Total synthesis of strobilurin B using a hetero-*bis*-metallated pentadiene linchpin†

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An efficient, six-step stereocontrolled total synthesis of the antifungal agent strobilurin B is reported and was based on a convergent bi-directional coupling featuring a hetero-*bis*-1,4-metallated pentadiene system as the linchpin.

The strobilurins are a widely occurring family of natural products produced by higher fungi that possess potent and effective antifungal activity. These compounds possess a β-methoxyacrylate group as a common and critical structural element, and there has been extensive industrial development of these compounds and their analogs for use as agricultural chemicals.[1] This family of compounds inhibits the mitochondrial respiratory chain by binding to the ubihydroquinone oxidation center in the bc_1 complex, arresting ATP formation.[2] In producing organisms such as *Srobilurus tenacellus*, specific mutations in the cytochrome b protein reduce the binding affinity of the strobilurins in the host organism.[3]

Syntheses of members of this family of natural products have been reported,[4] including a 1989 account by Sutter[5] of the total synthesis of strobilurin B. This synthesis was accomplished in a non-stereocontrolled manner in 11 linear steps, wherein the final product was isolated as a 1 : 1 mixture of olefin stereoisomers in 52% combined yield.

Our goal in undertaking this work was to employ modern palladium-catalyzed coupling protocols for the convergent and efficient syntheses of these natural products. This goal was achieved and the total synthesis of strobilurin B (**1**) was accomplished in 6 steps. The synthetic plan we implemented (Fig. 1) was based on a bi-directional coupling of novel hetero-*bis*-metallated pentadiene **2** with known iodoacrylate **3**,[6,7] *via* a Stille coupling,[8] and with aryl iodide **4**, *via* a Suzuki/Miyaura coupling.[9] This linchpin strategy has proven useful in other natural product contexts.[10] The synthesis as proposed is convergent and occurs with control of olefin geometry, a problem that has plagued other syntheses.[4,5] Because of the modular nature of the synthetic plan, introduction of structural diversity becomes straightforward by simple variation in the three coupling partners.

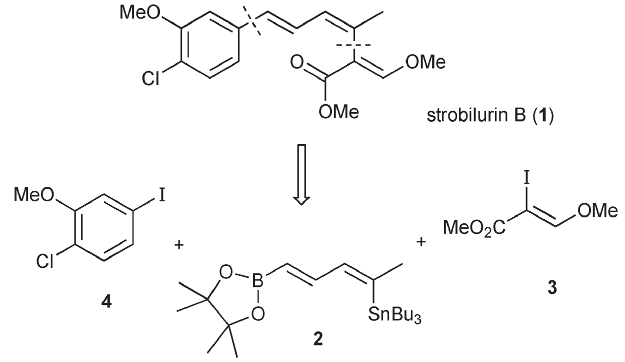
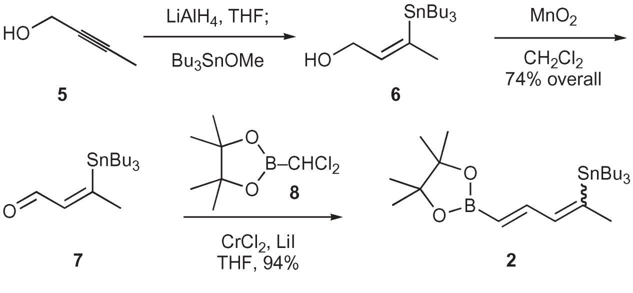


Fig. 1 Retrosynthetic analysis of strobilurin B, illustrating use of the hetero-*bis*-metallated pentadiene reagent **2**.

Our initial attempt towards the synthesis of hetero-*bis*-metallated pentadiene **2** started with hydroalumination/transmetallation of 2-butyn-1-ol (**5**), which afforded vinyl stannane **6** as a single isomer (Scheme 1). Oxidation to the corresponding aldehyde using MnO_2 afforded known enal **7** (74% for two steps).[11] Takai olefination[12] of aldehyde **7** with dichloromethylborinate **8**[13] proceeded smoothly, but afforded pentadiene **2** (94%) as a 1 : 1 mixture of stereoisomers about the vinylstannane olefin, presumably as a result of the intermediacy of delocalized radical or cationic species.[14]

An alternative route to pentadiene **2** relied on hydroboration to introduce the *trans*-vinylborinate (Scheme 2). Monolithiation of 1,4-*bis*-trimethylsilyl-1,3-butadiyne (**9**, THF, 25 °C) and alkylation of the lithium acetylide with iodomethane (THF, −80 °C) afforded pentadiyne **10** (56%). Regio- and stereoselective stannylcupration[15] afforded the known vinylstannane **11**[16] (quantitative); removal of the trimethylsilyl group (KF, MeOH, 25 °C) afforded enyne **12** (quantitative). Hydroboration of the triple bond of **12** using the reagent system developed by Snieckus and co-workers[17] cleanly introduced the *trans*-vinylboronate and afforded **2** (75%).

Stille coupling of vinylstannane **2** and vinyl iodide **3** occurred extremely slowly under a variety of conditions,[18] and the coupled



Scheme 1

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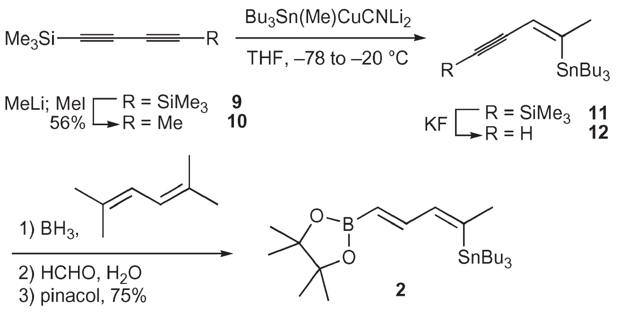
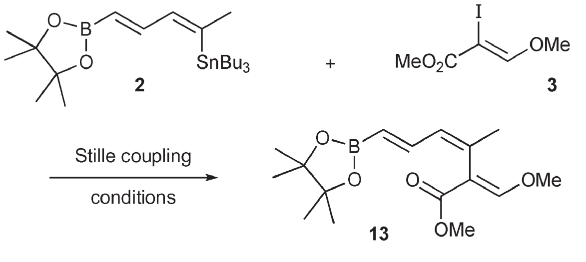


Scheme 2

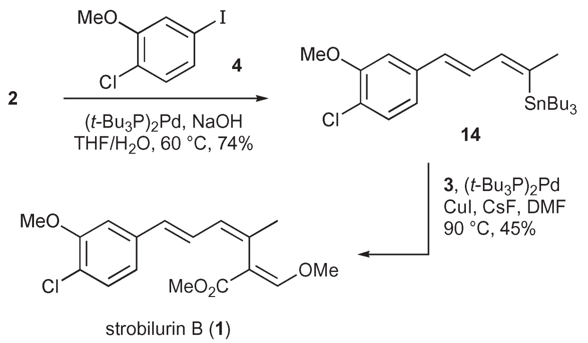
product **13** could be isolated in poor yield (Scheme 3). Under more forcing reaction conditions, diene **2** and the coupling product **13** were not stable, and no increases in yield were observed. Apparently, the combination of steric crowding of the vinylic stannane **2**, the unreactivity of the vinylic iodide **3**, and the instability of the boronate of product **13** combined to effectively shut-down this normally facile reaction manifold.

In developmental work on hetero-*bis*-metallated diene systems,[10] we successfully demonstrated that Stille coupling occurred cleanly and in high yield in the presence of a vinyl boronate. Furthermore, we showed that simple addition of fluoride to such Stille reaction mixtures permitted a subsequent Suzuki–Miyaura coupling to be performed in a sequential and one-pot fashion. We assumed that the opposite ordering of coupling reactions—Suzuki–Miyaura followed by Stille—would not be possible because Stille coupling would occur competitively with the desired Suzuki–Miyaura reaction. However, this assumption was never tested.

In the present case, the attenuated reactivity of the vinyl stannane of pentadienyl system **2** permitted chemoselective Suzuki–Miyaura coupling of the terminal vinyl boronate in this system (Scheme 4). Under aqueous coupling conditions using $(t\text{-Bu})_3\text{P}$ as the ligand[19] on palladium and aryl iodide **4**[20] as the coupling partner, chemoselective arylation of the vinyl boronate terminus of pentadiene **2** occurred,[21] and **14** could be isolated from the reaction as the only coupling product observed (74%). Subsequent Stille coupling of the vinyl stannane of **14** with vinyl iodide **3** now occurred using $t\text{-Bu}_3\text{P}$ as the palladium ligand and in the presence of CuI, and strobilurin B (**1**) was produced as a single stereoisomer in 45% yield. Further optimization of this coupling reaction was unsuccessful. Proton and carbon NMR spectral data for synthetic strobilurin B were identical with published data.[22]



Scheme 3



Scheme 4

The total synthesis of strobilurin B was short and efficient (longest linear sequence, six steps from butadiyne **9**; eight total steps from commercially available methyl β-methoxyacrylate, 4-chloro-3-methoxyaniline, and 1,4-*bis*-trimethylsilyl-1,3-butadiyne). Essentially complete control of geometry about the three stereogenic double bonds of **1** was obtained.

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20 Iodide **4** was prepared in 84% yield from commercially available 4-chloro-3-methoxyaniline by diazotization ($NaNO_2$, $HCl_{(aq)}$, 0 °C) and reaction of the aryl diazonium intermediate with KI.

21 Other reaction conditions were unsuccessful in providing useful yields of coupled product **14**: $(Ph_3P)_4Pd$, K_3PO_4, dioxane; Pd_2dba_3, *t*-Bu_3P, KF, THF; $(Ph_3P)_4Pd$, K_2CO_3, toluene/EtOH.

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