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# First Total Synthesis of Cassiarin A, a Naturally Occurring Potent Antiplasmodial Alkaloid

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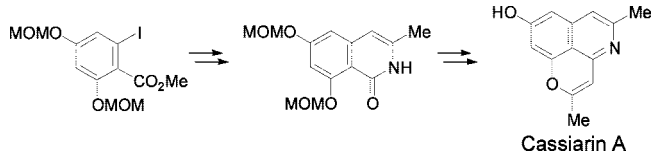
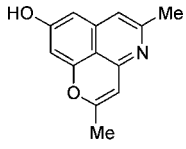
## ABSTRACT

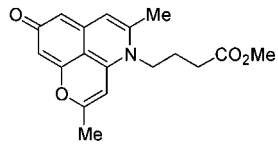



**The first total synthesis of cassiarin A, an antiplasmodial alkaloid isolated from *Cassia siamea*, was achieved via sequential alkynylation of arenes with Sonogashira coupling and 6-*endo*-dig-cyclization of phenolic oxygens to the resulting alkynes.**

The genus *Cassia* is widely distributed in tropical and subtropical regions and is used in traditional folk medicine, particularly for the treatment of periodic fever and malaria.[1]




Cassiarin A (**1**)




Cassiarin B (**2**)

Recently, we have isolated two novel heteroaromatic alkaloids, cassiarins A (**1**) and B (**2**), from the leaves of *Cassia siamea* (Leguminosae).[2] These alkaloids possess an unprecedented tricyclic skeleton and exhibit potent antiplasmodial activity.[1]

Due to the unique structural feature and also to the strong antiplasmodial activity of cassiarin A, we have been interested in the synthesis of this alkaloid.

Our basic strategy for the synthesis of cassiarin A is outlined in Figure 1.

We envisaged that exploitation of sequential Sonogashira coupling[3] for introducing alkyne groups to aromatic rings of **B** and **G** and subsequent 6-*endo*-dig cyclization[3b,4] of oxygen atoms to the resulting alkynes **A** and **E** would be the most straightforward way to achieve the goal for constructing heteroaromatic skeletons. Moreover, this strategy is expected to have broad utility in searching for new potential antiplasmodial compounds.

Thus, our synthesis commenced with the preparation of the benzoate derivative **G**, which would readily be accessible by application of known procedures to methyl 2,4-dihydroxybenzoate.[5]

The synthesis was started by MOM protection of the known dihydroxy-ester **3** that was prepared by Hegedus' procedures[6] (Scheme 1). While our attempts to convert iodobenzoate **4** directly to the isoquinolone derivative by a

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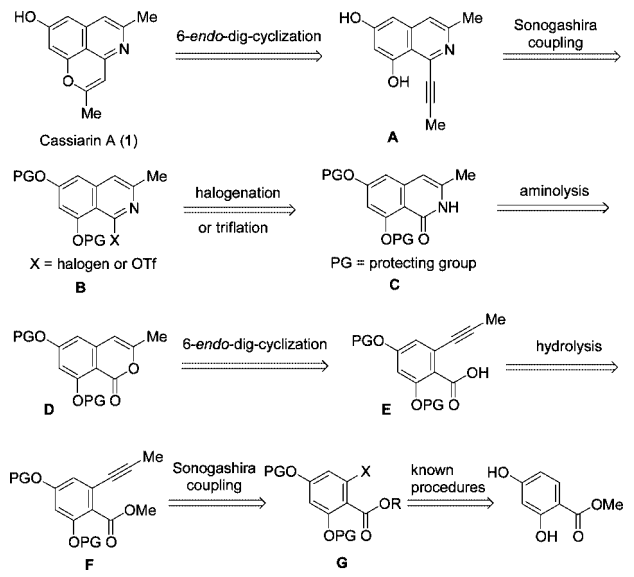
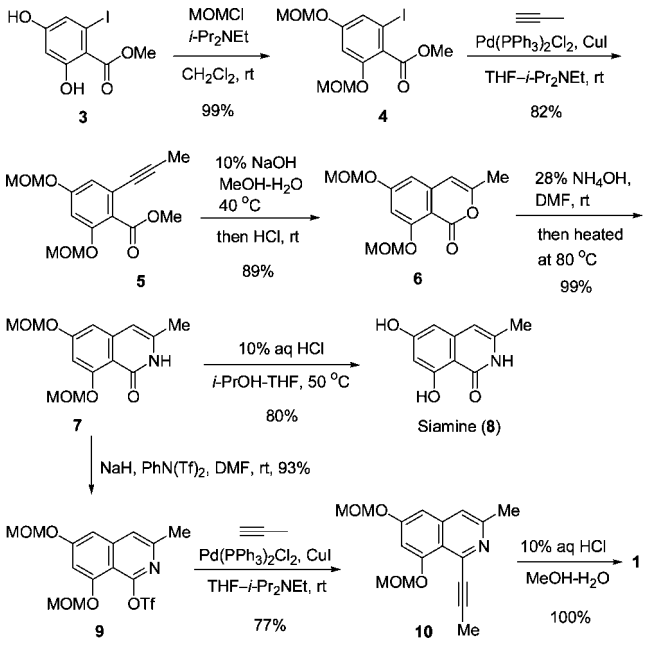



**Figure 1.** Retrosynthetic analysis for cassiarin A.

**Scheme 1.** Synthesis of Siamine and Cassiarin A




Heck-type reaction with methyl 2-acetamidoacrylate[6] did not give good results, Sonogashira coupling of iodide **4** with in situ generated propyne[3b] provided alkyne **5** in 82% yield. Hydrolysis of ester **5** with aqueous base followed by acidification of the reaction mixture provided, upon standing, the isocoumarine **6** (89% from **5**). Transformation of isocoumarine **6** to isoquinolone derivative **7** was carried out by stirring with 28% ammonium hydroxide in DMF at room temperature,[7] followed by heating at 80 °C to facilitate cyclization of the ketoamide intermediate.

Having the isoquinolone derivative **7** in our hands, we became intrigued by its transformation to siamine (**8**),[8] another alkaloid of *Cassia siamea*. Deprotection of the MOM group of **7** with HCl in *i*-PrOH−THF[9] provided siamine (**8**) in 80% yield. Spectral data ($^1$H and $^{13}$C NMR, MS, IR) of the obtained compound were in agreement with the published data of siamine.[8] Thus, we have accomplished a novel route to siamine.

Although conversion of the isoquinolone compound to the corresponding 1-bromoisoquinoline by using $POBr_3$ is well-known,[10] the method did not work with our isoquinolone **7**. Therefore, we focused on the corresponding isoquinolyl triflate.

Treatment of **7** with *N*-phenyl-bis(trifluoromethanesulfonimide)[11] in DMF in the presence of sodium hydride provided triflate **9** in 93% yield. Sonogashira coupling of triflate **9** with in situ generated propyne gave alkyne **10** in 77% yield. Finally, MOM deprotection of **10** and 6-*endo*-dig cyclization were performed in one step by employing 10% aq HCl in methanol to quantitatively give cassiarin A (**1**), whose spectroscopic data ($^1$H and $^{13}$C NMR, MS, IR) and TLC behavior were identical to those of the authentic sample of isolated compound.[2]

In summary, we were able to establish a concise synthetic route for **1** by employing Sonogashira reaction and 6-*endo*-dig cyclization as the key reactions. This is the first synthesis of cassiarin A. This synthesis afforded the target compound in 51% overall yield in seven steps from the readily accessible known starting material **3**. Further application of this methodology to various types of alkaloid syntheses, as well as synthesis of cassiarin B, are now under investigation in our laboratory.[12]

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**Supporting Information Available:** Experimental details and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Attempted conversion of cassiarin A to cassiarin B by direct alkylation with methyl bromo- or iodobutyrate under various reaction conditions failed, unfortunately. Similar alkylation of *O*-Bn or *O*-MOM cassiarin A did not give corresponding quaternary salts. When cassiarin A was treated with methyl bromobutyrate in the presence of a base, O-alkylated compound was isolated as the sole product.