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An *ortho*-Quinodimethane Route to Lasofoxifene and U23469

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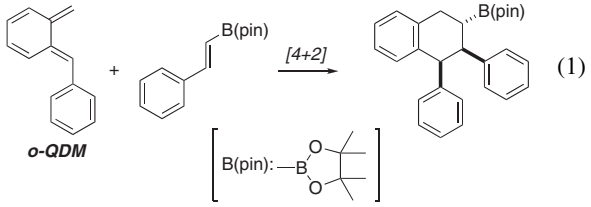
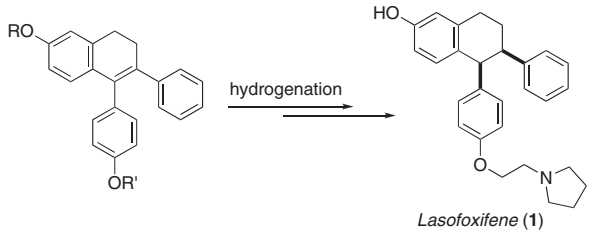
Lasofoxifene, a third-generation selective estrogen receptor modulator, could be synthesized via regio- and stereoselective [4 + 2] cycloaddition between an *ortho*-quinodimethane and a borylalkene. This protocol was also applicable to the synthesis of antiestrogen U23469.

Much attention has been riveted on synthetic utilization of *o*-quinodimethanes (*o*-QDMs) as an efficient four-carbon unit in constructing 6-membered carbocyclic frameworks via [4 + 2] cycloaddition (Diels–Alder reaction).[1] Although the cycloaddition enables diverse tetralin derivatives of synthetic significance such as steroids,[2] alkaloids,[3] polyacenes,[4] and fullerenes[5] to be synthesized in a straightforward manner, potential versatility of the reaction remains to be exploited.[6] In this regard, we have recently disclosed that the cycloaddition between *o*-QDMs and borylalkenes offered facile access to boryltetralins of structural diversity, which were further convertible into variously substituted borylnaphthalenes via oxidative aromatization.[7] Moreover, the cycloaddition of α-arylated *o*-QDMs with (*E*)-β-borylstyrene was found to proceed with a high level of regio- and stereoselectivities, affording high yields of *cis*-1,2-diaryltetralins in a straightforward manner (eq 1).



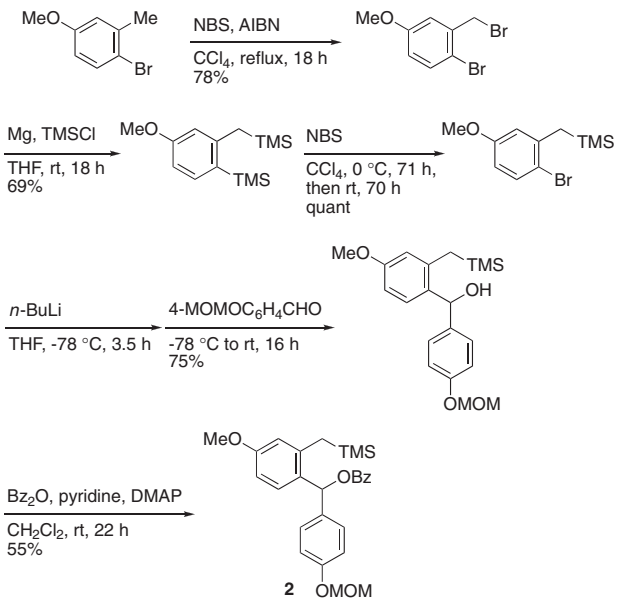
(1)

Lasofoxifene (**1**) is a potent third-generation selective estrogen receptor modulator (SERM), which reduces risks of fractures, ER-positive breast cancer and coronary heart disease in postmenopausal women with osteoporosis.[8] As shown in Scheme 1, the structural feature of **1** is the presence of *cis*-1,2-diaryltetralin motif, and all of the reported syntheses of **1** thus far utilize hydrogenation of 1,2-dihydronaphthalene derivatives for making the motif, to the best of our knowledge.[9] Herein we report on a unique route to **1**, whose core skeleton is assembled regio- and stereoselectively through cycloaddition using an *o*-QDM. Furthermore, a *cis*-1,2-diaryltetralin with antiestrogenic effect, U23469,[10] can also be synthesized depending upon this protocol.

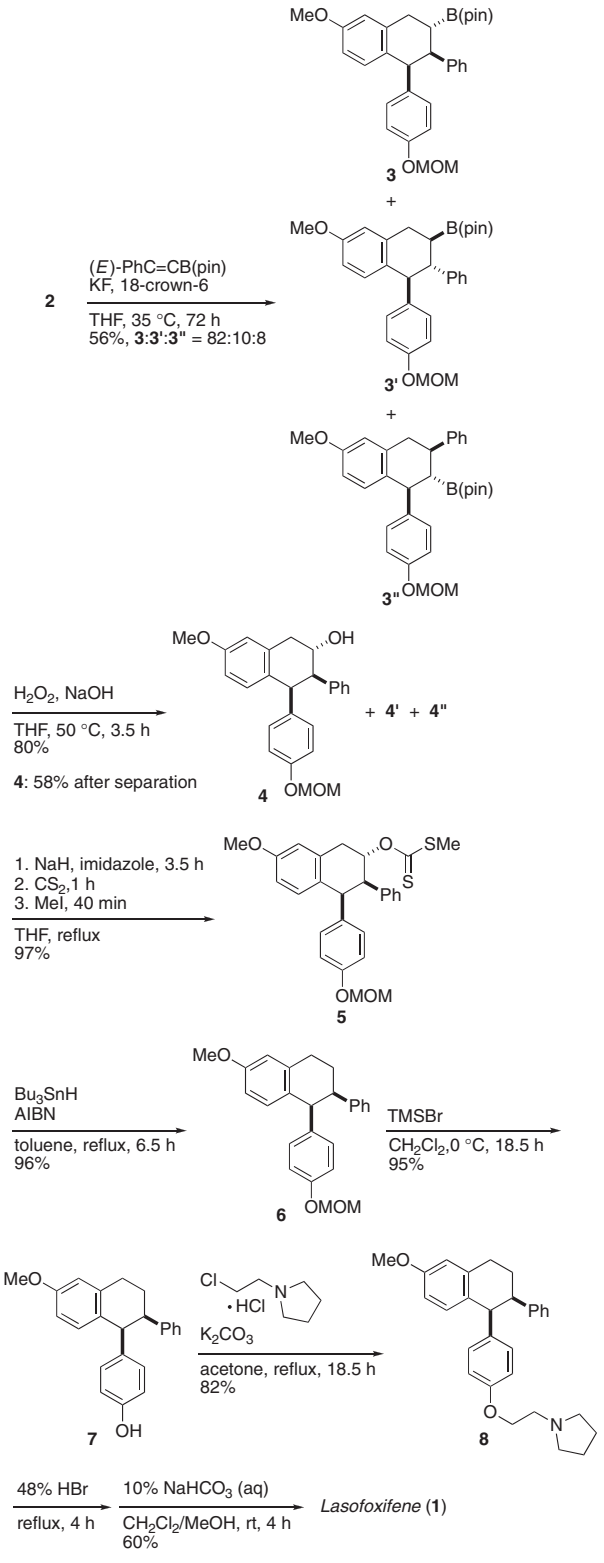


Scheme 1. Synthesis of lasofoxifene via hydrogenation of a 1,2-dihydronaphthalene derivative.

First we prepared the required *o*-QDM precursor **2** possessing a benzylsilyl and a benzhydryl benzoate moieties from commercially available 2-bromo-5-methoxytoluene in five steps as described in Scheme 2.[11,12] Subsequent cycloaddition of the *o*-QDM, generated in situ from **2** and a fluoride ion (KF/18-crown-6),[13] with (*E*)-β-borylstyrene in THF at 35 °C resulted in the preferential formation of boryltetralin **3** (**3**:**3′**:**3″** = 82:10:8, 56% yield), where two aryl groups are adjoining in *cis* configuration (Scheme 3). The observed regio- and stereoselectivities can be rationally explained by the following two factors: *exo* approach of the bulky B(pin) moiety which orients the α-aryl group of the *o*-QDM to a remote position, and a secondary orbital interaction between C-2 of the *o*-QDM and the phenyl group of (*E*)-β-borylstyrene. Oxidation of the C–B bond of boryltetralins provided alcohols **4**–**4″** in 80% yield, from which the requisite isomer was isolated by reversed-phase HPLC. The obtained alcohol **4** was then transformed into xanthate **5** by reaction with carbon disulfide and methyl iodide. Deoxygenation of **5** via the Barton–McCombie reaction[14] using tributyltin hydride gave a 96% yield of **6**,[15] whose methoxymethyl moiety was deprotected by treatment with TMSBr. The hydroxy group of **7** was alkylated with 1-(2-chloroethyl)pyrro-



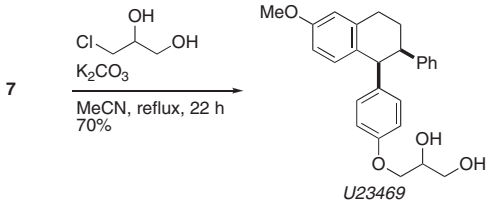
Scheme 2. Synthesis of *o*-QDM precursor **2**.



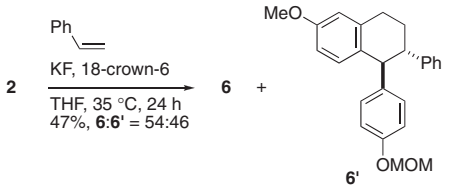
Scheme 3. Synthesis of lasofoxifene.

lidine to afford **8**, which was finally converted to lasofoxifene (**1**) by treatment with HBr.

The synthetic significance of the present protocol has also been demonstrated by application to the synthesis of a *cis*-1,2-diaryltetralin with biological activity. Thus, alkylation of **7** by use of 3-chloro-1,2-propanediol gave antiestrogen, U23469 in 70% yield (Scheme 4).



Scheme 4. Synthesis of U23469.



Scheme 5. [4 + 2] Cycloaddition using styrene.

Although [4 + 2] cycloaddition between the *o*-QDM and styrene was a promising shortcut to **1**, this reaction gave a mixture of **6** and its stereoisomer **6′** in almost the same ratio, demonstrating the indispensable role of the boryl group in achieving high stereoselectivity (Scheme 5).

In conclusion, the [4 + 2] cycloaddition between an *o*-QDM and a borylalkene has been demonstrated to be a potent protocol for regio- and stereoselective construction of a *cis*-1,2-diaryltetralin motif, allowing lasofoxifene and U23469 to be synthesized from 2-bromotoluene, arylaldehyde, and borylalkene.[16] The high availability of these components makes the present method advantageous in diversifying lasofoxifene framework. Efforts are currently directed toward synthesis of pharmacologically significant molecules of other types having *cis*-1,2-diaryltetralin motifs by use of the present protocol.

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15 Direct conversion of **3** into **6** under various protodeborylation conditions was unsuccessful.

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

