ORGANIC LETTERS

2005
Vol. 7, No. 15
3335−3338

Synthesis and Confirmation of the Absolute Stereochemistry of the (−)-Aflastatin A C_9−C_{27} Degradation Polyol

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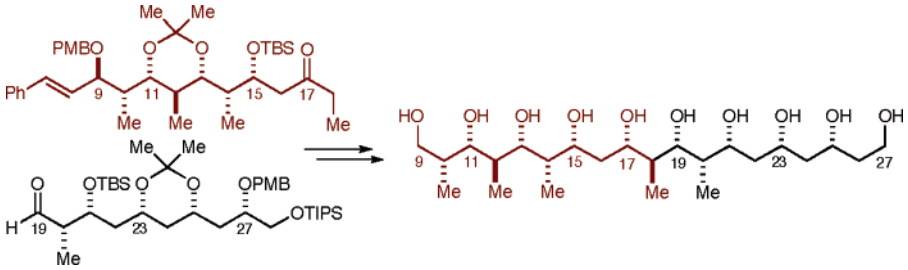
Received May 24, 2005

ABSTRACT



The C_8−C_{18} ethyl ketone and C_{19}−C_{28} aldehyde aflastatin A fragments were synthesized and coupled using a diastereoselective *anti* aldol reaction. This adduct was successfully converted into the C_9−C_{27} polyol degradation product of (−)-aflastatin A to confirm the relative and absolute stereochemistry of this region of the natural product.

In 1996, Sukuda and co-workers reported the isolation and gross structure of aflastatin A from the mycelia of *Streptomyces* sp. MRI 142. This natural product exhibits strong inhibitory activity against aflatoxin production without significantly affecting the growth of *A. parasiticus*.[1] The same group subsequently reported the relative and absolute structure of aflastatin A (**1**) (Figure 1).[2] Stereochemical assignments were based on both degradation and chemical correlation studies; however, the relative and absolute stereochemistry of the C_9−C_{27} degradation polyol **2** was predicted solely via extensive NMR studies. In this Letter, we describe an asymmetric synthesis of polyol **2** that verifies the stereochemical assignment of this region of aflastatin A.

The principal disconnections that were employed in the synthesis of the C_9−C_{27} polyol of aflastatin A are illustrated in Scheme 1. The important fragment coupling event was

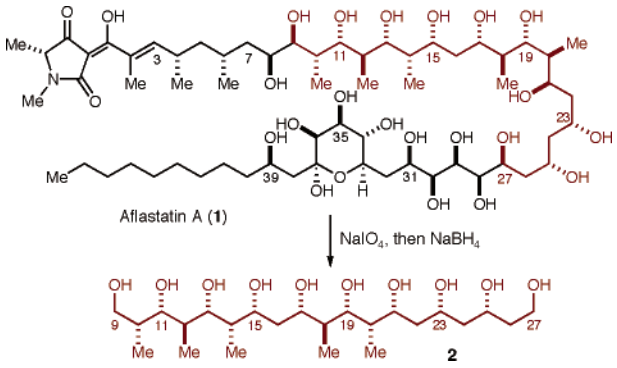


Figure 1. Sakuda's structure of aflastatin A.

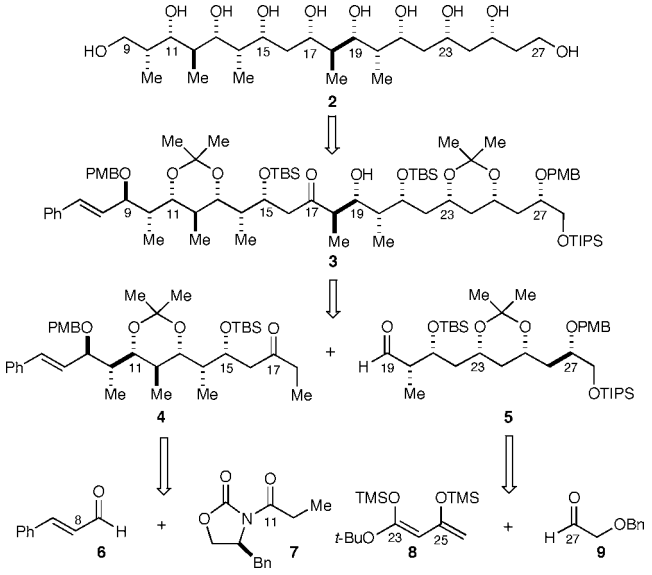
the *anti* aldol union of the (*E*) boron enolate derived from ethyl ketone **4** with the complex aldehyde **5**. In this case, the dominant control element was the anticipated enhanced Felkin selectivity from the C_{20} methyl-bearing stereocenter on the aldehyde fragment.[3] Our approach to fragments **4** and

(1) (a) Sakuda, S.; Ono, M.; Furihata, K.; Nakayama, J.; Suzuki, A.; Isogai, A. *J. Am. Chem. Soc.* **1996**, *118*, 7855. (b) Kondo, T.; Sakurada, M.; Okamoto, S.; Ono, M.; Tsukigi, H.; Suzuki, A.; Nagasawa, H.; Sakuda, S. J. *Antibiotics* **2001**, *54*, 650.

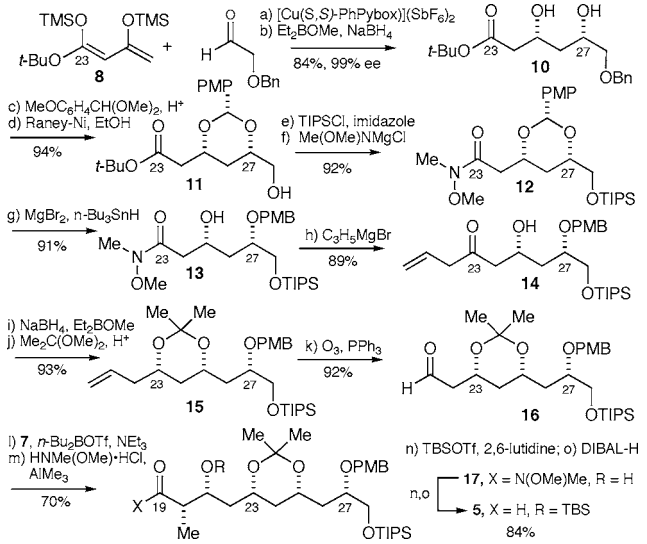
(2) Ikeda, H.; Matsumori, N.; Ono, M.; Suzuki, A.; Isogai, A.; Nagasawa, H.; Sakuda, S. *J. Org. Chem.* **2000**, *65*, 438.

10.1021/ol051225n CCC: $30.25
Published on Web 06/21/2005

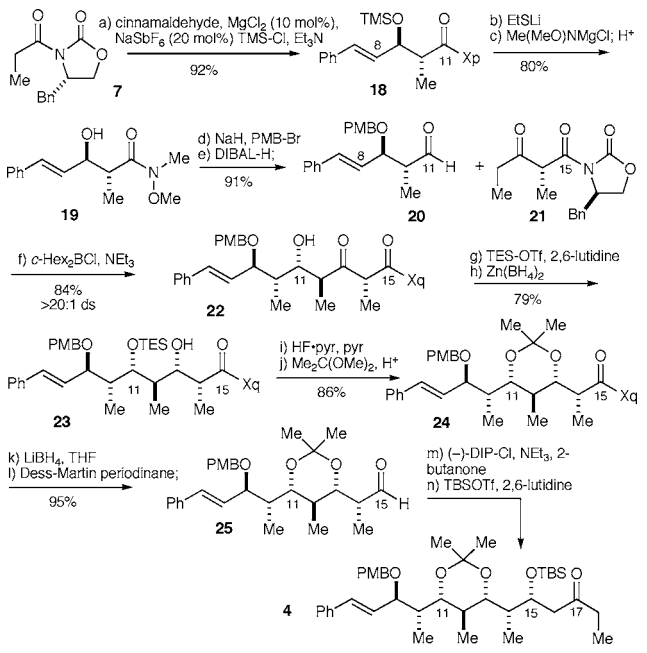
Scheme 1. Disconnection of C_9-C_{27} Degradation Polyol 2



Scheme 2. Synthesis of $C_{19}-C_{28}$ Aldehyde Fragment



Scheme 3. Synthesis of C_8-C_{18} Ketone Fragment



5 relied on the two stereoselective aldol processes illustrated in Scheme 1.

Synthesis of the $C_{19}-C_{28}$ fragment began with an enantioselective [Cu(S,S)-PhPybox)]$(SbF_6)_2$-catalyzed aldol addition followed by *syn*-selective reduction to give the previously reported diol **10** in 99% ee and 84% overall yield.[4] Treatment of **10** with anisaldehyde dimethylacetal afforded the PMP acetal, which underwent selective deprotection of the benzyl ether with Raney nickel to give hydroxy ester **11**.[5] Silylation followed by transamidation[6] provided the Weinreb amide **12**, which was an appropriate substrate for a carbonyl-directed acetal cleavage using $MgBr_2$ and Bu_3SnH.[7] Allylation, Et2BOMe-mediated *syn*-reduction,[8] and acid-catalyzed acetonide formation furnished the protected all-*syn* triol derivative **15**. Ozonolysis provided aldehyde **16**, which underwent an auxiliary controlled *syn*-aldol reaction with oxazolidinone **7** to deliver the corresponding aldol adduct as a single diastereomer. Cleavage of the imide auxiliary was achieved under standard conditions to provide Weinreb amide **17**. Silylation with TBSOTf and 2,6-lutidine followed by DIBAL completed the synthesis of aldehyde **5** (Scheme 2).

Scheme 3 illustrates the synthesis of the C_8-C_{18} ethyl ketone fragment. The synthesis was initiated with our recently reported $MgCl_2$-catalyzed direct aldol addition to provide the known *anti*-aldol adduct **18** (>20:1 dr, 92% yield).[9] Imide **18** was converted into the Weinreb amide **19**,[10] protected as the PMB ether, and reduced to afford the C_8-C_{11} aldehyde **20** in 91% yield. The $C_{12}-C_{15}$ carbon skeleton was introduced by a boron-mediated *anti*-aldol reaction between **20** and β-ketoimide **21**.[11] The high selectivity observed in this reaction (>95:5 dr) was anticipated as a result of the matched double stereodifferentiating nature of the aldehyde and ketone components. The hydroxy ketone

(3) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 9073.

(4) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669.

(5) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.

(6) William, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.

(7) For free hydroxyl-directed reduction of PMP acetal with $MgBr_2$ and *n*-Bu_3SnH, see: Zheng, B. Z.; Yamauchi, M.; Dei, H.; Kusaka, S. I.; Matsui, K.; Yonemitsu, O. *Tetrahedron Lett.* **2000**, *41*, 6441.

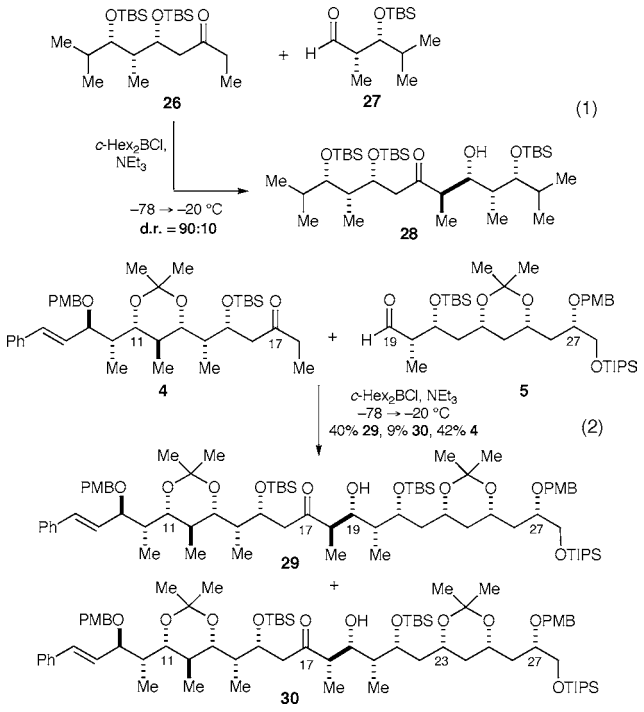
(8) Beck, G.; Jendralla, H.; Kesseler, K. *Synthesis* **1995**, 1014.

(9) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392.

(10) All attempts to convert **18** directly into **19** using either $Me_2AlNMe(OMe)$ or $ClMgNMe(OMe)$ failed because of preferred endocyclic cleavage.

(11) (a) Evans, D. A.; Clark, J. S.; Metternich, R.; Novak, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866. (b) Evans, D. A.; Kim, A. S. *J. Am. Chem. Soc.* **1996**, *118*, 11323.

Scheme 4. $C_{18}-C_{19}$ *anti*-Selective Fragment Coupling

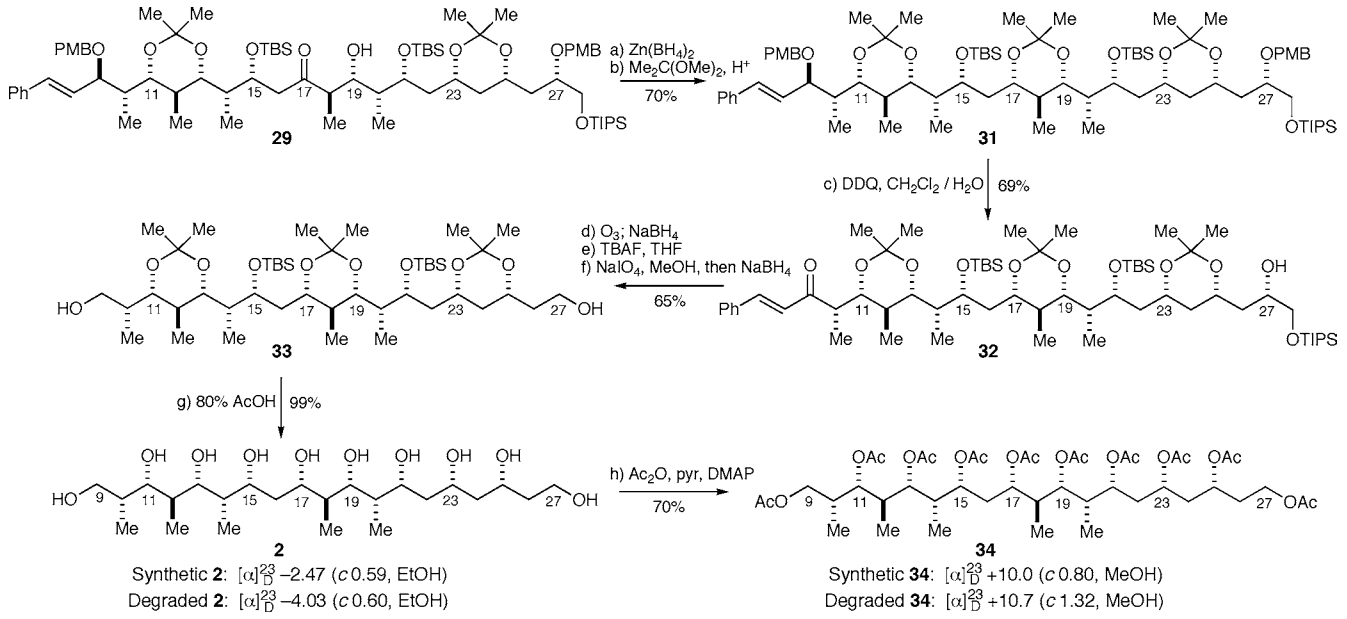


22 was protected as its derived triethylsilyl (TES) ether followed by a chelation-controlled reduction mediated by $Zn(BH_4)_2$ to afford **23** as a single diastereomer with a 1,3-*syn* relationship between $C_{11}-C_{13}$.[12] The high selectivity for this reduction can be rationalized through a bidentate chelate formed between C_{13} and C_{15} carbonyls, with the C_{14} methyl stereocenter controlling the subsequent hydride delivery. Protecting group interconversion, followed by $LiBH_4$ reduction and Dess−Martin oxidation,[13] provided C_8-C_{15} aldehyde **25**. A methyl ketone aldol reaction, mediated by (−)-diisopinocampheylboron chloride (DIP-Cl), between **25** and 2-butanone furnished the desired aldol adduct with modest diastereoselectivity (4:1 favoring the Felkin product).[14] Silylation of the aldol adduct afforded the C_8-C_{18} ethyl ketone fragment **4**.

In anticipation of the aldol fragment coupling, model studies for the $C_{18}-C_{19}$ *anti*-aldol bond construction were conducted (Scheme 4, eq 1). The dicyclohexylchloroborane-mediated aldol reaction between ethyl ketone **26** and aldehyde **27** exhibited high stereoselectivity favoring the desired Felkin product **28** (90:10 diastereomeric ratio) albeit in moderate conversion.[14] Equation 2 summarizes the results of the *anti*-aldol reaction between C_8-C_{18} ethyl ketone **4** and $C_{19}-C_{28}$ aldehyde **5**. The desired Felkin selective aldol adduct **29** was obtained as the major diastereomer, along with a minor amount of *syn*-aldol adduct **30** and unreacted ketone starting material.[15−16]

The major adduct **29** was converted into the C_9-C_{27} degradation polyol **2** as shown in Scheme 5. $Zn(BH_4)_2$-mediated reduction afforded the $C_{17}-C_{19}$ *syn*-diol, which was protected as the derived acetonide **31**. Although DDQ deprotection resulted in overoxidation to enone **32**, this compound could still serve as a precursor for the polyol since the C_9 stereocenter is inconsequential. Thus, ozonolysis of the styrenyl double bond followed by in situ $NaBH_4$ reduction gave a triol intermediate (as a mixture of stereoisomers). Selective deprotection of the primary TIPS ether with TBAF to provided the tetraol intermediate. $NaIO_4$-mediated diol cleavage of both termini followed by in situ $NaBH_4$ reduction furnished diol **33** in a 65% yield over three steps. Treatment of **33** with 80% aqueous acetic acid at room temperature afforded the C_9-C_{27} degradation polyol **2** in quantitative yield.

Scheme 5. Synthesis of C_9-C_{27} Degradation Polyol



The synthetic C_9-C_{27} polyol **2** was identical in all respects with the authentic sample derived from the natural product (^{1}H NMR, ^{13}C NMR, HRMS). The optical rotation of the synthetic material ($[\alpha]^{23}_D$ −2.47 (c = 0.59, EtOH)) was in agreement with that reported for degradation product **2** (lit.[2] $[\alpha]^{23}_D$ −4.03 (c = 0.60, EtOH)), indicating that the relative and absolute stereochemistry of polyol **2** is correct as assigned. As further proof of structure, polyol **2** was converted into the polyacetate **34** using acetic anhydride and pyridine (Scheme 5). Synthetic polyacetate **34** exhibited indistinguishable analytical data (^{1}H NMR, ^{13}C NMR, HRMS) from material derived from the natural sample, and the optical rotations were also in agreement (synthetic **34** $[\alpha]^{23}_D$ +10.0 (c = 0.80, MeOH); lit.[17] $[\alpha]^{23}_D$ +10.7 (c = 1.32, MeOH)).

In summary, the C_8-C_{18} and $C_{19}-C_{28}$ fragments of aflastatin A have been efficiently synthesized, and preliminary conditions for their diastereoselective coupling have been developed. The C_8-C_{28} aldol adduct was successfully converted into the C_9-C_{27} polyol **2**. By comparison of the synthetic material with that derived from the natural product, we conclude that the relative and absolute stereochemistry of C_9-C_{27} polyol was correctly assigned. The total synthesis of aflastatin A will be reported in due course.

Acknowledgment. Support has been provided by the National Institutes of Health (GM 033327-19), Amgen, and Merck. We thank professor Sakuda for kindly providing us a sample of the C_9-C_{27} degradation polyol.

Supporting Information Available: Experimental procedures, characterization of compounds **2**−**34**, and stereochemical proofs for adducts **28**−**30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) Direct reduction of hydroxy ketone **25** with $Zn(BH_4)_2$ provided the 1,3-*syn* diol with only modest diastereoselectivity (4:1 *syn*/*anti*). The diminished selectivity could be attributed to the preferred chelation between C_{11} hydroxyl and C_{13} carbonyl with C_{12} methyl stereocenter interfering with the β-face hydride delivery. (b) Halstead, D. P. Ph.D. Thesis, Harvard University, 1998.

(13) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(14) (a) Paterson, I.; Cumming, J. G.; Smith, J. D.; Ward, R. A. *Tetrahedron Lett.* **1994**, *35*, 441. (b) Fernandez-Megia, E.; Gourlaouen, N.; Ley, S. V.; Rowlands, G. J. *Synlett* **1998**, 991.

(15) The stereochemistry of the aldol adducts was proven via Mosher ester analysis; see Supporting Information. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(16) See Supporting Information for experiments that provide proof of stereochemical assignments.

(17) Ono, M.; Sakuda, S.; Ikeda, H.; Furihata, K.; Nakayhama, J.; Suzuki, A.; Isogai, A. J. *Antibiotics* **1998**, *51*, 1019.