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# Mulberry Diels−Alder Adducts: Synthesis of Chalcomoracin and Mulberrofuran C Methyl Ethers

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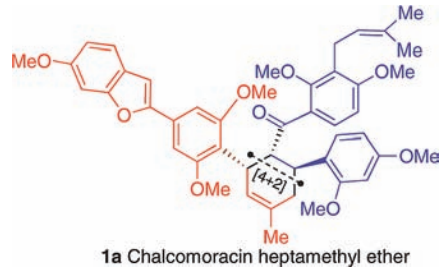
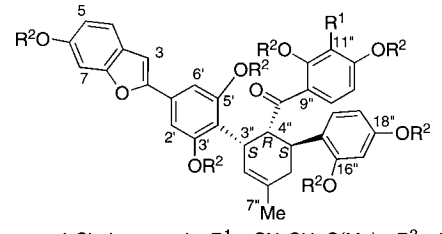
## ABSTRACT




**1a** Chalcomoracin heptamethyl ether

**The synthesis of each of the heptamethyl ethers of the mulberry Diels−Alder adducts chalcomoracin (1) and mulberrofuran J (2) is described. The key steps in each approach involved a biomimetic intermolecular [4+2]-cycloaddition between a dehydroprenylphenol diene derived from an isoprenoid-substituted phenolic compound and an α,β-unsaturated alkene of a chalcone as the dienophile. Critical to the success of the Diels−Alder reaction was the presence of the free phenol in the 2′-hydroxychalcone.**

Moraceous plants are a rich source of isoprenoid-substituted phenolic compounds, in particular the so-called mulberry Diels−Alder-type adducts isolated from the mulberry tree.[1] Common examples of this large class of Diels−Alder adducts are (+)-chalcomoracin (**1**)[2] and mulberrofuran C (**2**)[3] (Figure 1). Interestingly, *Morus alba* L. cell cultures produce compound **1** in yields up to 100 times greater than the intact plant.[4] These naturally occurring cyclohexenes were the first examples of natural products biosynthesized by an enzyme-controlled[5,6] *intermolecular* Diels−Alder reaction between a dehydroprenylphenol diene derived from an isoprenoid-substituted phenolic compound and an alkene of a chalcone as the dienophile.[1]




**1** Chalcomoracin: $R^1 = CH_2CH{=}C(Me)_2$; $R^2 = H$
**1a** $R^1 = CH_2CH{=}C(Me)_2$; $R^2 = Me$
**2** Mulberrofuran C: $R^1 = R^2 = H$
**2a** $R^1 = H$; $R^2 = Me$

**Figure 1.** Structures of chalcomoracin (**1**) and muberrofuran C (**2**).

Chalcomoracin (**1**) exhibits considerable antibacterial activity against MRSA strains K3 and ST 28 (MIC 0.78 μg/

(1) Nomura, T.; Hano, Y. *Nat. Prod. Rep.* **1994**, *20*, 5–218.
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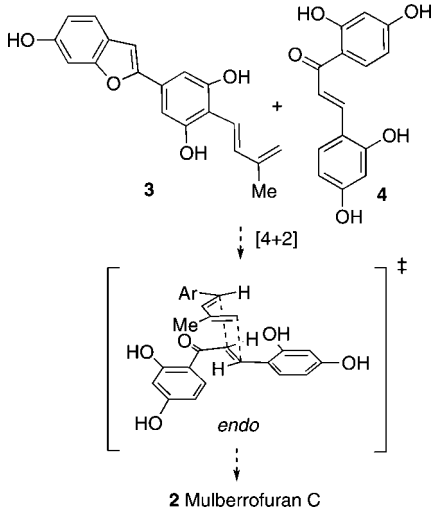
mL)[7] and moderate cytotoxicity against five human cancer cell lines, with $IC_{50}$ values ranging from 5.5 to 7.0 $\mu$g/mL.[8] Mulberrofuran C (**2**) has been shown to possess hypotensive activity with intravenous injection of 1 mg $kg^{-1}$ causing significant hypotension in rabbits.[3] The absolute configuration of these mulberry Diels−Alder-type adducts was determined as 3″*S*,4″*R*,5″*S* by a combination of X-ray crystallographic analysis and CD spectroscopy.[9]

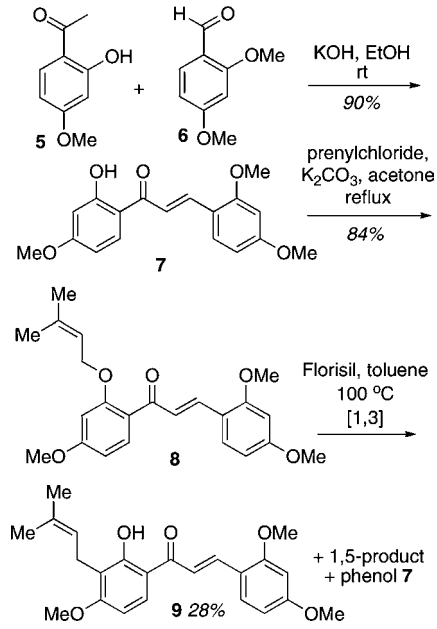
The enzyme-mediated [4+2]-cycloaddition between a diene such as the dehydro derivative **3** of phytoalexin moracin C[10] and dienophile chalcone **4** proceeds via the *endo* transition state to afford the *cis*,*trans*-adduct mulberrofuran C (**2**) as one enantiomer (Scheme 1). The alternative *exo* transition state would give the *trans*,*trans* stereochemistry, which is found in other Diels−Alder-type metabolites.[1] Support for this biosynthetic hypothesis arose from a range of pyrolysis[2] and partial synthesis studies[11,12] as well as elegant feeding experiments.[13]

**Scheme 1.** Proposed Biosynthesis of Mulberrofuran C (**2**)




Interestingly, a [4+2]-cycloaddition between a 2′-hydroxychalcone[14] and dehydroprenylphenol has not been achieved in vitro.[15] We now report a successful [4+2]-cycloaddition between synthetic dienes and 2′-hydroxychalcone dienophiles to afford the heptamethyl ether derivatives **1a** and **2a** of mulberry Diels−Alder adducts chalcomoracin (**1**) and mulberrofuran C (**2**), respectively.

**Scheme 2.** Synthesis of the 2′-Hydroxychalcone Dienophiles




The synthesis of the requisite Diels−Alder partners began with the preparation of the chalcone dienophiles **7** and **9** as shown in Scheme 2. Claisen−Schmidt condensation[16] between ketone **5** and aldehyde **6** proceeded smoothly in the presence of KOH as base to afford the mulberrofuran chalcone **7**[17] in excellent yield. For the synthesis of chalcomoracin precursor, phenol **7** was prenylated under standard conditions and the resultant prenyl ether **8** was subjected to a Florisil promoted [1,3]-sigmatropic rearrangement[18] to afford the prenylated chalcone **9**. A significant amount of the corresponding [1,5]-rearranged product was also produced along with the deprenylated chalcone **7**.

The route to the benzofurandehydroprenyl diene partner is detailed in Scheme 3. A selective[19] Sonogashira coupling[20] between the alkyne **10**[21] and iodide **11** gave the alkyne **12**

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(15) For the confirmation of the structures of mulberry Diels−Alder adducts kuwanon G and H by partial synthesis [pyrolysis of the octamethyl ether derivatives (retro-Diels−Alder fragmentation) and reconstruction via Diels−Alder reaction of the fragments] see ref 11.
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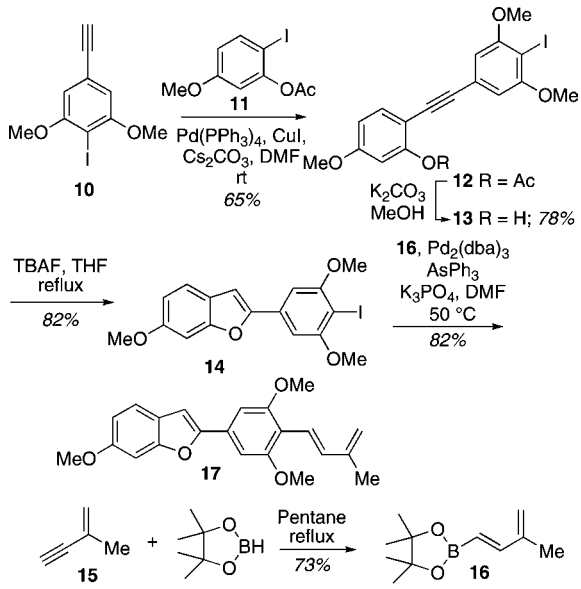
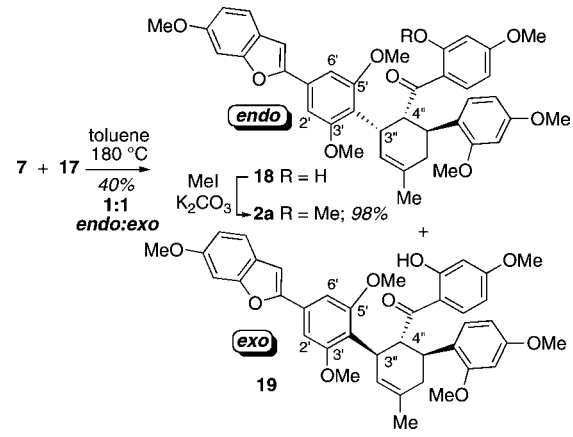
**Scheme 3.** Synthesis of Diene **17**




in good yield. Key to the success of this reaction was the use of $Cs_2CO_3$[22] rather than amine bases.[23] Methanolysis of the acetate afforded the phenol **13** ready for cyclization; however, attempts at forming the benzofuran with gold[24] or platinum catalysis[25] gave low yields. Fortunately, cyclization of phenol **13** could be achieved in good yield, using TBAF[26] to afford the benzofuran **14**. Formation of the dehydroprenyl diene proved challenging. After extensive experimentation, it was found that Suzuki−Miyaura coupling[27] of iodide **14** and pinacolboronate **16** (Scheme 4),[28] prepared by simple hydroboration of enyne **15** with pinacolborane,[29] afforded the labile diene **17** in excellent yield. This intermediate proved somewhat unstable and was used immediately after rapid purification on $SiO_2$. The instability of **17** perhaps explains why putative biosynthetic precursors such as **3** have not been isolated.

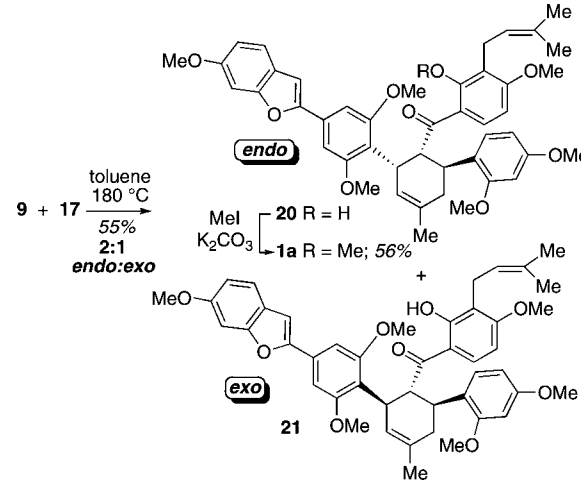
The cycloaddition between diene **17** and chalcone **7** failed to occur in boiling toluene and was not promoted effectively by Lewis acids. Eventually, we found that the intermolecular Diels−Alder reaction proceeded at 180 °C in toluene in a sealed tube giving the *endo* and *exo* adducts *cis,trans*-**18** and *trans,trans*-**19**, respectively, in a 1:1 ratio after separation by preparative HPLC. Interestingly, the fully methylated version of **7** failed to undergo clean cycloaddition. This demonstrated that the phenol in chalcone was critical for the success of the [4+2]-cycloaddition possibly due to the H-bond to the carbonyl group activating the dienophile.[30] The *endo*-adduct **18** corresponds to hexamethyl mulberrofuran C while the *exo* adduct **19** is the hexamethyl ether derivative of mulberrofuran J.[31] Methylation of **18** afforded mulberrofuran C heptamethyl ether (**2a**), which had been reported previously[3] but, unfortunately, no NMR data were quoted so a direct comparison was not possible. Unfortunately, several attempts at deprotection of either **18** or **2a** to give mulberrofuran C (**2**) only led to incomplete demethylation or decomposition.

**Scheme 4.** Synthesis of Mulberrofuran C Heptamethyl Ether (**2a**)




The assignment of the stereochemistry for each adduct arose from comparison of key proton NMR data with that reported for related natural products. Typically, the coupling constant between H3″ and H4″ is of the order of 5 Hz (*cis*) in the *endo*-isomer while in the *exo*-isomer it is 10 Hz (*trans*). In addition, the signal for C3′ and C5′ OMe groups in *endo*-

**Scheme 5.** Synthesis of Chalcomoracin Heptamethyl Ether (**1a**)

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isomer **18** was observed as a broad singlet at $\delta$ 3.59 (6H) and the H2′ and H6′ signals appeared as a broad singlet at $\delta$ 6.95 (2H). On the other hand the C3′ and C5′ OMe signals where separated at $\delta$ 3.71 (3H) and 4.08 (3H) in the *exo* isomer **19** and the signals for H2′ and H6′ appeared at $\delta$ 6.89 (1H) and 7.09 (1H), indicating that there is significant restricted rotation about the C3″−C4′ bond in the *exo*-isomer **19**.

The synthesis of chalcomoracin heptamethyl ether (**1a**) is detailed in Scheme 5. Cycloaddition between chalcone **9** and diene **17** proceeded at 180 °C to give the *endo* and *exo* adducts chalcomoracin hexamethyl ether **20** and mongolicin F[32] hexamethyl ether **21** in a 2:1 ratio favoring *endo*-isomer **20**. Methylation of **20** then afforded chalcomoracin heptamethyl ether (**1a**). In this case, the data for synthetic **1a** could be matched to the compound obtained by permethylation of an authentic sample of chalcomoracin (**1**), thus confirming the stereochemistry of the *endo* adduct **20**.

In conclusion, we have reported examples of H-bond accelerated intermolecular [4+2]-cycloadditions between 2′-hydroxychalcone dienophiles **7** and **9** and labile dehydroprenyl diene **17** to afford the methyl ether derivatives **1a** and **2a** of the mulberry Diels−Alder adducts chalcomoracin (**1**) and mulberrofuran C (**2**), respectively. Efforts toward the synthesis of other compounds in this class are underway.

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**Supporting Information Available:** Experimental details as well as characterization data and copies of the NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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