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An Aryne Route to Cytosporone B and Phomopsin C

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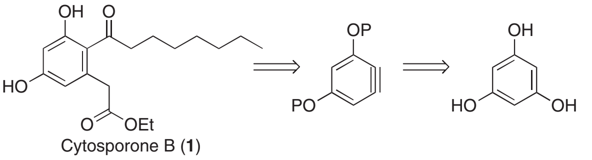
The octaketide cytosporone B has been synthesized in six steps using 1,3,5-trihydroxybenzene as a starting material via aryne insertion reaction into a carbon–carbon σ-bond.

Cytosporones are octaketide metabolites isolated by Clardy's group from the broth of two endophytic fungi, *Cytospora* sp. CR200 and *Diaporthe* sp. CR146 (Figure 1).[1,2] Among these, cytosporone B (**1**) has been recently demonstrated to bind to the ligand-biding domain of nuclear orphan receptor Nur77 and stimulate the transactivational activity of Nur77.[3] Moreover, cytosporone B enhances gluconeogenesis in mouse liver, increases Nur77-mediated induction of apoptosis, and retards xenograft tumor growth. These biological effects clearly reveal that cytosporone B would be useful in developing new therapeutic drugs for cancers and hypoglycemia; however, its total synthesis has hitherto appeared only in a Chinese patent,[4] to the best of our knowledge. We report herein the shortcut to cytosporone B starting from commercially available 1,3,5-trihydroxybenzene through aryne insertion into a carbon–carbon σ-bond (eq 1).[5,6]



(1)

Initially we examined the synthesis of 3,5-di-*O*-methylcytosporone B (**3**)[7] via the insertion of 3,5-dimethoxybenzyne into a carbon–carbon σ-bond of ethyl 3-oxodecanoate.[8] As described in Scheme 1, the required aryne precursor **2** was prepared from 3,5-dimethoxyphenol in six steps in 20% overall yield.[9,10a] Subsequent reaction of **2** with ethyl 3-oxodecanoate in the presence of a fluoride ion (KF/18-Crown-6) led to the selective formation of **3** in 43% yield among four possible insertion products, where cleavage of the C–C σ-bond (between the active methylene moiety and the ketone carbonyl) and introduction of the octanoyl moiety into the aromatic ring (*ortho* to the 3-MeO group) took place regioselectively.[11] Although an attempt to convert **3** into **1** by use of BBr_3 (3 equiv) was unsuccessful, a 71% yield of phomopsin C (**4**), which has been recently isolated from mangrove endophytic fungus, *Phomopsis* sp. ZSU-H76,[12] was found to be formed as the sole product through the regioselective monodemethylation instead.[13] Unfortunately, treatment of **3** with other demethylation reagents including Me_3SiCl/NaI[14] and HBr/NaI[15] also failed to provide **1**.

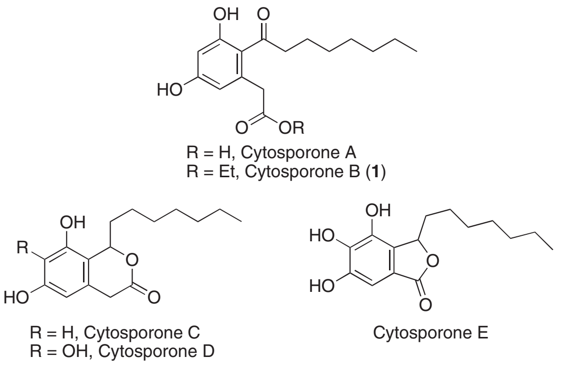
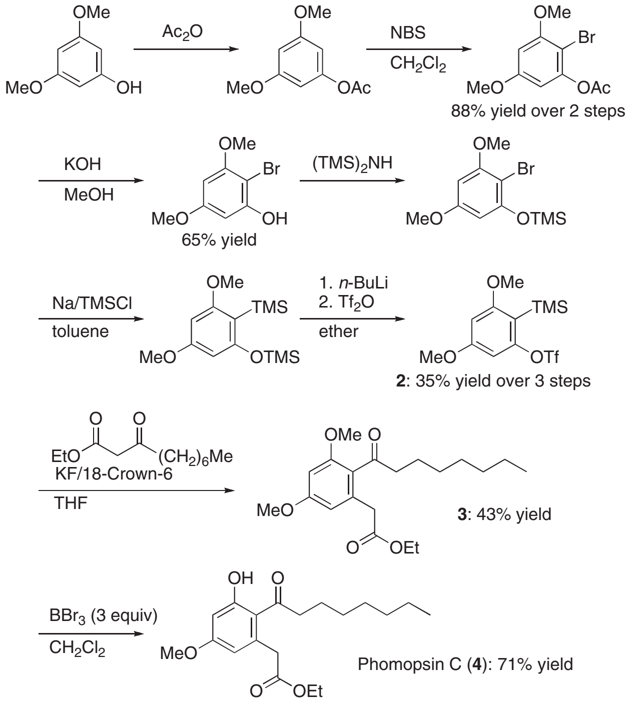
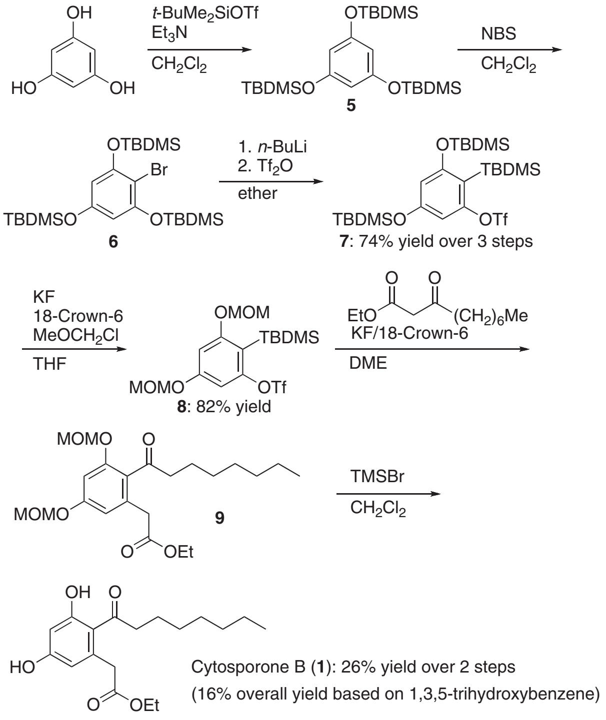


Figure 1. Cytosporones isolated from endophytic fungi.



Scheme 1. Synthesis of phomopsin C.

We thus turned our attention to 3,5-bis(methoxymethoxy)-benzyne, envisaging that deprotection of MOM moieties would occur more smoothly. At first we attempted to transform 1,3,5-trihydroxybenzene into 3,5-bis(methoxymethoxy)phenol, which should be convertible into the required aryne precursor according to Scheme 1, however selective introduction of two MOM moieties into 1,3,5-trihydroxybenzene proved to be difficult.[16] Hence we designed another route to the aryne precursor by use of TBDMS-protected trihydroxybenzene **5**, which was readily accessible by the reaction with t-$BuMe_2SiOTf$ as outlined in Scheme 2. Monobromination of **5** followed by the reaction of the resulting product **6** with n-$BuLi/Tf_2O$ gave 3,5-disiloxybenzyne precursor **7** (74% yield over three steps),[10b] which was then treated with chloromethyl methyl ether in the presence of



Scheme 2. Synthesis of cytosporone B.

fluoride ion to furnish the target aryne precursor **8** without loss of the C(aryl)–Si bond (82% yield). As was the case of 3,5-dimethoxybenzyne, 3,5-bis(methoxymethoxy)benzyne (from **8**) was found to be also inserted into the active methylene–ketone carbonyl σ-bond of ethyl 3-oxodecanoate, providing 3,5-di-*O*-(methoxymethyl)cytosporone B (**9**) in a regioselective manner,[17] which could be finally transformed into the desired cytosporone B (**1**) by deprotection using TMSBr (16% overall yield based on 1,3,5-trihydroxybenzene).[18] It should be noted that only three isolations sufficient to obtain the final product throughout the process, showing the efficacy of the present method.

In conclusion, the aryne insertion reaction into a carbon–carbon σ-bond has been demonstrated to be potent for the total synthesis of octaketides, allowing cytosporone B to be fabricated in 6 steps from commercially available 1,3,5-trihydroxybenzene. Moreover, the first synthesis of phomopsin C has also been accomplished relying on the present method.[19] Further studies on the total synthesis of other natural products by use of arynes as key intermediates are in progress.

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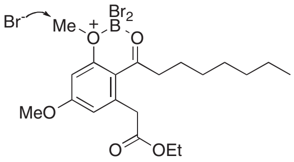

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16 For example, the reaction of 1,3,5-trihydroxybenzene, which was pretreated with NaH (2.2 equiv), with chloromethyl methyl ether (2.1 equiv) in DMF at 0 °C afforded the desired product only in 21% yield, accompanied by the formation of mono- and trimethoxymethylated products. Furthermore, attempted monobromination of the resulting 3,5-bis(methoxymethoxy)phenol using NBS gave a mixture of a desired monobrominated and a dibrominated products. Therefore, we abandoned the synthesis of 3,5-bis(methoxymethoxy)benzyne precursor from 3,5-bis-(methoxymethoxy)phenol.

17 In addition to **9**, we also observed the formation of small amounts of unidentified by-products.

18 We also examined the reaction of **7** with ethyl 3-oxodecanoate in the presence of a fluoride ion, expecting the direct formation of **1** via the insertion reaction accompanied by the deprotection of the silyl ether moieties, however, this reaction only gave a complex mixture.

19 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.