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Progress toward the Total Synthesis of Bafilomycin A_1: Stereoselective Synthesis of the C15–C25 Subunit by Additions of Nonracemic Allenylzinc Reagents to Aldehydes

James A. Marshall* and Nicholas D. Adams

Department of Chemistry, McCormick Road, P.O. Box 400319, University of Virginia, Charlottesville, Virginia 22904

jam5x@virginia.edu

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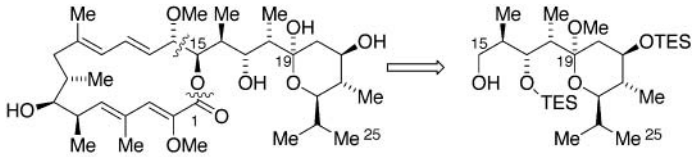
ABSTRACT



Bafilomycin A_1 (**1**) **2**

A highly stereoselective synthesis of the C15–C25 subunit (2) of bafilomycin A_1 (1) has been accomplished by a route utilizing additions of chiral nonracemic allenylzinc reagents to aldehydes.

Bafilomycin A_1 (**1**), a polyketide isolated from the fermentation broth of *Streptomyces griseus* by Werner et al. in 1984,[1] is a member of a macrolide family including the bafilomycins,[1] the concanamycins,[2] and the hygrolidins.[3] The stereochemistry was initially proposed by Corey and Ponder[4] on the basis of molecular modeling and NMR data and was later confirmed by X-ray crystallography.[5] This 16-membered macrolide is a potent and specific inhibitor of vacuolar ATPases (V-ATPases).[6] Given that V-ATPases are known to participate in bone resorption (i.e., the loss of bone),[7] inhibitors of such enzymes may serve as potential treatments for osteoporosis. In light of its relative scarcity (several tedious extractions and chromatographies of a 100-L culture filtrate of *S. griseus* provide 45 mg of bafilomycin A_1), diverse biological activity, and combination of interesting structural features, bafilomycin A_1 represents an attractive target for total synthesis. An approach that would allow for the production of sufficient amounts of the natural product or analogues to be used for screening as possible chemotherapeutic agents for osteoporosis would be particularly desirable.

To date three total syntheses of bafilomycin A_1 have been reported. The Evans and Calter approach utilizes stereoselective aldol reactions for subunit assemblage and fragment coupling.[8] Toshima and co-workers employ chiral pool materials and substrate-controlled additions for the construc-

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tion of subunits.[9] Most recently, Roush and co-workers effected a stereoselective aldol condensation for fragment coupling and diastereoselective aldehyde crotylboration methodology to set key stereocenters.[10] A stereocontrolled aldol-based route to a C13−C25 subunit has also been reported by Paterson and co-workers.[11]

In recent years our laboratory has been interested in the synthesis of bioactive polyketide-derived natural products through use of chiral allenylmetal reagents.[12] Along those lines, we have recently reported a method for the formation of enantioenriched allenylzinc reagents from transient allenylpalladium intermediates by treatment of nonracemic propargylic mesylates with a palladium(0)−phosphine catalyst in the presence of diethylzinc (Figure 1).[13] These zinc

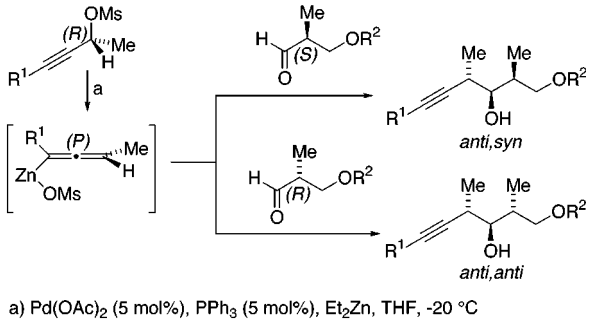


Figure 1. Synthesis of anti,syn and anti,anti stereotriads by additions of allenylzinc reagents to α-methyl aldehydes.

reagents undergo highly diastereoselective S_E2' additions to aldehydes, to yield anti-homopropargylic alcohol adducts of high enantiomeric excess without significant reagent/substrate mismatching. The several anti-propionate stereochemical arrays found in bafilomycin A_1 make it an attractive target for possible applications of this methodology in the synthesis of moderately complex natural products.

Herein we report a highly stereoselective nonaldol-based approach to the C15−C25 subunit of bafilomycin A_1. This work demonstrates the efficient application of anti-selective allenylzinc methodology to polyketide fragment synthesis. Of special interest is the use of the alkynyl moiety produced in these additions as a versatile functional handle for further synthetic elaborations. For example, it can be envisaged that the alkyne moiety in pivalate **3** could be used to install the required stereogenic centers at C16 and C17 (Figure 2). Pivalate **3** could be readily accessed through an allenylzinc addition to the C19−C25 aldehyde **5**.

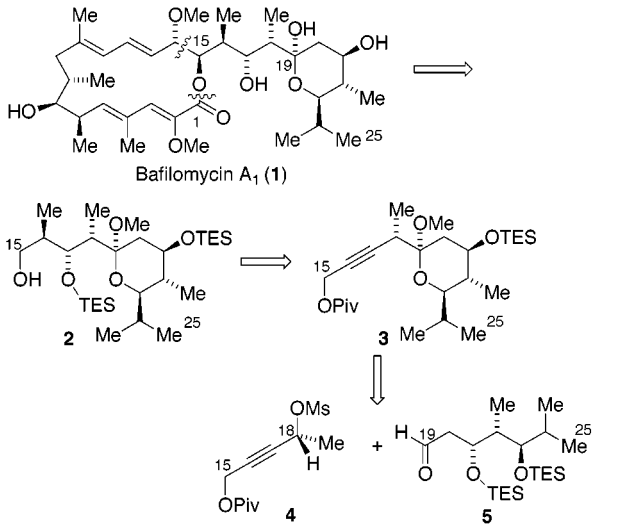
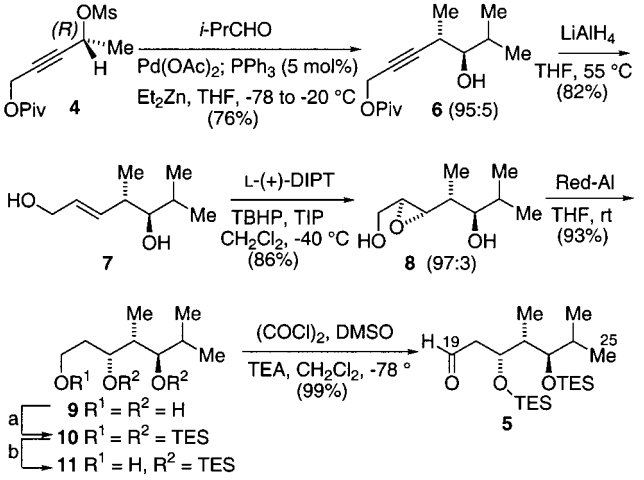


Figure 2. Retrosynthetic analysis.

Our synthesis commenced with an addition of the allenylzinc reagent derived from mesylate **4** to isobutyraldehyde, providing homopropargylic alcohol **6** with 95:5 diastereoselectivity (Scheme 1).

Scheme 1[a]



[a] Key: (a) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (99%); (b) AcOH/H_2O/THF (3:1:10), rt (82%): DIPT = diisopropyl tartrate; TBHP = *tert*-butyl hydroperoxide; TIP = titanium isopropoxide; Red-Al = Na bis(2-methoxyethoxy)aluminum hydride; TEA = triethylamine.

One-pot pivalate deprotection and partial reduction of the alkyne was accomplished with $LiAlH_4$ to afford (*E*)-allylic alcohol **7**. Red-Al could also be used to carry out this transformation; however shorter reaction times (2 h versus 24−48 h) and the lack of byproduct formation (Red-Al liberates copious amounts of ethylene glycol monomethyl ether upon quenching which was difficult to remove from diol **7**) make $LiAlH_4$ a superior reagent in the present case.

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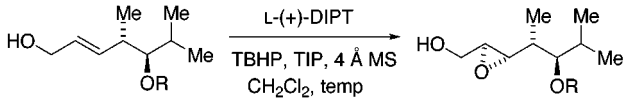
Allylic alcohol **7** was epoxidized by using the Sharpless protocol with (+)-diisopropyl tartrate as the ligand.[14] It was found that a reaction temperature of −40 °C was essential for obtaining high levels of diastereoselectivity (97:3) (Table 1). If the epoxidation was performed at −20 °C, an erosion

Table 1. Optimization of Epoxidation Conditions



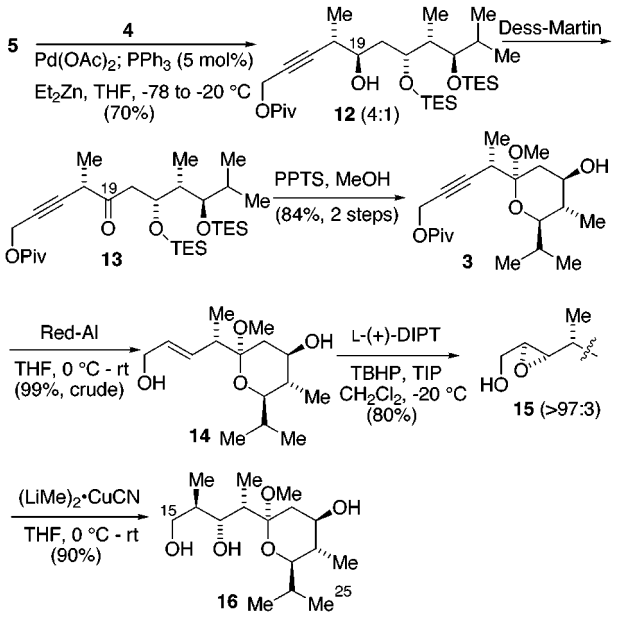
entry	temp, 0 °C	R	α:β	yield, %
1	−20	TBDMS	>97:3	89
2	−20	MOM	>97:3	80
3	−20	H	91:9	71
4	−40	H	97:3	86

of selectivity (91:9) was observed. Interestingly, protection of the C23 hydroxyl as the TBS or MOM ether resulted in a selectivity of >97:3 at −20 °C. Evidently the free secondary hydroxyl at C23, although homoallylic, influences the stereoselectivity of the epoxidation.

Regioselective epoxide opening was effected with Red-Al to give triol **9** in high yield. At this stage, an efficient protecting group-oxidation strategy was pursued through global protection of triol **9** with TESOTf. However, attempts at selective one-pot deprotection/oxidation of the primary TES ether under a variety of modified Swern conditions[15] were largely unsuccessful. Therefore, a two-step sequence was implemented. Accordingly, the primary TES ether was cleaved with dilute AcOH in THF−H_2O to give alcohol **11** in 82% yield (95% based on recovered starting material) and the resultant primary alcohol was oxidized in near quantitative yield under Swern conditions[16] to aldehyde **5**.

Addition of the allenylzinc reagent derived from propargylic mesylate **4** to aldehyde **5** proceeded in high yield to give a 4:1 inseparable mixture of anti and syn isomers (Scheme 2). The low diastereoselectivity was somewhat surprising in light of our previous findings with α-unbranched aliphatic aldehydes (typically 7−9:1 anti selectivity is observed).[13] In the present case diastereoselectivity is not an issue as the subsequent step involves oxidation of the C19 alcohol. Accordingly, the 4:1 mixture of alcohols **12** was treated with the Dess−Martin periodinane[17] reagent to afford ketone **13**, a single diastereomer, which was carried on to the next step without purification. It should be noted that the use of the Swern protocol in the oxidation step resulted in base-induced isomerization of the propargylic ketone to the allenone.

Scheme 2



Treatment of ketone **13** with a stoichiometric amount of PPTS in MeOH resulted in deprotection of both TES ethers, stereoselective cyclization, and ensuing conversion of the resultant hemiacetal to the methyl pyranoside **3**. The cyclization was complete in 1 h and provided **3** in 84% yield from alcohol **12**. Formation of the corresponding (*E*)-allylic alcohol, necessary for subsequent installation of the final two stereocenters, was then addressed. In keeping with our protecting group strategy, it was desirable to protect alcohol **3** as the TES ether. Because such ethers are unstable to Red-Al under the requisite conditions of the subsequent hydroalanation reaction, we chose not to protect the free hydroxyl of alcohol **3** at this stage. This decision ultimately led to a more efficient route, as this hydroxyl could remain unprotected until the final steps of the sequence.

Treatment of the propargylic pivalate **3** with excess Red-Al in THF resulted in clean conversion to allylic alcohol **14**. This material was found to be highly acid sensitive and was therefore carried on immediately without purification. Stereoselective Sharpless epoxidation[14] with the (+)-isopropyl tartrate ligand and subsequent regioselective opening of the epoxide with lithium dimethylcyanocuprate[18] provided triol **16** as a crystalline solid. Suitable crystals were obtained by recrystallization from EtOAc, to enable confirmation of the relative configuration by X-ray analysis.

Once again we were faced with protecting group orthogonality issues. A global protection followed by a selective deprotection strategy was considered; however we foresaw difficulty in the latter steps. Therefore, the primary hydroxyl was protected selectively as the pivalate (Scheme 3). Triethylsilyl ethers were chosen for the remaining secondary hydroxyls because of their facile cleavage from hindered

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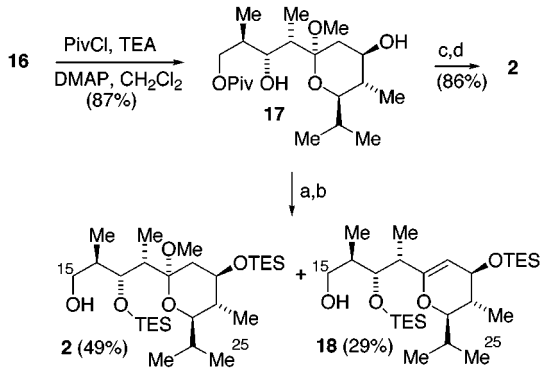
Scheme 3[a]



[a] Key: (a) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (b) DIBAL-H, CH_2Cl_2, −78 °C; (c) TESCl, imidazole, DMF, rt (94%); (d) DIBAL-H, CH_2Cl_2, −78 °C (92%).

alcohols in late-stage deprotections. Initially, TESOTf was employed as the silylating reagent. However, it was found that a significant amount of enol **18** was formed under these conditions even at −78 °C. Formation of the enol presumably arises from coordination of the TESOTf to the methoxy group leading to oxonium formation and subsequent elimination.

To circumvent this problem, the less reactive TESCl was employed, which resulted in a high yield of the bis-TES ether with minimal enol formation. A 5-fold excess of TESCl was required to drive the reaction to completion within a reasonable timeframe. This is most likely a consequence of the sterically encumbered environment of the secondary hydroxyls. Removal of the pivalate with DIBAL-H completed the synthesis of the C15−C25 subunit **2**.

In conclusion, a highly efficient synthesis of the C15−C25 subunit of bafilomycin A_1 has been accomplished. The present study advantageously employs nonracemic allenylzinc additions to aldehydes for complex fragment assemblage and subsequent use of the adducts for key carbon−carbon bond formation and the introduction of adjacent stereocenters.

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra for adducts **2**, **3**, and **5**−**17** and the ORTEP diagram for triol **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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