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Total Synthesis of Basiliskamides A and B

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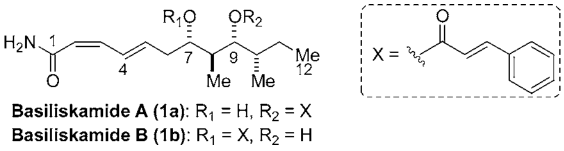
ABSTRACT



Basiliskamide A (1a): R_1 = H, R_2 = X
Basiliskamide B (1b): R_1 = X, R_2 = H

The first enantioselective synthesis of the polyketide antibiotics basiliskamides A and B, which exhibit potent in vivo activity against *Candida albicans* and *Aspergillus fumigatus*, has been achieved. Serial asymmetric crotylsilane and crotylboronate additions established the C7–C10 stereochemical tetrad. Takai iodoolefination and palladium-mediated cross-coupling were used to install the (*Z*,*E*)-vinyl acrylamide. Spectroscopic data is consistent with the assignment of the absolute configurations of the natural products as (7*S*,8*S*,9*R*,10*S*).

The search for new antifungal agents represents a major challenge for researchers concerned with combating mycotic diseases. Basiliskamides A (**1a**) and B (**1b**) were co-isolated in 2002 from the marine bacterium PNG-276 off the coast of Papua New Guinea. In initial biological screens, basiliskamide A showed activity against *Candida albicans* and *Aspergillus fumigatus* with MIC values of 1.0 and 2.5 μg/mL, respectively; basiliskamide B had slightly higher MICs against the same targets (3.1 and 5.0 μg/mL, respectively). Although basiliskamide A showed efficacy comparable to that of amphotericin B against *C. albicans*, basiliskamide A is less cytotoxic, showing minimal toxicity against human diploid fibroblast cells in vitro at 100 μg/mL. In contrast, amphotericin B showed toxic effects at only 12 μg/mL and destroyed the cells completely at 100 μg/mL.[1] Basiliskamides A and B are structurally identical in every respect except for the position of the cinnamate ester: C9 in basiliskamide A and C7 in basiliskamide B.

Structural elucidation studies by Andersen and co-workers rigorously assigned three of the four stereocenters of the basiliskamides (Figure 1). The *anti-anti* relative relationship of the C7−C9 stereochemical triad of the molecule was established through ^{1}H and ^{13}C NMR analysis of the acetonide derivative of basiliskamide A.[2] The absolute configuration at the C7-hydroxyl of the natural product was determined to be *S* by ^{1}H NMR analysis of the corresponding (*R*)- and (*S*)-MTPA esters.[3] Although impossible to assign through synthetic means, the final stereocenter, as postulated by Andersen, is 10*S*[4,5] through comparison to YM-47522 (**2**),[6] a natural product whose absolute stereochemistry was

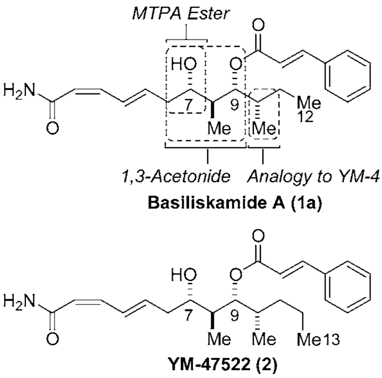


Figure 1. Andersen's stereochemical assignment of basiliskamide A (**1a**) through NMR analysis and analogy to YM-47522 (**2**).

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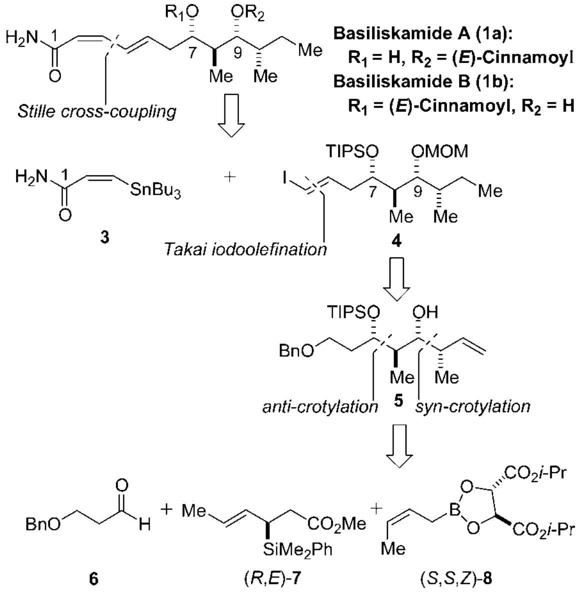
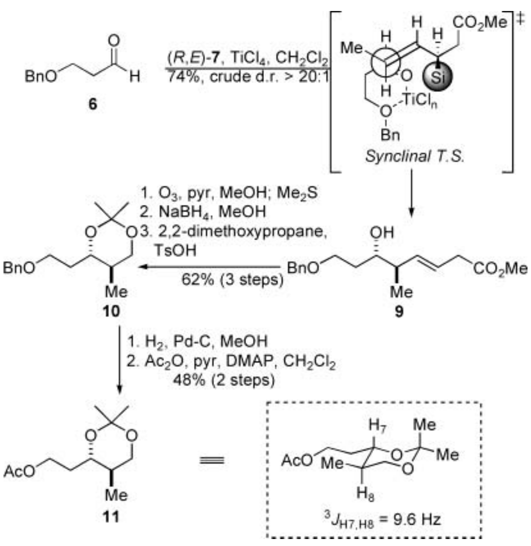
[1] For isolation, structure, and biological activity, see: Barsby, T.; Kelly, M. T.; Andersen, R. J. *J. Nat. Prod.* **2002**, *65*, 1447−1451.

10.1021/ol048574m CCC: $27.50

Scheme 1. Retrosynthetic Analysis of the Basiliskamides



Scheme 2. Synthesis and Stereochemical Assignment of Homoallylic Alcohol **9**



recently determined through chemical synthesis of its enantiomer.[7] Despite the similar structures, YM-47522 possesses a biological profile remarkably different from that of basiliskamide A, displaying greater than 20-fold loss in activity against *C. albicans* and *A. fumigatus*. Interestingly, the gross structure of YM-47522 is incorporated into the natural product nagahamide A,[8] a seven-residue depsipeptide possessing weak antibacterial activity against *E. coli* and *S. aureus*. In addition to the complete stereochemical determination of the natural products, total synthesis of basiliskamides A and B should facilitate investigation of the structural determinants of the biological activity in this class of molecules.

Our retrosynthetic analysis of the basiliskamides is outlined in Scheme 1. Initial bond disconnection at the conjugated (*E*,*Z*)-diene suggests coupling between the known stannane **3**[7] and vinyl iodide **4**, which upon selective deprotection and acylation provides access to both natural products. Homoallylic alcohol **5** can be derived in a stereoselective manner using two successive crotylmetal addition reactions. While the stereochemical configuration of **5** is readily accessible through two chiral organosilane additions, we rationalized that *anti*-selective addition of silane reagent **7**, followed by complementary *syn*-selective reaction with (*Z*)-crotylboronate reagent **8**,[9] would efficiently provide the fully elaborated C5−C12 fragment. Vital to our synthetic route is the stereochemical flexibility inherent to these protocols, as the absolute configuration of the natural product was not certain from the isolation text.

Accordingly, using the chiral organosilane methodology developed in our laboratory,[10] addition of (*R*,*E*)-**7**[11] to aldehyde **6**[12] afforded homoallylic alcohol **9** in 74% yield with high diastereoselectivity (Scheme 2). In accordance with literature precedent, a $TiCl_4$-mediated addition proceeded through an open transition state: presumably, a six-membered chelate affected a synclinal relationship between the aldehyde carbonyl and the nucleophilic alkene, heavily favoring the formation of an *anti*-homoallylic alcohol. To confirm the stereochemical outcome of this reaction, we initiated a synthetic sequence to form acetonide **10**. ^{1}H NMR analysis of this material at 400 MHz, however, proved difficult as a result of overlapping resonances of seven protons adjacent to oxygen. Exchange of the benzyl ether to the corresponding acetate yielded compound **11**, whose ^{1}H NMR was readily interpretable. The $^3J_{H7,H8}$ coupling constant of 9.6 Hz is consistent with a *trans*-diaxial relation and thus an *anti*-addition of organosilane **7**.

En route to common intermediate **4**, homoallylic alcohol **9** was protected as the TIPS ether in near-quantitative yield

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(3) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

(4) Although the *text* of ref 1 correctly indicates the stereochemistry of basiliskamides A and B, the published *structures* are inadvertently illustrated as the enantiomers of each natural product (personal communication with R. J. Andersen).

(5) During publication, a recent report of this assignment came to our attention: Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2004**, *21*, 1−49.

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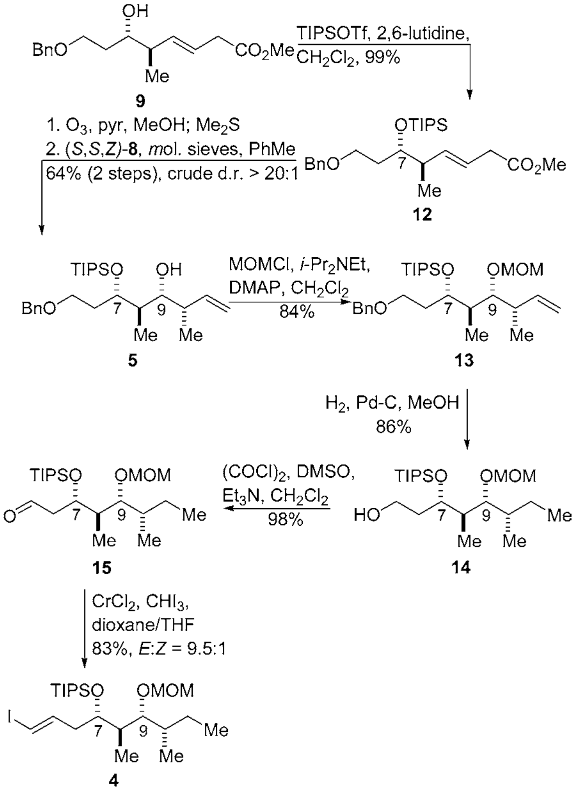
(12) Seo, M. H.; Lee, Y. Y.; Goo, Y. M. *Bull. Korean Chem. Soc.* **1996**, *17*, 314−321.

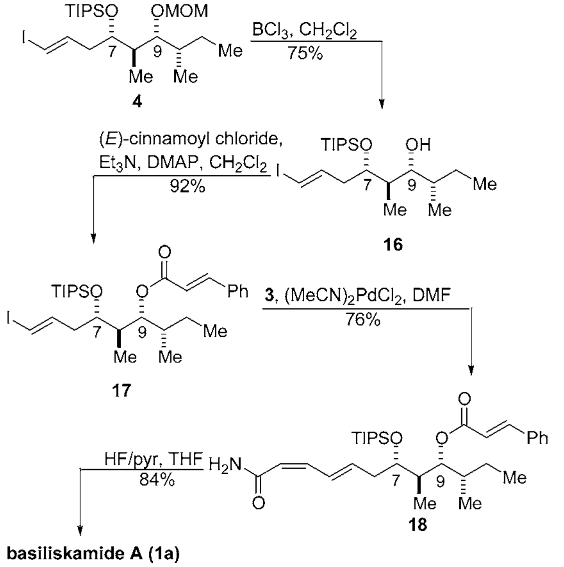
Scheme 3. Completion of Common Intermediate **4**



(Scheme 3). Ozonolysis of the alkene yielded a chiral aldehyde that was immediately subjected to crotylboration with (*S*,*S*,*Z*)-**8**, yielding adduct **5** in 64% yield over two steps in a stereochemically matched case. Transition state analysis has shown that the stereochemical course of the condensation is heavily biased toward *syn*-addition.[13] Following protection of the C9 hydroxyl as MOM ether **13**, Pd−C-catalyzed hydrogenation in MeOH reduced the alkene with simultaneous cleavage of the benzyl ether. The resulting primary alcohol **14** was subjected to Swern oxidation in 98% yield. Aldehyde **15** was homologated upon exposure to Takai's iodoolefination: $CrCl_2/CHI_3$ in 6:1 dioxane/THF provided vinyl iodide **4** with an *E*/*Z* ratio of 9.5:1 in 83% yield.[14,15] Common to both basiliskamides A and B, the orthogonally protected intermediate **4** served as the branch point in the synthesis of the two natural products.

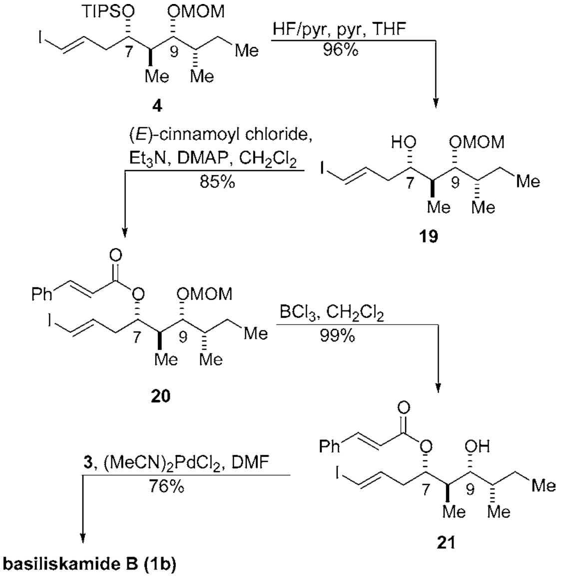
With advanced intermediate **4** in hand, we envisioned the completion of the synthesis of basiliskamide A would be carried out in a straightforward manner. To that end, BCl_3 deprotection of the MOM ether followed by acylation with (*E*)-cinnamoyl chloride yielded the C4−C12 fragment **17** (Scheme 4). A $(MeCN)_2PdCl_2$-catalyzed Stille cross-coupling between vinyl iodide **17** and vinyl stannane **3** proceeded smoothly to afford 76% yield of triene **18** in DMF at ambient temperature.[7,16] Deprotection of the TIPS ether by HF/pyridine furnished synthetic basiliskamide A in 12 steps with 12% overall yield from aldehyde **6**. Synthetic basiliskamide A possesses spectroscopic properties identical to those reported for the natural product. Measurement of the optical rotation ($[\alpha]^{D}_{23} = -79°$, $c = 0.12$; lit. $[\alpha]^{D}_{23} = -78°$, MeOH) supports the absolute stereochemical assignment of basiliskamide A of (7*S*,8*S*,9*R*,10*S*), thus substantiating Andersen's assertion that the basiliskamides share the same overall absolute configuration with YM-47522.

Scheme 4. Total Synthesis of Basiliskamide A



As outlined in Scheme 5, the completion of basiliskamide B proceeded in a similar fashion. Selective removal of the TIPS group in buffered HF/pyridine, acylation of the C7

Scheme 5. Total Synthesis of Basiliskamide B



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hydroxyl with (*E*)-cinnamoyl chloride, and deprotection of the MOM ether gave C4−C12 vinyl iodide fragment **21**. Employing the same cross-coupling conditions as described for basiliskamide A, synthetic basiliskamide B was obtained in 12 steps with 17% overall yield. Spectral data for the synthetic material are identical in all respects to those reported for the natural product. The measured optical rotation ($[\alpha]^{D}_{23} = -14°$, $c = 0.20$; lit. $[\alpha]^{D}_{23} = -12°$, MeOH) is consistent with that of the isolated material, further supporting the absolute configuration of the natural product.

In summary, the first total syntheses and absolute stereochemical assignments of basiliskamides A and B were achieved. This work extends the utility of chiral crotylmetalations in the synthesis of polyketide natural products via successive crotylations using mechanistically complementary crotylsilane and crotylboronate bond construction methodologies. Additionally, this synthetic route will provide a means for probing the structure−activity relationships of these and other related antifungal agents. Further investigations toward this goal will be disclosed in due course.

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Note Added after ASAP Posting. There was an error in the transition state shown in Scheme 2 in the version posted ASAP September 1, 2004; the corrected version was posted September 14, 2004.

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

OL048574M

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