Efficient Total Synthesis of Khafrefungin: Convergent Approach Using Suzuki Coupling under Thallium-free Conditions Toward Multigram-scale Synthesis

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Abstract: An efficient and practical synthetic route to khafrefungin, an antifungal agent, has been developed based on successive coupling of three components, **3**, **4**, and then **2**. A key step of the synthesis is the Suzuki coupling of **2** and **10**, in which the use of toxic thallium ethoxide has been avoided, and the coupling adduct (**11**) was obtained in multigram-scale quantities.

Key words: khafrefungin, total synthesis, antifungal agents, Suzuki coupling, multigram-scale synthesis

Khafrefungin (**1**) is a novel antifungal agent isolated from the fermentation culture MF6020 by a Merck group in 1997 (Figure).[1] It has been shown to inhibit IPC (inositol phosphorylceramide) synthase, which catalyzes the fungal specific step, in *Saccharomyces cerevisiae* and pathogenic fungi. Unlike other inhibitors that inhibit the corresponding enzyme in fungi and mammals to the same extent, khafrefungin does not impair sphingolipid synthesis of mammals.[2] Although the Merck group revealed the plane structure of khafrefungin, the stereochemistry of khafrefungin had been unknown until we disclosed the relative and absolute configuration of khafrefungin.

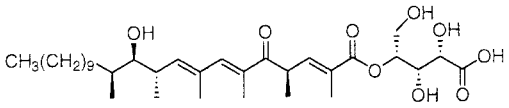
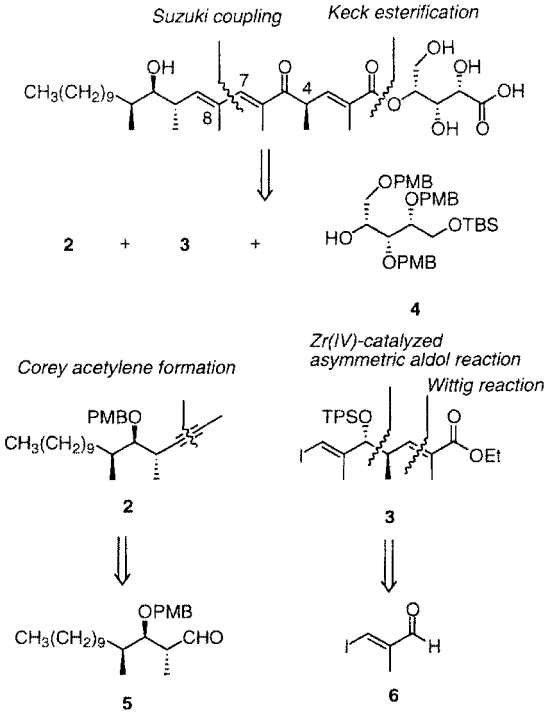


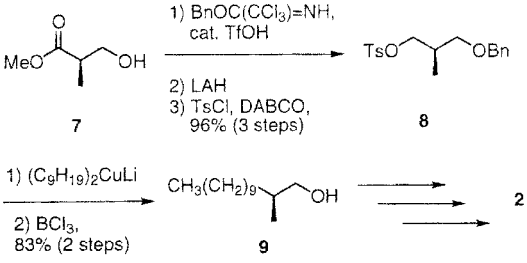
Figure Khafrefungin (**1**)

We have already completed the first total synthesis and developed a convergent route to khafrefungin.[3] In order to synthesize various derivatives of khafrefungin, more efficient strategies, which tolerates multigram-scale preparation is necessary. We now report here an efficient synthesis of khafrefungin under thallium-free conditions.

Our convergent synthetic strategy of khafrefungin is shown in Scheme 1. Khafrefungin is divided into three fragments; alkyne **2**, alkenyliodide **3**, and protected alcohol **4** (aldonic acid part). In the previous report, **2** was connected with **3** using Suzuki coupling, followed by esterification with **4** to convert to khafrefungin (**1**). However, synthesis of fragment **2** needs the most multiple transformations among the three fragments. It is more efficient that **3** is connected with **4** by esterification first, followed by Suzuki coupling with **2**.[4] Another drawback of the previous convergent synthesis is the use of a thallium reagent as a base in the Suzuki coupling.



Scheme 1 Retrosynthetic analysis for the synthesis of **1**.



Scheme 2 Synthesis of chiral alcohol **9**.

First, we developed an alternative synthetic pathway to **9**, which is a key intermediate for the preparation of **2** (Scheme 2). Benzylation of commercially available methyl (*R*)-(–)-3-hydroxy-2-methylpropionate (**7**) followed by

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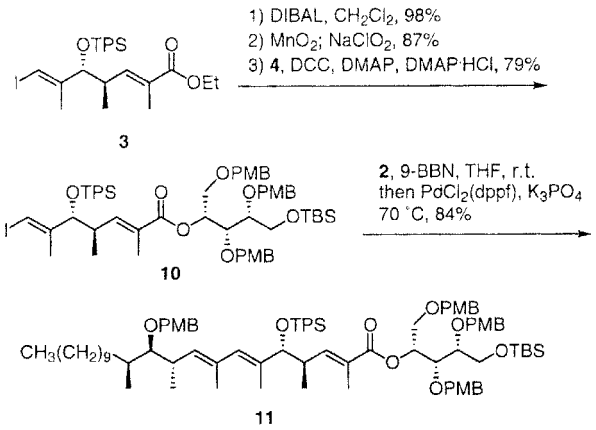
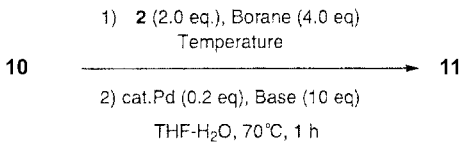
reduction using lithium aluminium hydride and tosylation gave **8** (96%, 3 steps). Benzyl ether **8** was alkylated and the benzyl group was deprotected to give **9**. Chiral alcohol **9** was converted to alkyne **2** according to the reported procedure.[3] The synthesis has been achieved in multigram-scale quantities, and we have also completed the syntheses of the other two units (**3** and **4**) in multigram-scale quantities.[5] The coupling reaction of **3** with **4** was then investigated (Scheme 3). Ester **3** was converted to the carboxylic acid, which was treated with alcohol **4** under Keck's esterification conditions[6] to afford the coupling adduct (**10**). We next examined the Suzuki coupling reaction of **10** with alkyne **2** (Table). In the previous synthesis, catecholborane and thallium ethoxide[7] were used as reagents for the Suzuki coupling reaction. Thallium ethoxide is not suitable for large-scale synthesis and analogous derivatization due to its high toxicity. We tested several conditions, and found that one-pot procedure with 9-BBN, $PdCl_2$(dppf), and K_3PO_4 gave **11** in better yield (76%, Table, entry 4). In a larger-scale reaction, the yield was improved to 84% (Scheme 3).[8] After purification by column chromatography (silica gel), no regioisomer of **11** was observed by NMR analysis. It is noted that multigram-preparation of **11** has been successfully achieved based on the novel synthetic strategy.



Scheme 3 Synthesis of **11**.

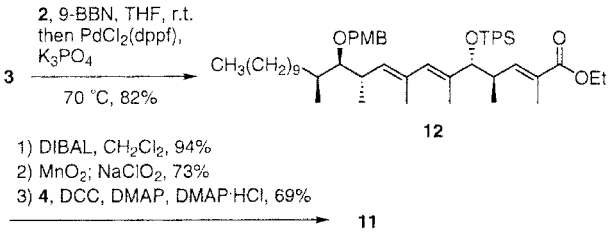
Table Suzuki Coupling Reaction



Entry	Borane	Temp.	Pd	Base	Yield (%)
1	catecholborane	50 °C	$Pd(PPh_3)_4$	TlOEt	42 (33)[a]
2	catecholborane	50 °C	$Pd(PPh_3)_4$	Na_2CO_3	27 (53)[a]
3	catecholborane	r.t.	$PdCl_2$(dppf)	K_3PO_4	50
4	9-BBN	r.t.	$PdCl_2$(dppf)	K_3PO_4	76

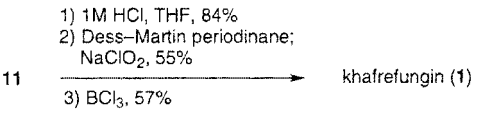
[a] Recovered **10** (%).

In addition, it was revealed that the Suzuki coupling reaction of alkenyliodide **3** with alkyne **2** also proceeded smoothly under thallium-free conditions. As highlighted in Scheme 4, the Suzuki coupling reaction of **3** with **2** successfully provided the desired product **12**. After reduction with DIBAL, the resulting alcohol was oxidized to the corresponding aldehyde, which was treated with sodium chlorite[9] to afford the carboxylic acid in 73% yield for two steps. The Keck esterification reaction of the carboxylic acid with alcohol **4** furnished ester **11** in 69%.



Scheme 4 Synthesis of **11**.

The completion of the synthesis of khafrefungin from **11** is shown in Scheme 5.[3] Deprotection of the two silyl groups with 1 M aqueous hydrochloric acid in THF gave the corresponding diol in 84% yield. Oxidation of the diol was successfully performed using Dess–Martin periodinane[10] to afford the ketoaldehyde, which was treated with sodium chlorite to furnish the ketocarboxylic acid. Finally, the four PMB groups were removed with BCl_3 to afford khafrefungin in 57% yield.



Scheme 5 Synthesis of khafrefungin (**1**).

In conclusion, we have developed efficient and practical synthetic routes to khafrefungin and its analogues. The synthesis is based on successive coupling reactions of **3** and **4**, and then **2**. Multigram-scale synthesis of the three fragments has been accomplished. A key step in this synthesis is the Suzuki coupling of **2** and **10**. The use of toxic thallium ethoxide has been avoided to attain multigram-scale preparation of the coupling product (**11**). Our continued effort toward exploration of structure activity relationships of khafrefungin will be reported in due course.

Acknowledgement

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(5) Multigram-scale synthesis of alkyne **2**, alkenyliodide **3**, and alcohol **4**: Alkyne **2** (5.2 g) was synthesized from methyl (*R*)-(–)-3-hydroxy-2-methylpropionate (10 mL) according to the literature (14 steps).[3b] In the present synthesis, chiral alcohol **9** was synthesized by the procedure shown in Scheme 2. Alkenyliodide **3** (18.2 g) was prepared from diethyl methylmalonate (40 mL) according to the literature (9 steps).[3b] Alcohol **4** (5.5 g) was synthesized from D-arabinose (4.7 g) according to the literature (5 steps).[3a]

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(8) Suzuki coupling reaction of alkyne **2** with alkenyliodide **10**: To a stirred solution of alkyne **2** (1.09 g, 2.82 mmol) in THF (18 mL) was added 9-BBN (6.00 mmol, 0.5 M solution in THF) at 0 °C. The reaction mixture was stirred for 12 h at room temperature. Alkenyliodide **10** (2.76 g, 2.34 mmol) in THF (10 mL), H_2O (10 mL), K_3PO_4 (2.50 g, 11.8 mmol), and $PdCl_2$(dppf) (0.38 g, 0.47 mmol) were added subsequently, and the mixture was stirred for 30 min at 70 °C. After the mixture was cooled to room temperature, saturated aqueous $NaHCO_3$ was added and the organic layer was extracted with EtOAc. The organic layer was washed with brine, dried, and concentrated. Purification by silica gel chromatography (EtOAc–hexane, 1:6) gave the coupled product **11** (2.93 g, 84%) as a colorless oil.

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