

An Aryne Route to Cytosporone B and Phomopsin C

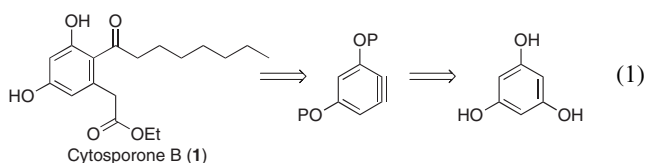
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The octaketide cytosporone B has been synthesized in six steps using 1,3,5-trihydroxybenzene as a starting material via aryne insertion reaction into a carbon–carbon σ -bond.

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-binding 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}



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

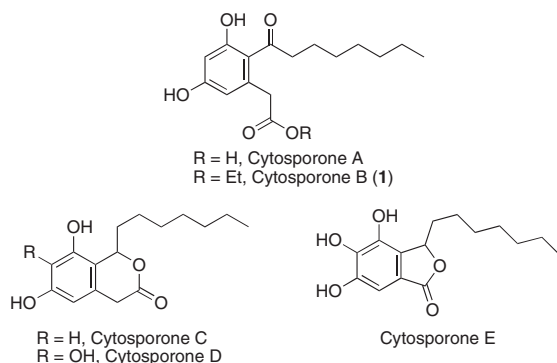
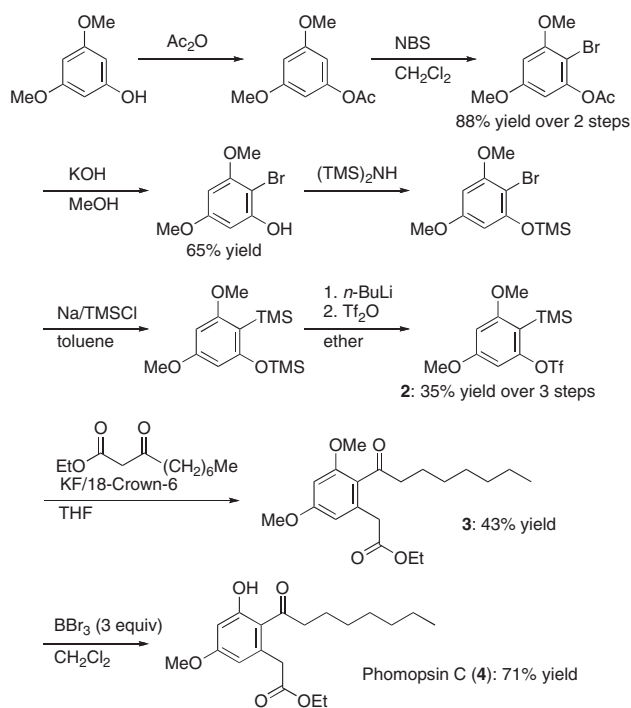


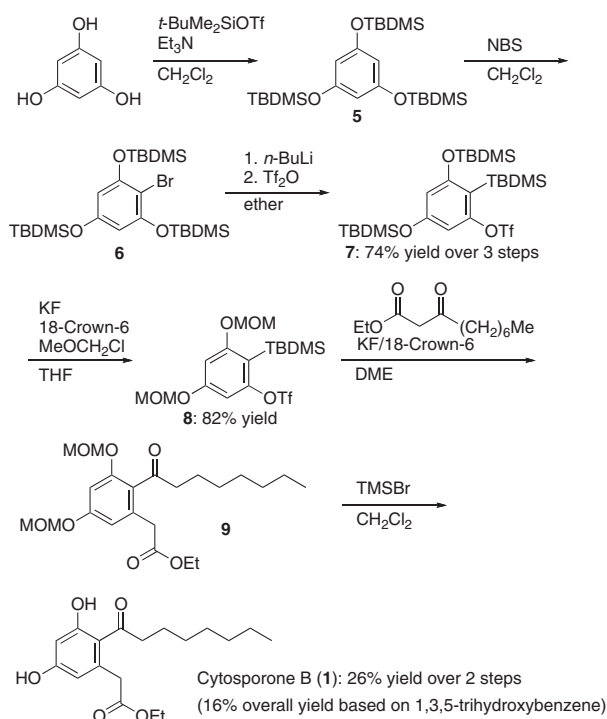
Figure 1. Cytosporones isolated from endophytic fungi.



Scheme 1. Synthesis of phomopsin C.

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 BBr₃ (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 Me₃SiCl/NaI¹⁴ and HBr/NaI¹⁵ also failed to provide **1**.

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*-BuMe₂SiOTf as outlined in Scheme 2. Monobromination of **5** followed by the reaction of the resulting product **6** with *n*-BuLi/Tf₂O 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-dimethoxybenzynes, 3,5-bis(methoxymethoxy)benzynes (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.

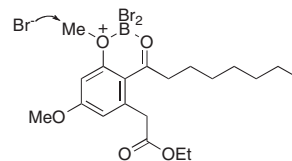
In conclusion, the aryne insertion reaction into a carbon–carbon σ -bond has been demonstrated to be potent for the total synthesis of octaketides, allowing cytosporone B to be fabricated in 6 steps from commercially available 1,3,5-trihydroxybenzene. Moreover, the first synthesis of phomopsis C has 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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- 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)benzynes 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>.