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Modular Synthesis of the C9−C27 Degradation Product of Aflastatin A via Alkyne−Epoxide Cross-Couplings

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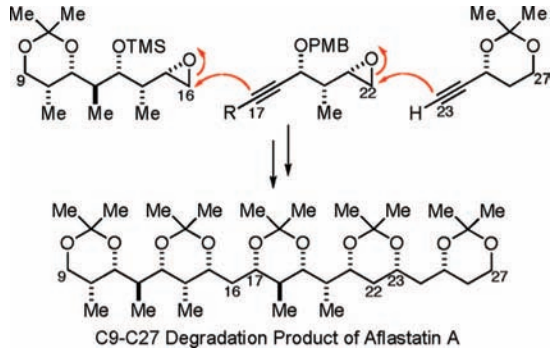
ABSTRACT



C9-C27 Degradation Product of Aflastatin A

A modular approach to the synthesis of complex polyketide natural products is demonstrated for the synthesis of the C9−C27 degradation product from aflastatin A. The product of the cross-coupling of C23−C27 terminal alkyne with C17−C22 epoxide underwent functionalization of the resulting internal alkyne, which was then coupled similarly with C9−C16 epoxide. This synthesis concluded with regio- and stereoselective addition of methyl onto the internal alkyne followed by stereoselective hydroboration−oxidation.

The polyketide natural product aflastatin A (**1**) (Figure 1) was isolated from the mycelium of *Streptomyces* sp. MRI 142 by Sakuda and co-workers.[1] Aflastatin A was observed to inhibit the biosynthesis of aflatoxin in *Aspergillus parasiticus*, without significantly inhibiting the growth of this aflatoxin-producing organism. The structure of aflastatin A has been determined by chemical degradation and extensive spectroscopic analysis,[2] with recent revision of the chiral centers at C8−C9 and C28−C31.[2c] Herein we report the asymmetric synthesis of the aflastatin C9−C27 pentaacetonide degradation product (**2**) by iterative cross-coupling of nucleophilic alkynes with electrophilic epoxides, followed by functionalization of the internal alkynes.[3,4]

Our retrosynthetic analysis envisioned that the C9−C27 substructure could be efficiently assembled by coupling modules **3**, **4**, and **5**. Utilizing modern methods for stereoselective synthesis, each module was efficiently prepared. Epoxide **3** was synthesized from the known homoallylic alcohol **8** (Scheme 1),[5] which arose from application of Brown's enantioselective crotylborane addition[6] followed by the diastereoselective crotyltrifluorosilane methodology of Chemler and Roush (dr 11:1).[5] After removal of the silyl ether protective group from **8**, the terminal acetonide was

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(2) (a) Ikeda, H.; Matsumori, N.; Ono, M.; Suzuki, A.; Isogai, A.; Nagasawa, H.; Sakuda, S. *J. Org. Chem.* **2000**, *65*, 438. (b) Higashibayashi, S.; Czechtizky, W.; Kobayashi, Y.; Kishi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14379. (c) Sakuda, S.; Matsumori, N.; Furihata, K.; Nagasawa, H. *Tetrahedron Lett.* **2007**, *48*, 2527.
(3) For an iterative aldol approach to the C9−C27 polyol, see: (a) Evans, D. A.; Trenkle, W. C.; Zhang, J.; Burch, J. D. *Org. Lett.* **2005**, *7*, 3335.
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(5) Chemler, S.; Roush, W. R. *J. Org. Chem.* **2003**, *68*, 1319.
(6) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293.

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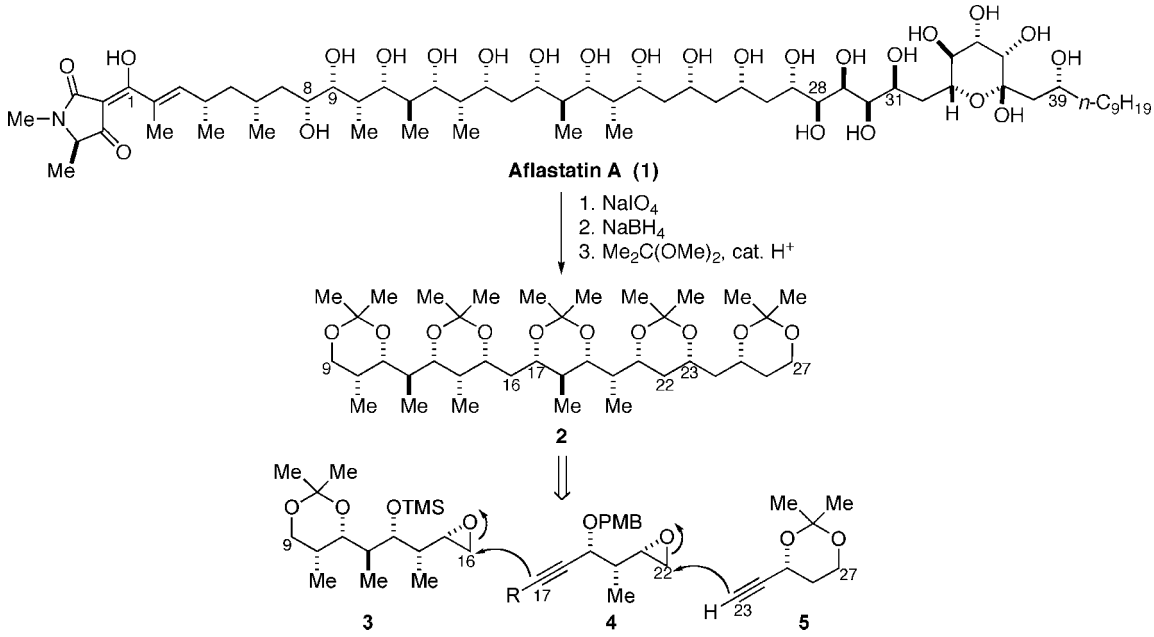
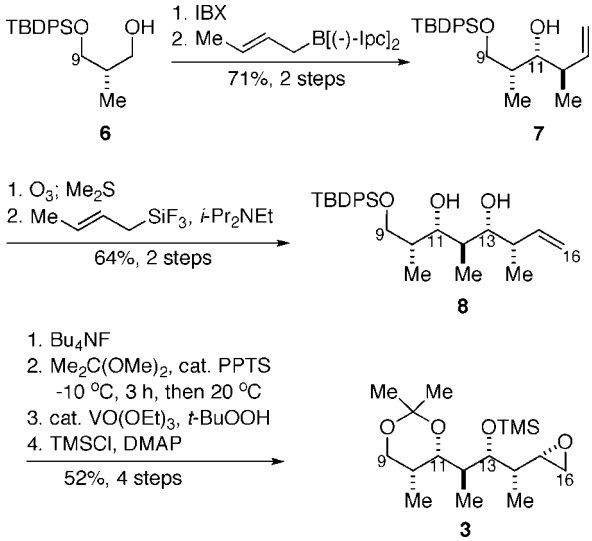


Figure 1. Structure of aflastatin A (**1**) and retrosynthesis for **2**.

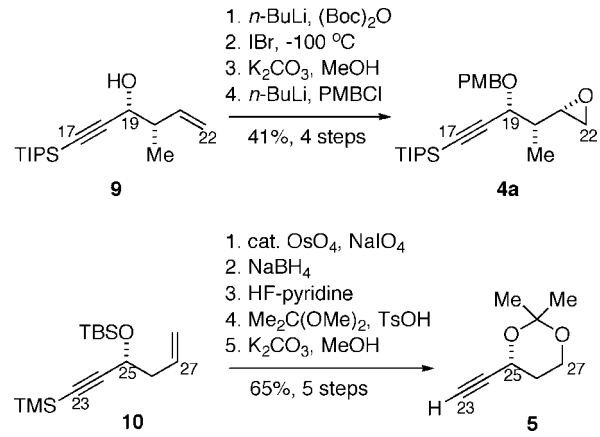
selectively installed onto the C9,C11-diol under kinetic conditions, leaving the C13 alcohol unprotected for diastereoselective hydroxyl-directed vanadium-catalyzed epoxidation (dr 8:1)[7] to provide compound **3** after TMS protection of the free alcohol.

Epoxyalkyne module **4** was synthesized (Scheme 2) from the known enynol **9**.[8] The C21−C22 epoxide was introduced by IBr-promoted cyclization of the derived C19-*O*-*tert*-butylcarbonate (dr 9:1), followed by basic methanolysis of the resulting cyclic iodocarbonate,[9] and PMB protection of the C19 alcohol to provide **4a** bearing a triisopropylsilyl (TIPS) substituent on the alkyne. The terminal alkyne **5** arose from enyne **10**[4] by oxidative cleavage of the terminal olefin followed by aldehyde reduction to provide the C25−C27 diol and straightforward protective group manipulations.

Scheme 1. Synthesis of Epoxide Module **3**



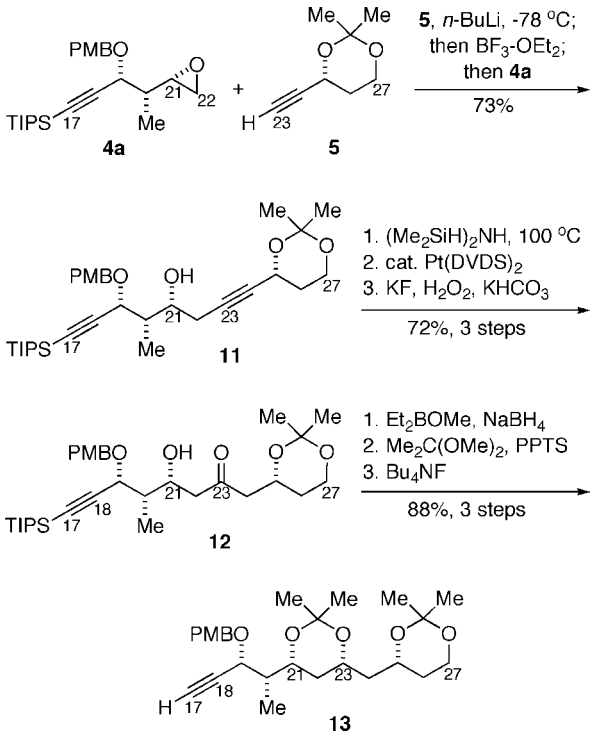
Scheme 2. Synthesis of Modules **4** and **5**



With modules **3**, **4**, and **5** in hand, we began to assemble the aflastatin C9−C27 degradation product (**2**) by first coupling modules **4a** and **5** (Scheme 3). Treatment of **5** with 1 equiv of *n*-butyllithium and $BF_3{-}OEt_2$[10] followed by addition of the electrophilic epoxide **4a** provided alkynyl alcohol **11** in 73% isolated yield (Scheme 3). The resulting

(7) Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690.
(8) Park, S.-K.; Kim, S.-i.; Cho, I.-H. *Bull. Korean Chem. Soc.* **1995**, *16*, 12.
(9) Duan, J. J. W.; Smith, A. B. *J. Org. Chem.* **1993**, *58*, 3703.

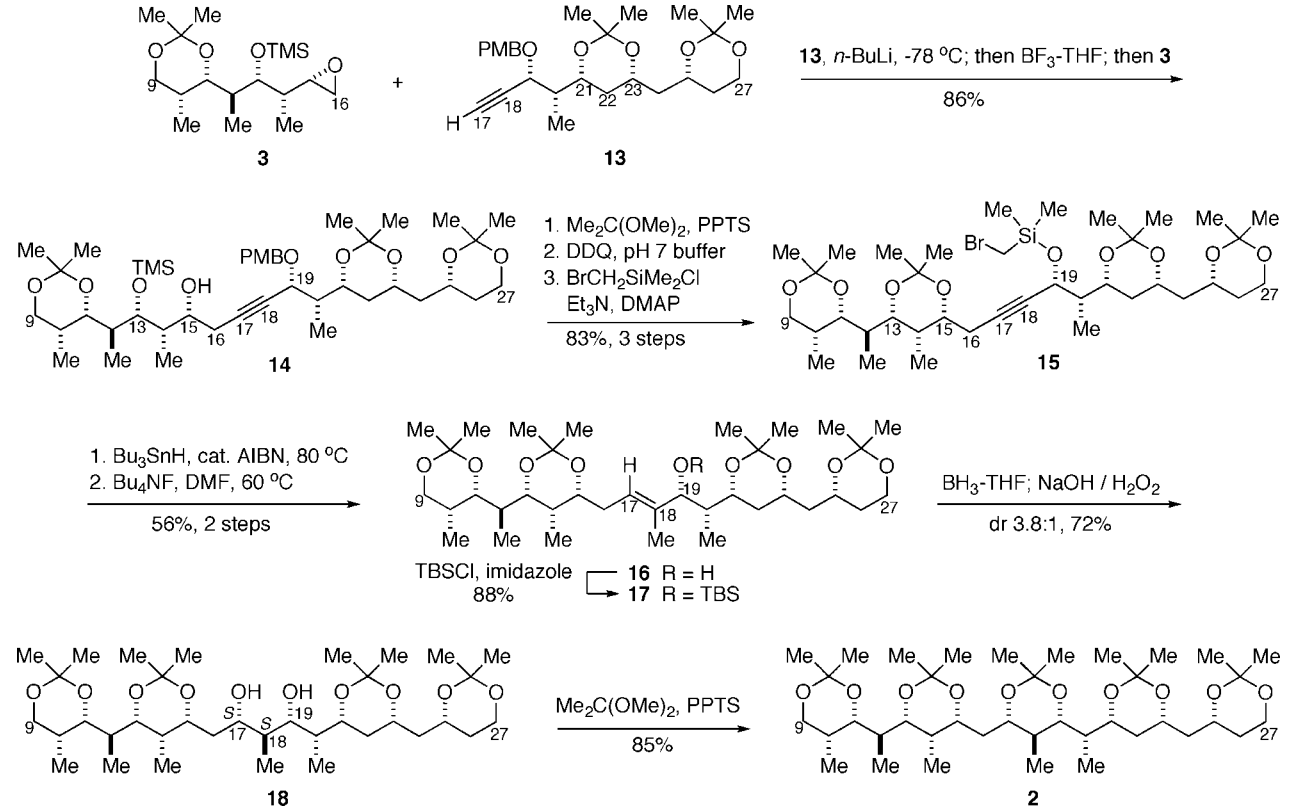
Scheme 3. Cross-Coupling of Modules **4** and **5** To Form the C17−C27 Sector (**13**)



C21-alcohol then regioselectively directed hydration of the internal alkyne to the corresponding β-hydroxyketone **12**, via intramolecular platinum-catalyzed hydrosilylation and Tamao−Fleming oxidation.[11] The C21 hydroxyl group also directed diastereoselective reduction of the ketone to provide the *syn*-C21,C23-diol, which after protective group manipulation afforded terminal alkyne **13**.

The original plan to introduce a methyl group at C18 via carbocupration of the terminal alkyne **13** and cross-coupling of the resulting vinyl cuprate with epoxide **3** failed due to the high degree of functionalization in both coupling patterns, but returning to the reliable cross-coupling of the alkynyl lithium from **13** with epoxide **3** provided an excellent yield of alkynyl alcohol **14**, provided that BF_3−THF[12] was utilized (Scheme 4). After some protective group manipulations, the introduction of the C18-methyl substituent was accomplished by attachment of a bromomethylsilyl ether at O19 of **15**, which underwent radical cyclization followed by protiodesilylation to stereoselectively afford the *E*-trisubstituted alkene **16**.[13] Hydroboration-oxidation of the allylic alcohol **16** with BH_3−THF initially favored the undesired (17*R*,18*R*)-diastereomer instead of **18**. With a chiral nonracemic borane (+)-IpcBH$_2$,[14] the preference of stereoisomers could be inverted to favor the (17*S*,18*S*) configuration of **18** but with only a 2:1 diastereomer ratio. However, formation of the silyl ether **17** substantially changed the conformation (based on ^{1}H NMR observations), and the hydroboration−oxidation of **17** with BH_3−THF afforded a separable 3.8:1 mixture of

Scheme 4. Cross-Coupling of Module **3** with **13** Leading to the Aflastatin C9−C27 Degradation Product (**2**)



C17−C19 diols favoring **18** (the TBS ether was lost under the basic oxidation conditions). The structures of our synthetic materials were confirmed by formation of the pentaacetonide **2**, agreeing with the reported spectroscopic and physical data for this compound obtained by oxidative degradation of aflastatin A.[2]

In conclusion, we have demonstrated the efficacy of alkyne−epoxide cross-couplings in the synthesis of structurally complex and stereochemically rich polypropionates in our construction of the aflastatin C9−C27 degradation product **2**. The successful and high-yielding union of epoxide **3** and alkyne **13** to provide internal alkyne **14** represents the most complex structure prepared to date by this type of transformation.

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Supporting Information Available: Detailed experimental procedures and characterization for all synthetic compounds and spectral comparisons of synthetic **2** with naturally derived material. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) Tamao, K.; Maeda, K.; Tanaka, T.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 6955. (b) Marshall, J. A.; Yanik, M. M. *Org. Lett.* **2000**, *2*, 2173.

(12) Evans, A. B.; Knight, D. W. *Tetrahedron Lett.* **2001**, *42*, 6947. The corresponding transformation with $BF_3{-}OEt_2$ proceeded in much lower yield and was not highly reproducible.

(13) (a) Gulea, M.; López-Romero, J. M.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2000**, *2*, 2591. For the corresponding reaction with alkenes, see: (b) Stork, G.; Sofia, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 6826. (c) Koreeda, M.; Hamann, L. G. *J. Am. Chem. Soc.* **1990**, *112*, 8175.

(14) Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *J. Org. Chem.* **1993**, *58*, 3703.