

Enantioselective Synthesis of
(–)-Basiliskamide A

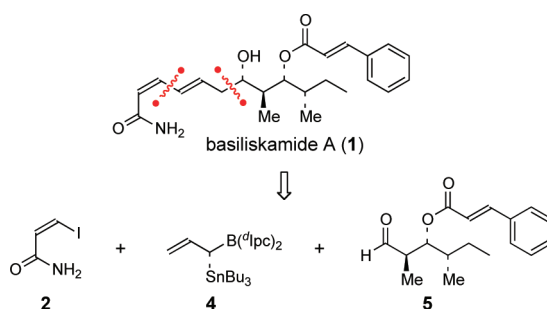
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ABSTRACT



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 $\mu\text{g/mL}$, 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 $> 50 \mu\text{g/mL}$, respectively. Furthermore, studies with seven fresh clinical isolates of *C. albicans* indicated that basiliskamide A has activity comparable to the oxo polyene macrolide antibiotic

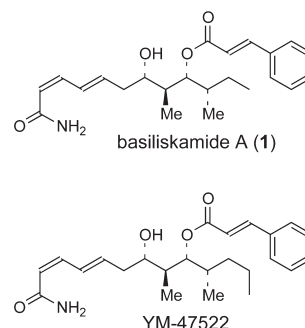


Figure 1. Structures of basiliskamide A and YM-47522.

amphotericin B, with both compounds having identical MICs (0.5 $\mu\text{g/mL}$) 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 $\mu\text{g/mL}$, while amphotericin B destroyed all the cells at the same concentration.¹

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.

(2) (a) Lipomi, D. J.; Langille, N. F.; Panek, J. S. *Org. Lett.* **2004**, 6, 3533. (b) Dias, L. C.; Gonçalves, C. C. S. *Adv. Synth. Catal.* **2008**, 350, 1017. (c) Dias, L. C.; Gonçalves, C. C. S. *J. Braz. Chem. Soc.* **2010**, 21, 2012. (d) Yadav, J. S.; Rao, P. P.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2008**, 49, 5427.

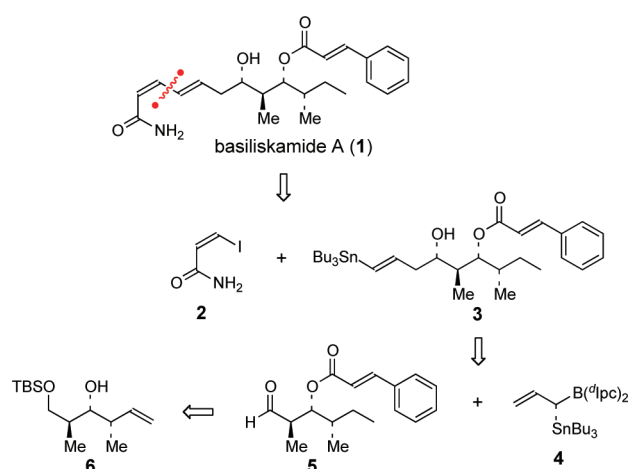


Figure 2. Retrosynthetic analysis of basiliskamide A (**1**).

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 coupling⁷

(3) (a) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408. (b) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497. For recent examples, see: (c) Palimkar, S. S.; Uenishi, J. *Org. Lett.* **2010**, *12*, 4160. (d) Li, P.; Li, J.; Arikian, F.; Ahlbrecht, W.; Dieckmann, M.; Menche, D. *J. Org. Chem.* **2010**, *75*, 2429. (e) Crimmins, M. T.; Haley, M. W.; O'Bryan, E. A. *Org. Lett.* **2011**, *13*, 4712.

(4) (a) Chen, M.; Ess, D. H.; Roush, W. R. *J. Am. Chem. Soc.* **2010**, *132*, 7881. (b) Stewart, P.; Chen, M.; Roush, W. R.; Ess, D. *Org. Lett.* **2011**, *13*, 1478.

(5) Reviews of reactions of carbonyl compounds with crotylmethyl reagents: (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 1. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, 93, 2207. (c) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; p 299. (d) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, 103, 2763. (e) Lachance, H.; Hall, D. G. *Org. React.* **2008**, 73, 1.

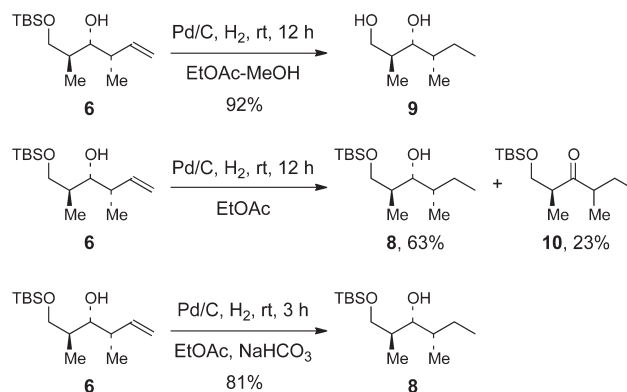
(6) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(7) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, 25, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, 50.

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, H₂, 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 NaHCO₃ 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**

(8) (a) Ma, S.; Lu, X.; Li, Z. *J. Org. Chem.* **1992**, 57, 709. (b) Buynak, J. D.; Vogeti, L.; Chen, H. *Org. Lett.* **2001**, 3, 2953.

(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.

(10) (a) Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron Lett.* **2000**, *41*, 5711. (b) Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2001**, *57*, 2109. (c) Ikawa, T.; Sajiki, H.; Hirota, K. *Tetrahedron* **2004**, *60*, 6189. (d) Espeel, P. E. R.; Piens, K.; Callewaert, N.; Van Der Eycken, J. *Synlett* **2008**, 2321.

Scheme 2. Total Synthesis of Basiliskamide A (1)

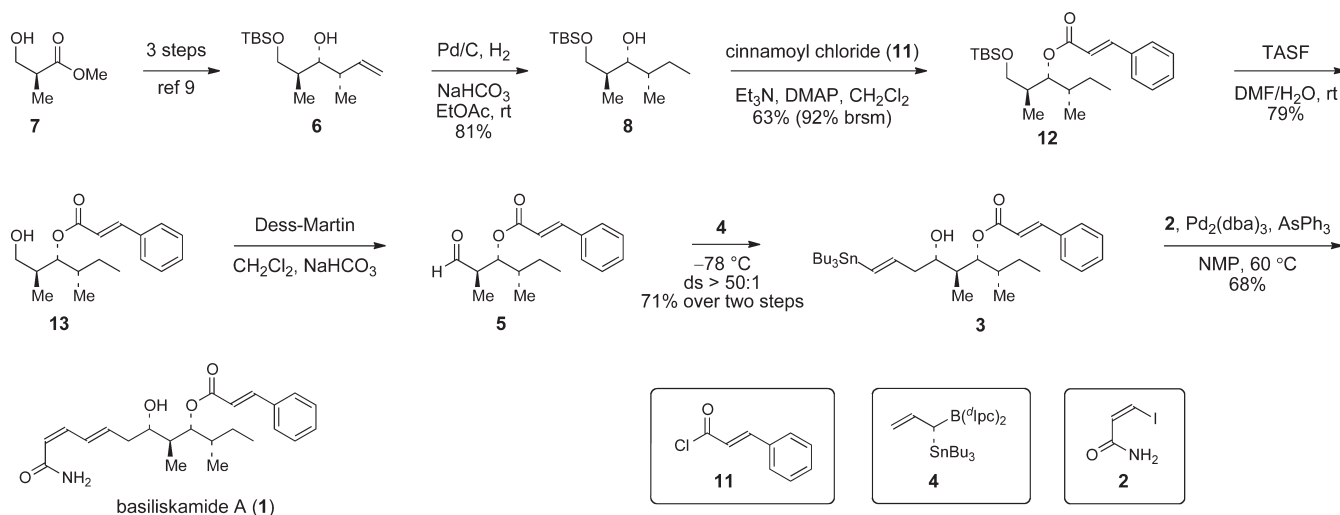
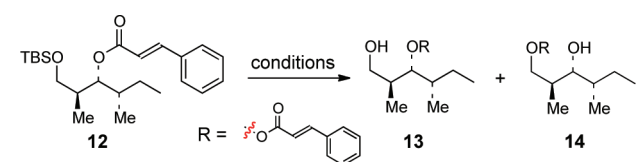


Table 1. Optimization of the Deprotection of TBS Ether **12**



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 ₂ O, rt, 8 h	9:1	79

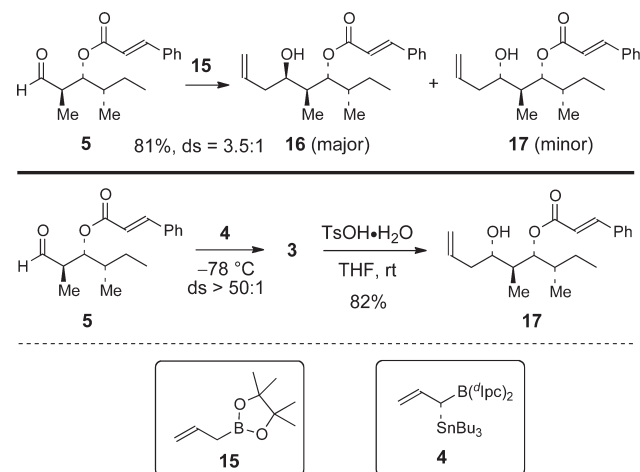
^a Based on ¹H NMR analysis of the crude reaction mixture. ^b Yield of isolated desired alcohol **13**.

(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–H₂O 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 reagent¹² provided aldehyde **5**, which was used directly in the subsequent reaction. The intrinsic diastereofacial 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**. Protodesstannylation of **3** under acidic conditions (TsOH·H₂O) 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 coupling⁷ of vinylstannane **3** with vinyl iodide **2**⁸ provided (–)-basiliskamide A (**1**) in 68% yield. The spectroscopic data (¹H NMR, ¹³C NMR, [α]_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

(11) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436.

(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.