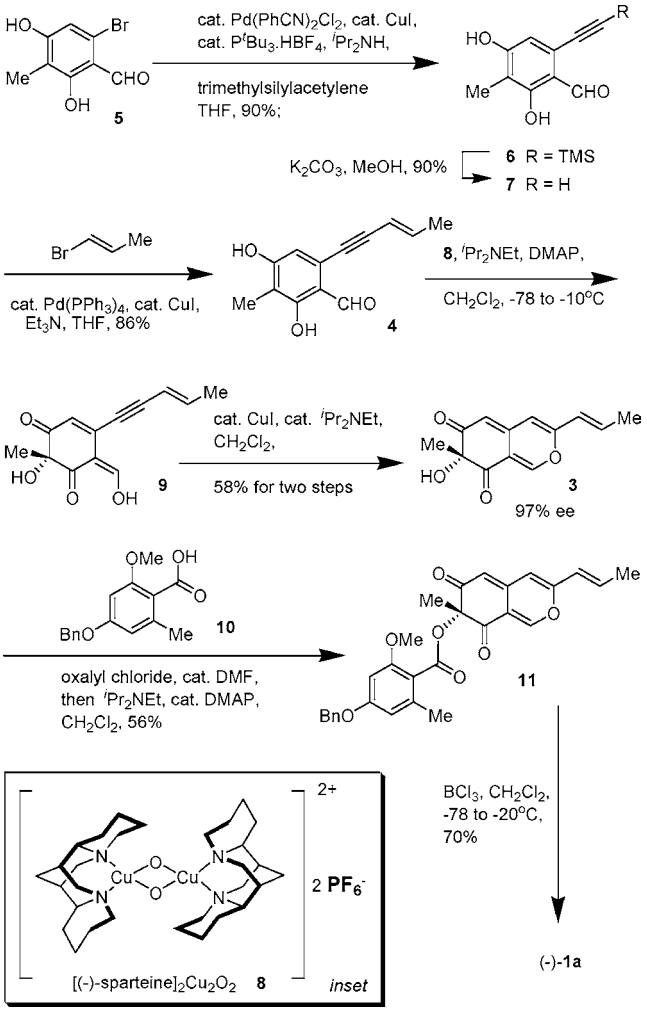


Figure 2. Retrosynthetic analysis of (−)-mitorubrin and related azaphilone natural products.

in their side-chain oxidation state may be derived from mitorubrin, in analogy with their proposed biosyntheses.[1c] Azaphilones **1** may be derived from mitorubrin core structure **3** by attachment of an orsellinate fragment. Mitorubrin core **3** may be prepared from alkynylbenzaldehyde **4** using copper-mediated, enantioselective oxidation followed by cycloisomerization.[9] Enyne benzaldehyde **4** may be derived from the readily available aryl bromide **5**.[8]

$Pd(PhCN)_2Cl_2$/P^tBu_3-mediated Sonogashira coupling[10] of aryl bromide **5**[8] with trimethylsilylacetylene, followed by

Scheme 1. Synthesis of (−)-Mitorubrin **1a**



desilylation, afforded alkynylbenzaldehyde **7** (Scheme 1).[11] A second Sonogashira coupling of **7** and *trans*-1-bromo-1-propene produced the desired alkynylbenzaldehyde **4** (86%). [(−)-Sparteine]$_2$$Cu_2O_2$ (**8**; inset, Scheme 1) mediated oxidative dearomatization[9] of **4** afforded vinylogous acid **9** which, after workup, was directly submitted to Cu(I)-catalyzed cycloisomerization to afford mitorubrin core structure **3** (58% yield, two steps, 97% ee).[12] The protected orsellinic acid fragment **10** (Scheme 1) was prepared from commercially available ethyl 2,4-dihydroxy-6-methylbenzoate via selective benzylation,[13] methylation, and ester hydrolysis.[11] Treatment of **3** with the corresponding acyl chloride derived from **10** using DMAP as the catalyst provided the desired (−)-mitorubrin precursor **11** (56%). Finally, global deprotection

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(11) See Supporting Information for complete experimental details.

(12) Cycloisomerization of vinylogous acid **9** to azaphilone **3** using our previously reported conditions (aqueous KH_2PO_4/K_2HPO_4 buffer, ref 9) was found to be ineffective. For CuI/Et_3N-mediated cycloisomerization, see: (a) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (b) Kel'in, A. V.; Gevorgyan, V. *J. Org. Chem.* **2002**, *67*, 95.

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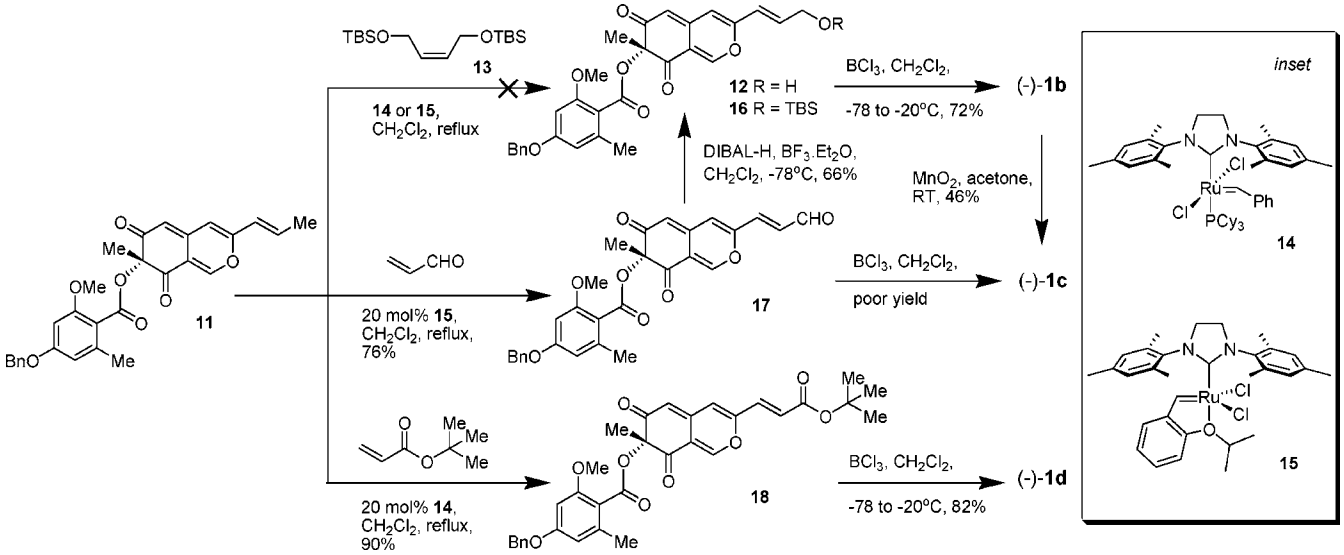
Scheme 2. Syntheses of (−)-Mitorubrinol **1b**, (−)-Mitorubrinal **1c,** and (−)-Mitorubrinic Acid **1d**



of the methyl and benzyl ethers of **11** using BCl_3[6] cleanly produced (−)-mitorubrin **1a** (70%) which provided spectral data matching those reported for natural **1a**.[1a,b,4a]

Unfortunately, direct allylic oxidation of **11** to alcohol **12** using selenium dioxide[14] was found to be problematic. As an alternative approach, we envisioned that (−)-mitorubrinol, (−)-mitorubrinal, and (−)-mitorubrinic acid could be accessed from **11** via side-chain installation employing olefin cross-metathesis.[15] In the event, cross-metathesis of **11** with *cis*-1,4-bis(*tert*-butyldimethylsiloxy)-2-butene **13** in the presence of Grubbs second-generation catalyst **14**[15a,b] or Hoveyda−Grubbs catalyst[16] **15** (inset, Scheme 2) did not afford the desired product **16** (Scheme 2). However, cross-metathesis of **11** with acrolein using catalyst **15** successfully produced aldehyde **17**. Although BCl_3-mediated deprotection of **17** did not cleanly produce (−)-mitorubrinal **1c**, treatment of a mixture of **17** and $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −78 °C with DIBAL-H in hexanes resulted in selective reduction of the aldehyde to afford allylic alcohol **12** (66%).[17] Preincubation of **17** with $BF_3{\cdot}Et_2O$ was found to be crucial to minimize conjugate reduction of the azaphilone core. Compound **12** was finally deprotected with BCl_3 to afford (−)-mitorubrinol **1b**. MnO_2 oxidation of **1b** afforded **1c** in moderate yield.[1c] Cross-metathesis of **11** with *tert*-butyl acrylate in the presence of catalyst **14** afforded the desired *tert*-butyl enoate **18**, which was cleanly deprotected (BCl_3) to afford (−)-mitorubrinic acid **1d**.[11]

In conclusion, concise syntheses of (−)-mitorubrin and related natural products have been accomplished. Copper-mediated, enantioselective oxidative dearomatization of an *o*-alkynylbenzaldehyde was used for construction of a mitorubrin intermediate. Olefin cross-metathesis was successfully employed to install the requisite side chains on this intermediate by variation of the alkene partner. Studies toward the synthesis of additional azaphilone natural product targets are currently in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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