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Enantioselective Synthesis of (−)-Basiliskamide A

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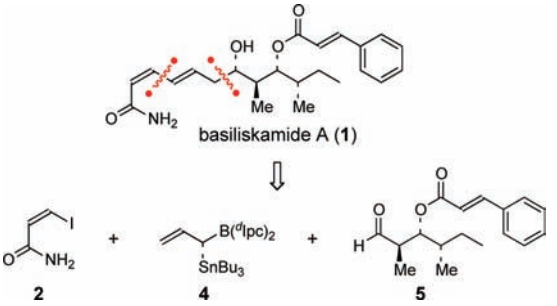
ABSTRACT



Basiliskamide A is an antifungal polyketide natural product isolated by Andersen and co-workers from a *Bacillus laterosporus* isolate, PNG-276. A nine-step enantioselective synthesis of (−)-basiliskamide A is reported, starting from commercially available β-hydroxy ester 7. The synthesis features a highly diastereoselective mismatched double asymmetric δ-stannylallylboration reaction of aldehyde 5 with the bifunctional allylborane reagent 4.

Basiliskamide A (**1**) is a polyketide natural product isolated by Andersen and co-workers from a *Bacillus laterosporus* isolate, PNG-276.[1] The structure of **1** was established by extensive NMR experiments and by comparison of its spectroscopic properties to that for the known one-carbon homologation analogue YM-47522 (Figure 1). The relative and absolute configuration assignments for basiliskamide A were subsequently verified by chemical synthesis.[2]

Basiliskamide A (**1**) displays biological activity against *C. albicans* and *A. fumigatus* with MIC values of 1.0 and 2.5 μg/mL, respectively. Intriguingly, in spite of the close structural similarities between basiliskamide A (**1**) and YM-47522 (Figure 1), the biological activity profile of YM-47522 is quite different, with MIC values against *C. albicans* and *A. fumigatus* of 25 and >50 μg/mL, respectively. Furthermore, studies with seven fresh clinical isolates of *C. albicans* indicated that basiliskamide A has activity comparable to the oxo polyene macrolide antibiotic amphotericin B, with both compounds having identical MICs (0.5 μg/mL) against each of the seven clinical isolates. More importantly, basiliskamide A displayed only minimal cytotoxicity against human diploid fibroblast cells at a concentration of 100 μg/mL, while amphotericin B destroyed all the cells at the same concentration.[1]

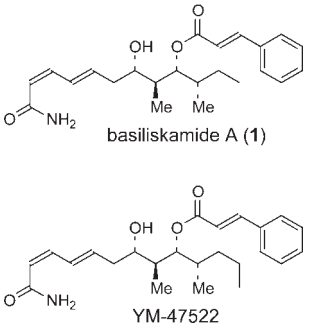


Figure 1. Structures of basiliskamide A and YM-47522.

This interesting biological profile has inspired the development of several total syntheses of basiliskamide A (**1**).[2] The shortest of the three current syntheses requires 14

(1) Barsby, T.; Kelly, M. T.; Andersen, R. J. *J. Nat. Prod.* **2002**, *65*, 1447.

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linear steps (16 steps total) from commercially available starting materials. Several steps in each synthesis are devoted to protecting group manipulations or to reduction or oxidation reactions needed to adjust the oxidation state of increasingly advanced intermediates. Each of the reported syntheses of **1** also utilized a Stille coupling of vinyl iodide intermediates, which were prepared via Takai olefination of appropriate aldehyde precursors.[2,3a,3b] One drawback associated with Takai olefination is that a mixture of *E*/*Z* olefin isomers is often obtained, with the ratio of the two isomers depending on structural features of the aldehyde substrate.[2,3c−3e] With the goals to develop an efficient synthesis of **1**, to demonstrate the synthetic utility of the highly diastereoselective mismatched double asymmetric δ-stannylallylboration reaction of reagent **4**,[4−6] and

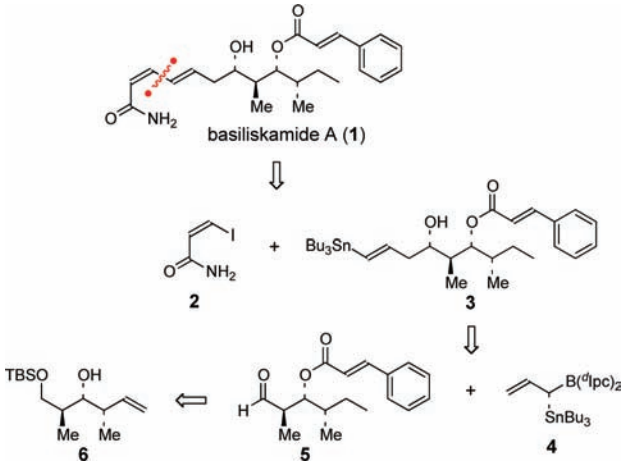


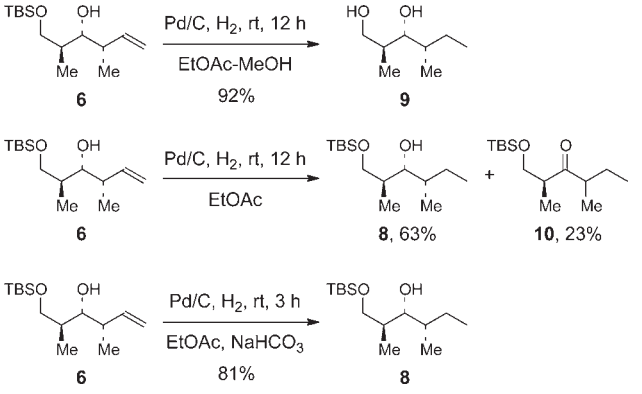
Figure 2. Retrosynthetic analysis of basiliskamide A (**1**).

ultimately to use this synthesis to gain further insight into the structure−activity relationships of these natural products, we have developed and report herein a nine-step, enantio- and highly diastereoselective synthesis of (−)-basiliskamide A (**1**).

As summarized in Figure 2, we envisioned that basiliskamide A (**1**) could be assembled via a Stille coupling[7] between the known vinyl iodide **2**[8] and vinylstannane **3**. The δ-stannyl-homoallylic alcohol moiety embedded in vinylstannane **3** provides a perfect platform to explore the mismatched double asymmetric δ-stannylallylboration reaction of aldehyde **5** with our recently disclosed allylborane reagent **4**.[4] Aldehyde **5** would be obtained from the known homoallylic alcohol **6**,[9] which in turn would be prepared from the commercially available β-hydroxy ester (*S*)-**7** according to published procedures.

Homoallylic alcohol **6** was synthesized in three steps according to known procedures, starting from β-hydroxy ester (*S*)-**7** (Scheme 2).[9] Hydrogenation of the olefin unit in **6** under standard conditions (Pd/C, H_2, MeOH-EtOAc) provided, unexpectedly, the deprotected diol **9** in 92% yield (Scheme 1).[10] When EtOAc was used as the reaction solvent, alcohol **8** with the primary TBS ether intact was obtained in 63% yield; however, a significant amount of the ketone byproduct **10** (23%) was also obtained. After a brief screening of reaction conditions, the formation of ketone **10** was minimized by adding $NaHCO_3$ to the hydrogenation reaction and by shortening the reaction time. Under optimized conditions, alcohol **8** was obtained in 81% yield from alcohol **6**.

Scheme 1. Optimization of Hydrogenation of Alcohol **6**



Acylation of alcohol **8** with (*E*)-cinnamoyl chloride (**11**) provided ester **12** in 63% yield (92% based on recovered starting material, Scheme 2). Deprotection of the primary TBS ether of ester **12** proved to be challenging (see Table 1). When this deprotection was attempted using TsOH in a THF−MeOH solvent mixture, a 1:1 mixture of alcohol **13** and the acyl transfer isomer **14** were obtained (Table 1, entry 1). Treatment of **12** with TBAF in THF again provided a 1:1 mixture of alcohols **13** and **14**

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(9) (a) Roush, W. R.; Palkowitz, A. D.; Palmer, M. J. *J. Org. Chem.* **1987**, *52*, 316. (b) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.

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Scheme 2. Total Synthesis of Basiliskamide A (**1**)

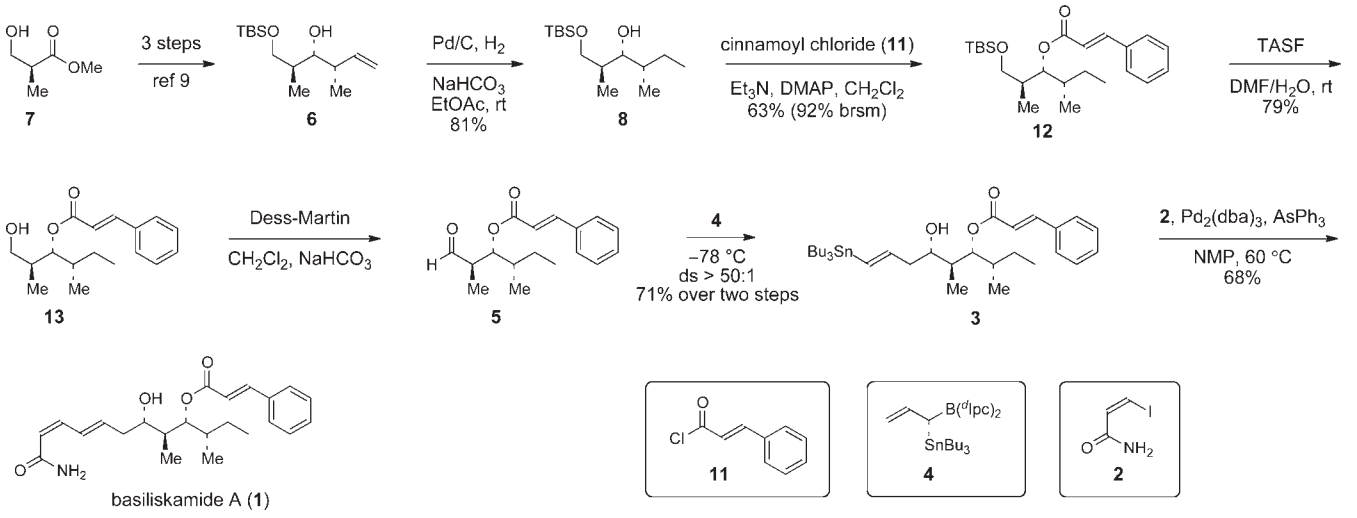
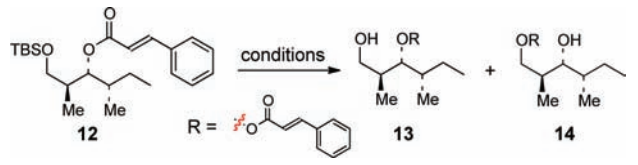


Table 1. Optimization of the Deprotection of TBS Ether **12**



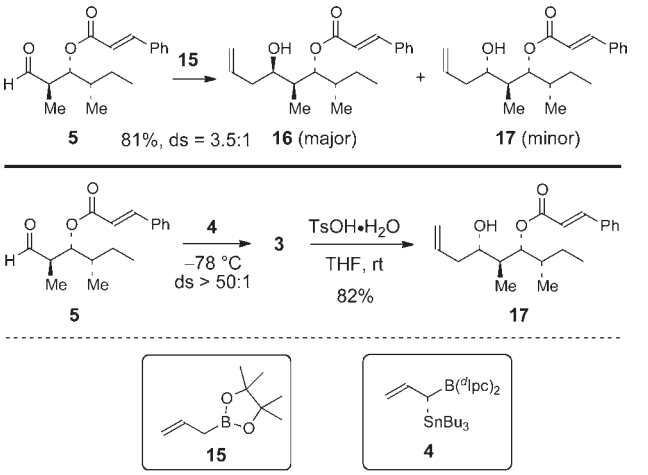
entry	conditions	**13**:**14**[a]	yield of **13**[b] (%)
1	TsOH, THF/MeOH, rt, 8 h	1:1	43
2	TBAF, THF, rt, 8 h	1:1	47
3	TBAF/HOAc, THF, rt, 8 h	1:1	41
4	TASF, DMF/H_2O, rt, 8 h	9:1	79

[a] Based on ^{1}H NMR analysis of the crude reaction mixture. [b] Yield of isolated desired alcohol **13**.

(Table 1, entry 2). Similar results were also obtained when TBAF buffered with HOAc was used (Table 1, entry 3). However, when **12** was treated with TASF in a DMF–H_2O mixture,[11] a 9:1 mixture of **13** and **14** was generated, from which alcohol **13** was obtained in 79% yield after chromatographic purification (Table 1, entry 4).

Oxidation of primary alcohol **13** with the Dess–Martin periodinane reagent[12] provided aldehyde **5**, which was used directly in the subsequent reaction. The intrinsic diasteofacial selectivity of **5** was accessed by subjecting **5** to an allylboration reaction with the achiral pinacol allylboronate **15** (Scheme 3). This reaction provided a 3.5:1 mixture of homoallylic alcohol **16** and **17**, favoring the expected Felkin adduct **16**. On the other hand, the mismatched double asymmetric δ-stannylallylboration of aldehyde **5** with allylborane **4**, prepared as described previously,[4a] gave homoallylic alcohol **3** with $>50{:}1$ diastereoselectivity and in 71% overall yield from **13**. Protodestannylation of **3** under acidic conditions (TsOH·H_2O) provided alcohol **17** in 82% yield, which matched the minor product obtained from allylboration of aldehyde **5** with allylboronate **15** (Scheme 3).

Scheme 3. Allylboration Studies of Aldehyde **5**



Finally, Pd-catalyzed Stille coupling[7] of vinylstannane **3** with vinyl iodide **2**[8] provided (−)-basiliskamide A (**1**) in 68% yield. The spectroscopic data (^{1}H NMR, ^{13}C NMR, $[\alpha]_D$) of synthetic (−)-basiliskamide A were in excellent agreement with the data previously reported for the natural product.[1,2]

In conclusion, the enantioselective total synthesis of (−)-basiliskamide A was completed in nine steps (longest linear

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(12) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

sequence, 10 steps total) from commercially available starting materials. The brevity of this synthesis was facilitated by the mismatched double asymmetric δ-stannylallylboration reaction of aldehyde **5** with allylborane **4**[4a] that provided homoallylic alcohol **3** with outstanding stereochemical control (> 50:1). The vinylstannane unit in **3** was used directly in a Stille coupling reaction to complete the total synthesis of (−)-basiliskamide A. Application of this methodology to the synthesis of other related polyketide natural products will be reported in due course.

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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.