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Total Synthesis of (−)-Bafilomycin A_1

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Abstract: A highly stereoselective total synthesis of (−)-bafilomycin A_1, the naturally occurring enantiomer of this potent vacuolar ATPase inhibitor, is described. The synthesis features the highly stereoselective aldol reaction of methyl ketone **8b** and aldehyde **60c** and a Suzuki cross-coupling reaction of the highly functionalized advanced intermediates **12** and **39**. Vinyl iodide **12** was synthesized by a 14-step sequence starting from the readily available β-alkoxy aldehyde **14**, while the vinylboronic acid component **39** was synthesized by a nine-step sequence from β-hydroxy-α-methyl butyrate **44** via a sequence involving the α-methoxypropargylation of chiral aldehyde **49** with the α-methoxypropargylstannane reagent **54**. Syntheses of fragments **12** and **39** also feature diastereoselective double asymmetric crotylboration reactions to set several of the critical stereocenters. The Suzuki cross-coupling of **12** and **39** provided seco ester **40**, which following conversion to the seco acid underwent smooth macrolactonization to give **41**. The success of the macrocyclization required that C(7)-OH be unprotected. The Mukaiyama aldol reaction between aldehyde **60c** and the TMS enol ether generated from **8b** provided aldol **65** with high diastereoselectivity. Finally, all silicon protecting groups were removed by treatment of the penultimate intermediate **65** with TAS-F (tris-(dimethylamino)sulfonium difluorotrimethylsilicate), thereby completing the total synthesis of (−)-bafilomycin A_1.

Introduction

Bafilomycin A_1 (**1**)[3] is a member of the plecomacrolide family (formerly known as the hygolide family)[4] of macrolide antibiotics that includes the hygrolidins,[5,6] the concanamycins (e.g., concanomycin A, **2**),[7] and formamicin, **3.**[8,9] Bafilomycin A_1 is a potent vacuolar H^+-ATPase inhibitor that displays broad antibacterial and antifungal activity.[10] The stereochemistry of bafilomycin A_1, initially assigned by Corey on the basis of a molecular modeling analysis of published NMR data,[4] was subsequently verified by X-ray crystallography.[11,12] Bafilomycin A_1 contains an acid- and base-sensitive six-membered hemiketal that participates in a hydrogen-bond network with the C(17) hydroxyl group and the carbonyl of the 16-membered lactone that is necessary for biological activity. The structurally distinctive C(2)−C(5) dienyl methyl ether system is also found in other members of this family.

In view of the interesting chemical structures and potent biological properties, considerable effort has been devoted to the development of efficient syntheses of members of this family. Total syntheses of bafilomycin A_1 have been recorded by Evans[13,14] and Toshima,[15−17] and very recently total syntheses of bafilomycin A_1 and V_1 have been accomplished by Hanessian and Marshall, respectively.[18,19] A total synthesis of hygrolidin has been accomplished by Yonemitsu,[20,21] and total syntheses of concanamycin F (the aglycone of concanamycin A) have been recorded by both the Toshima and Paterson groups.[22−24] Several studies on the synthesis of bafilomycin A_1[25−28] and of bafilo-

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(2) Indiana University.
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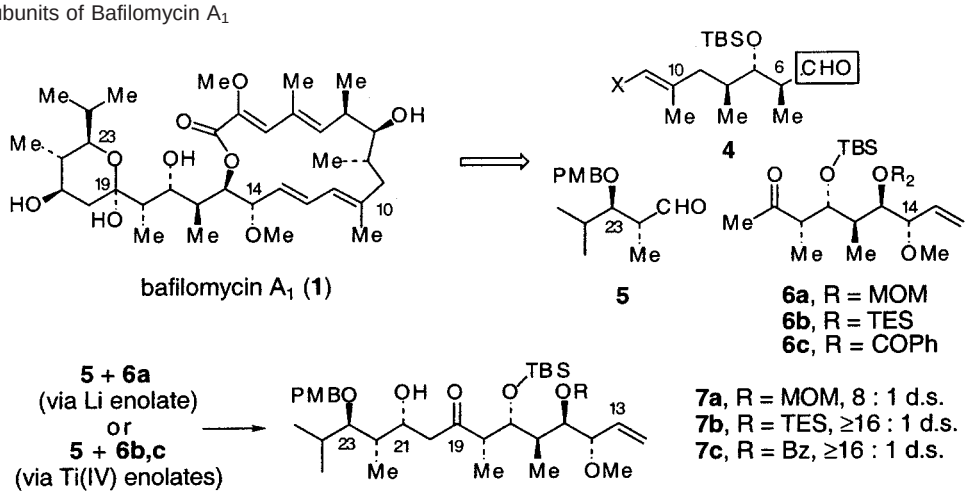
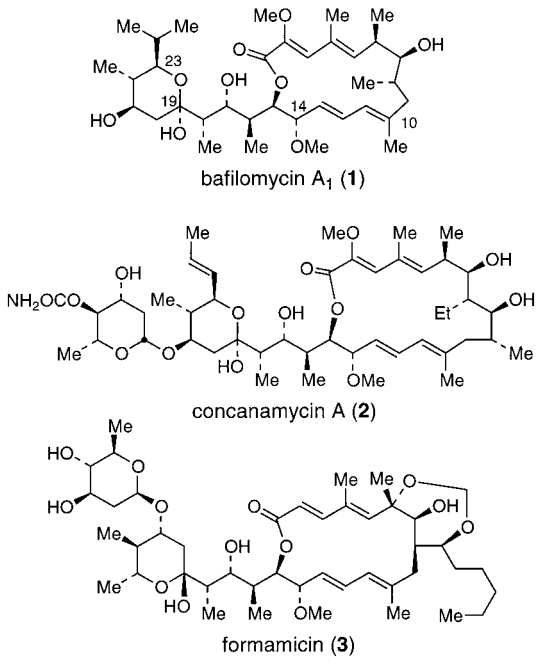
Scheme 1. Key Subunits of Bafilomycin A_1



mycin analogues[29−31] have also appeared. We report the details of our total synthesis of bafilomycin A_1, a preliminary account of which was published in 1999.[32]



Chemistry

Evolution of the Synthetic Strategy. From the outset, our strategy focused on the synthesis of bafilomycin A_1 from three key subunits: **4**, corresponding to the C(5)−C(11) segment of the natural product; aldehyde **5**, the C(21)−C(25) fragment; and methyl ketone **7**, the C(13)−C(20) unit. In studies described in detail elsewhere,[27,28,33] we established that the C(13)−C(25) segment could be synthesized with 8:1 selectivity (for **7a**), via the aldol reaction between **5** and the lithium enolate of **6a**, or with ≥ 16:1 selectivity (for **7b** or **7c**), by the coupling of **5** and the chlorotitanium enolates of **6b** or **6c**. We also found that the stereoselectivity of the lithium enolate aldol couplings was strikingly dependent on the C(23) protecting group of the aldehyde **5**, as well as on the nature of the functionality at C(15) of the methyl ketone fragment. Most troublesome, however, was our inability to devise a suitable means of protecting the C(19)-carbonyl group of intermediates such as **7**, which would be required if **7** were to be used as an intermediate for further elaboration to the natural product. Accordingly, we decided to postpone the aldol reaction between **5** and the C(20) methyl ketone until after fragments **4** and **6** were coupled via the C(10)−C(14) diene. We recognized that it would be preferable to postpone the aldol step until after the bafilomycin macrocycle was assembled, since this approach would minimize protecting group manipulations of the C(15)-hydroxyl group (Scheme 1).

On the basis of this analysis, we targeted the fully elaborated macrocyclic methyl ketone **8** as a key synthetic intermediate. We envisaged that **8** could be assembled via macrocyclization of the seco ester precursor **9**[34] and that **9** in turn could be generated by coupling of suitably functionalized fragments deriving from **4** and precursors to **6**. Two distinct olefination sequences were envisaged. One involved the Horner[35] coupling of **10a** and aldehyde **11** or, equivalently, the modified Julia coupling of **11** and the allylic sulfone **10b**.[36] The second strategy would utilize the Suzuki cross coupling reaction of vinyl iodide **12** and vinylboronic acid **13** (Scheme 2).[37]

Both of these olefination strategies were explored during the course of this synthesis. However, despite extensive efforts to implement the Horner and the Julia olefination sequences, these approaches were ultimately abandoned, since we were unable to devise a high-yielding and highly stereoselective synthesis of the targeted (*E*,*E*)-diene system by using these reactions; a summary of these efforts is provided in the Supporting Information. Consequently, we focus here on the Suzuki cross-coupling strategy for completion of the bafilomycin A_1 total synthesis.

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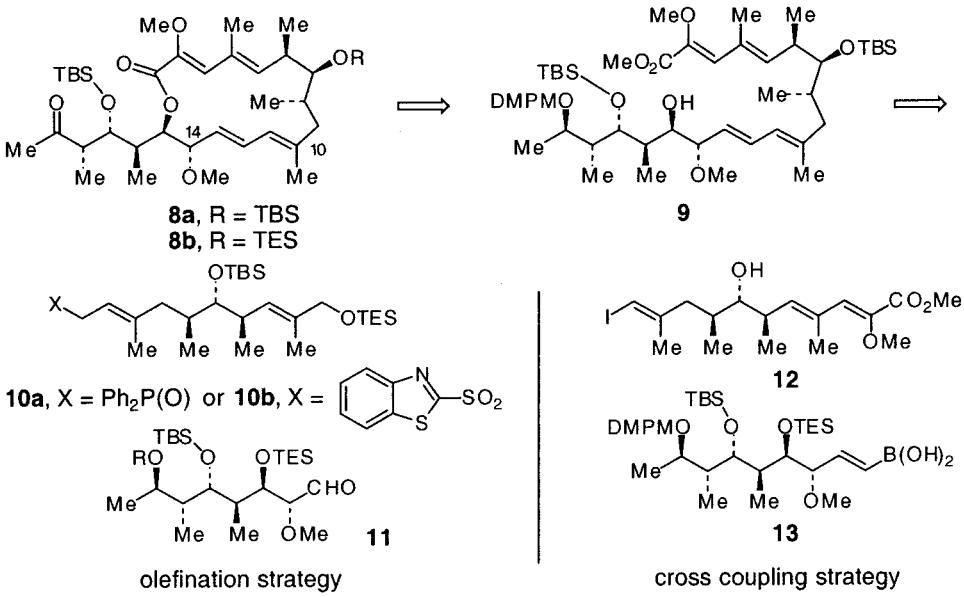
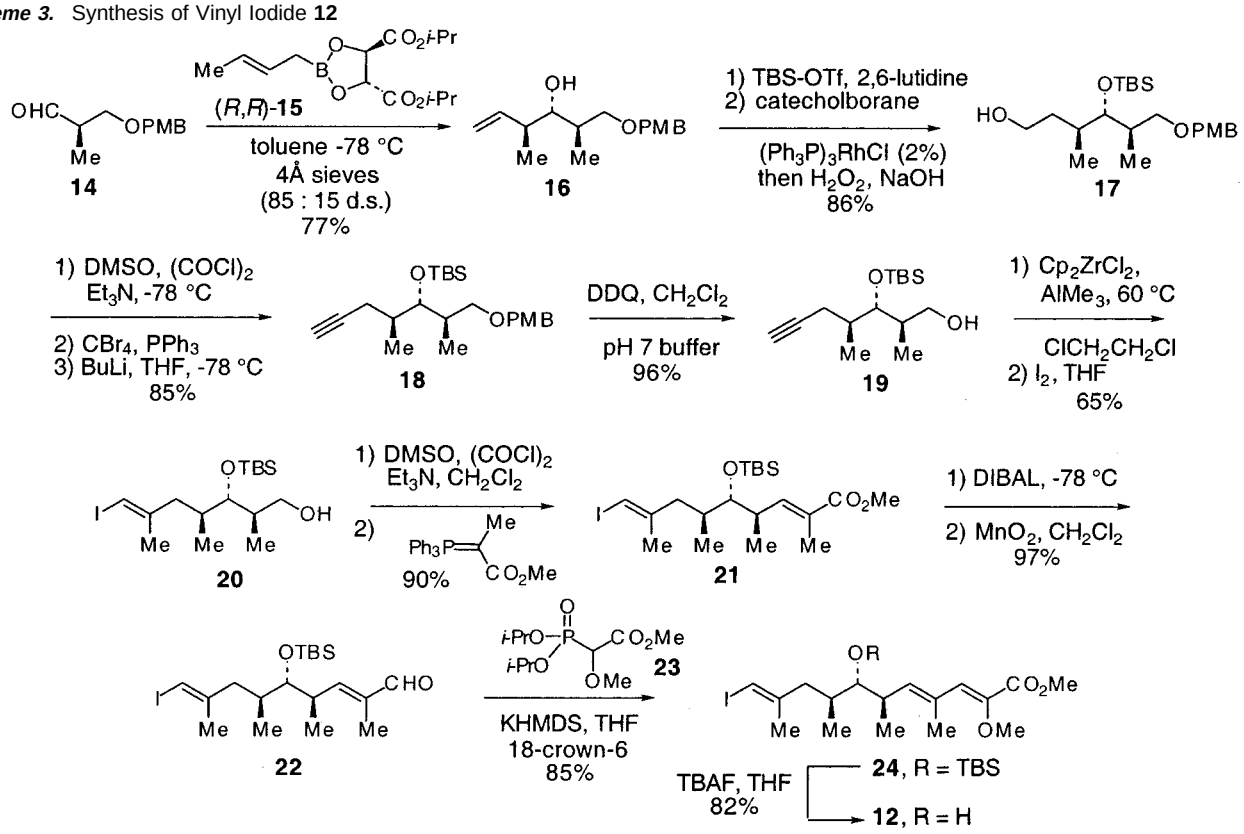
Scheme 2. Key Synthetic Intermediates



Scheme 3. Synthesis of Vinyl Iodide **12**



Transition metal-mediated cross-coupling reactions have been used in many natural product syntheses.[37,38] The Stille reaction, in particular, has proven to be extremely useful for the synthesis of structurally complex intermediates and targets. Indeed, Evans,[13,14] Toshima,[17] and recently also Hanessian[18] employed Stille cross-coupling reactions to generate the (*E*,*E*)-dienes in their syntheses of bafilomycin A_1. In contrast, there are far fewer applications of the Suzuki reaction for the late-stage union of complex intermediates—the most notable of the limited examples being those in Kishi's palytoxin synthesis[39] and Evans' rutamycin B synthesis.[40] The cross coupling reactions of **12** and **13** reported herein thus expands the number of successful applications of the Suzuki cross-coupling reaction for the late-stage union of highly functionalized intermediates in the total synthesis of complex natural products.

Synthesis of Vinyl Iodide 12. Vinyl iodide **12** was synthesized starting from the known aldehyde **14**[41] by a route that

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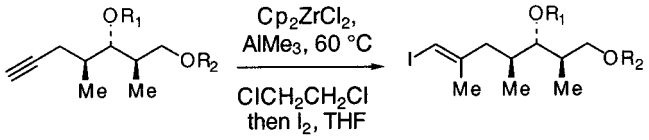
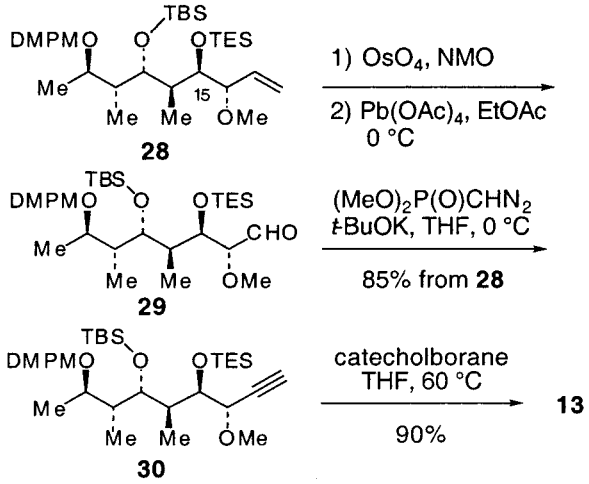
features the synthesis of the challenging anti−anti stereotriad[42,43] by using our diastereoselective aldehyde crotylboration technology[44] in the mismatched manifold (Scheme 3).[45] Thus, the double asymmetric reaction of **14** and (*R*,*R*)-diisopropyl tartrate (*E*)-crotylboronate (**15**) provided an 85:15 mixture of **16** and its 3,4-anti-4,5-syn diastereomer (77% isolated yield of **16**). The free hydroxyl group of **16** was protected as a *tert*-butyldimethylsilyl (TBS) ether, and then the vinyl group was converted to the primary alcohol in **17** via Rh(I)-catalyzed hydroboration with catecholborane.[46] Oxidation of **17** using the standard Moffatt−Swern conditions[47] provided the corresponding aldehyde that was then transformed smoothly to alkyne **18** by using the Corey−Fuchs protocol.[48] The *p*-methoxybenzyl (PMB) ether was removed (96%) by using the standard DDQ protocol,[49] and then the alkynol **19** was converted to vinyl iodide **20** using Negishi's carbozirconation methodology (65%).[50] It was necessary to use 1,2-dichloroethane as the reaction solvent, as the reaction was considerably slower and gave significantly diminished yields when performed in CH_2Cl_2 at reflux (40 °C). Interestingly, the Negishi reaction also proved to be very sensitive to the presence of a free hydroxy group in the substrate. The reaction was entirely unsuccessful using **18** or **25** in which both hydroxyl groups were fully protected. Diol **26** proved to be the best substrate and gave the vinyl iodide **27** in 91% yield.[17] However, intermediate **27** was not pursued, owing to the additional steps that would be required to differentiate the two hydroxyl groups for use of this compound in the bafilomycin synthesis.



	yield	Product
18, R_1 = TBS, R_2 = PMB	0%	--
25, R_1 = TBS, R_2 = TES	0%	--
26, $R_1 = R_2$ = H	91%	**27**
19, R_1 = TBS, R_2 = H	65%	**20**

Vinyl iodide **20** was elaborated to enoate **21** in 90% yield via Moffatt−Swern oxidation and stabilized Wittig olefination using $Ph_3P{=}C(Me)CO_2Me$ in toluene at 60 °C. DIBAL reduction of the ester gave the allylic alcohol, which was oxidized to the enal **22** by using MnO_2 (97% for the two steps). Finally, the dienoate unit was introduced with greater than 95:5 (*Z*,*E*:*E*,*E*)-selectivity (85% yield) by using a Horner−Wadsworth−Emmons reaction with $(i\text{-PrO})_2P(O)CH(OMe)CO_2Me$ (**23**) in the presence of $KN(SiMe_3)_2$ (KHDMS) and 18-crown-6 in THF, using the conditions developed by Paterson for the installation of this unit in his concanamycin A synthesis.[51] Selectivity for **24** was only ca. 2:1 when the corresponding dimethylphosphonate reagent was employed. Because initial macrolactonization experiments indicated that the C(7) TBS ether prevented cyclization (vide infra), the offending TBS group was removed by treatment of **24** with TBAF to generate vinyl iodide **12** (82%).

Synthesis of Vinylboronic Acid 13. Vinylboronic acid **13** was synthesized starting from homoallylic TES ether **28**, which we had initially prepared during our studies on the fragment assembly aldol reaction of **5** and **6** en route to the C(13)−C(25) segment of the natural product.[33] Oxidative cleavage of the vinyl group to give aldehyde **29** was accomplished by olefin dihydroxylation followed by cleavage of the diol with $Pb(OAc)_4$. Oxidative cleavage of the diol with $NaIO_4$ resulted in epimerization at C(14) of sensitive α-methoxy aldehyde **29**; epimerization at C(14) was also observed when **29** was prepared by ozonolysis of **28**. The fully protected aldehyde **29** was smoothly converted to the corresponding alkyne **30** by using the Gilbert−Seyferth α-diazomethylphosphonate reagent.[52,53] The synthesis of vinylboronic acid **13** was then completed by hydroboration of **30** with catecholborane.



Fragment Assembly and Macrocyclization−Initial Studies. The Suzuki coupling of vinyl iodide **12** and vinylboronic acid **13** was performed by using TlOH as the base and provided the (*E*,*E*)-diene **31** in 80% yield.[54] Deprotection of the C(15)-TES ether by using trifluoroacetic acid (TFA) in THF/water provide the seco ester in 85% yield. Saponification of the methyl ester with 1 N KOH in dioxane then provided the unpurified seco acid that was treated with 20 equiv of 2,4,6-trichlorobenzoyl chloride and 40 equiv of $i\text{-Pr}_2NEt$ in THF.[55] Large excesses of both the acid chloride and base were necessary to prevent symmetrical anhydride formation, which we have isolated and found to be relatively unreactive under the macrocyclization conditions. This phenomenon has also been observed in the hygrolide synthesis by Yonemitsu.[21] The THF used in the formation of the mixed anhydride was removed and replaced

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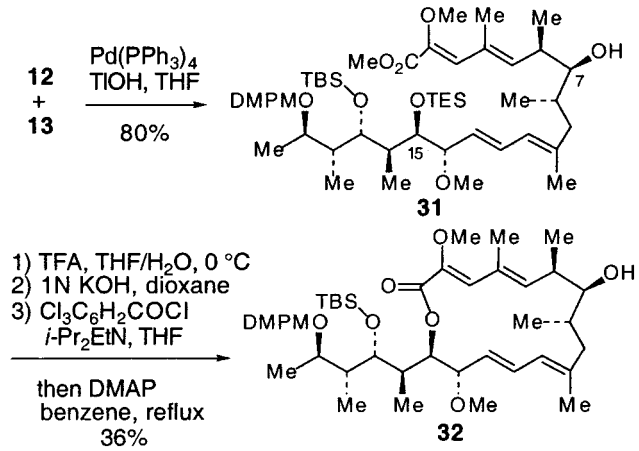
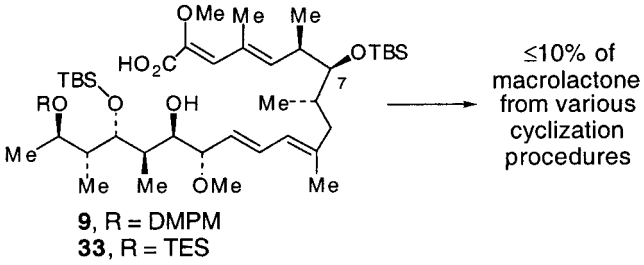
with benzene, DMAP was added, and the resulting solution was heated to reflux for 15 h, thereby providing macrolactone **32** in 45% yield from the seco ester (36% yield from **31**).

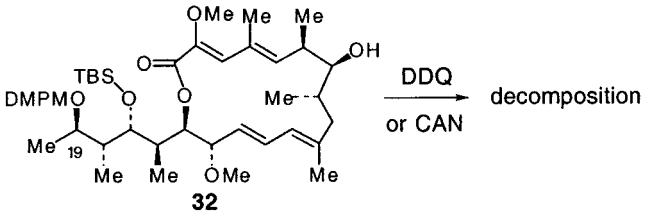


Critical to the success of this macrolactonization is the fact that the C(7)-hydroxyl is unprotected in the lactonization substrate. Earlier attempts to effect macrolactonization of seco acids **9** or **33** with C(7)-TBS ethers were largely unsuccessful.[56] In one case (cyclization of **9**, R = DMPM, using the Yamaguchi mixed anhydride protocol),[55] the 16-membered lactone was obtained in ca. 10% yield. However, this result could not be reproduced, and no lactone was obtained under any of the other conditions examined.[57]



Inspection of the X-ray crystal structure[11,12] of bafilomycin A_1 reveals that the C(7)-hydroxyl is axial with respect to the plane of the relatively flat 16-membered macrocycle. Moreover, inspection of molecular models indicated that the C(7)-TBS ether protecting group experiences destabilizing interactions with the pseudoequatorial C(6) methyl or the C(9) methylene groups, depending on the conformation of the C(7)-OSiMe$_2$*t*-Bu unit. Accordingly, we presume that the C(7)-OTBS unit influences the conformational distribution of seco acid **33**, such that the precyclization conformer required for macrocyclization is less significantly populated than is the case with the seco acid precursor to **32**, which lacks the offending C(7)-OTBS group. This analysis is consistent with Evans' observation that the macrocylization of his bafilomycin seco acid containing a C(7)-OTBS protecting group took 7 times longer (72 h) than the cyclization of the seco acid where the C(7)-OH is unprotected (10 h).[14]

Another issue concerning protecting groups was immediately encountered during attempts to remove the dimethoxybenzyl ether (DMPM) protecting group from macrolactone **32**: all conditions explored to unmask the C(19) hydroxy group of **32** promoted substantial decomposition (DDQ, wet CH_2Cl_2; Ce-$(NH_4)_4(NO_3)_6$; $MgBr_2 \cdot OEt_2$, Me_2S, etc.). We presume that allylic oxidation of the dienylic methyl ether unit is a facile process with strong oxidants such as DDQ or CAN[58] and that nucleophilic conditions are harmful to the macrocycle. It is interesting to note that attempted DDQ deprotection of seco ester **31** also resulted in decomposition, while deprotection of the DMPM ether of allylic methyl ether **30** proceeds in 94% yield.

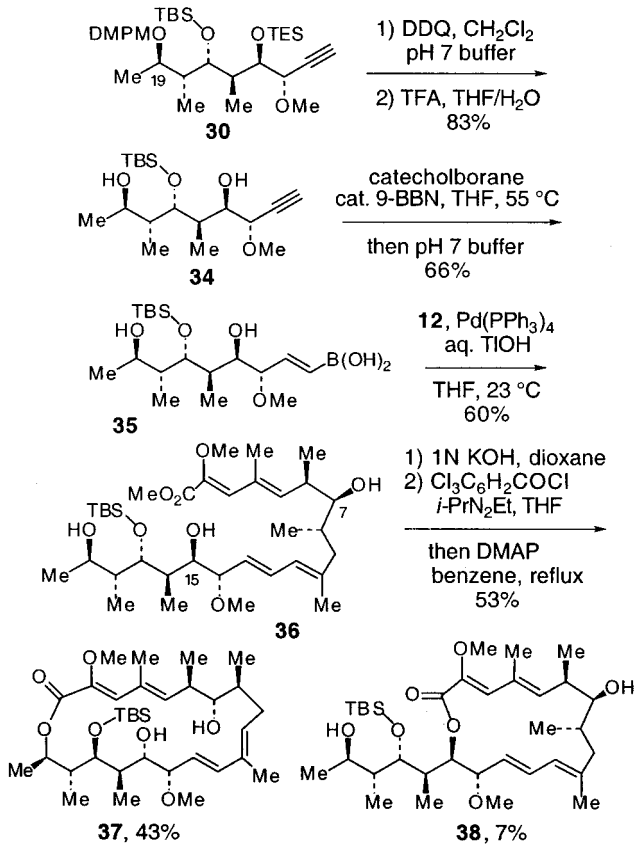


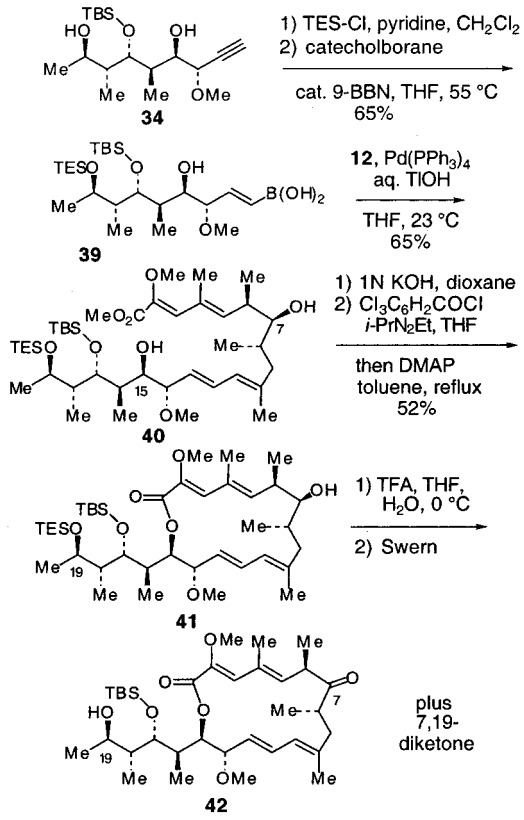
Revisions of the Protection Group Scheme. Our experience with attempted deprotections of macrocycle **36** and its seco ester precursor **31** necessitated that the offending DMPM group be removed before the macrocylization. Because free hydroxyl groups are fully compatible with the Suzuki cross coupling protocol, we anticipated that it might be possible to proceed with C(19)-OH unprotected. Accordingly, the DMPM group of alkynyl methyl ether **30** was removed using DDQ and the C(15)-OTES ether was hydroylzed under acidic conditions, giving diol **34** in 83% yield. This intermediate was hydroborated using catecholborane and a catalytic amount of 9-BBN, which provided vinylboronic acid **35** after aqueous workup and column chromatographic purification.[59]

The Pd(0)-mediated cross-coupling of vinylboronic acid **35** and vinyl iodide **12** proceeded smoothly, giving the seco ester **36** in 60% yield (unoptimized). We hoped that the macrocyclization of the seco acid derived from **36** would close preferentially on C(15)-OH to give the 16-membered macrolide **38**, rather than on C(19), which would provide the 20-membered macrocycle **37**. In the event, however, saponification of **36** and cyclization of the resulting seco acid using the modified Yamaguchi conditions provided the undesired 20-membered lactone **37** in 43% yield, along with only 7% of the desired 16-membered macrocycle **38**. We also were unable to develop conditions to effect isomerization of **37** to **38**, although ring contractions of this type have been demonstrated previously in both the *iso*-bafilomycin and scytophycin series.[60,61]

Synthesis of Macrocylic Methyl Ketone 8b. It was clear from the results with **31** and **36** that the macrocyclization substrate must have an easily removable protecting group at C(19). Accordingly, we elected to protect the C(19)-OH as a triethylsilyl (TES) ether. Thus, the less hindered C(19)-hydroxyl of diol **34** was selectively protected by treatment with TES−Cl and pyridine (92% yield). Hydroboration of the alkyne using

(56) Macrocyclization substrate **33** was synthesized from intermediates generated from the Horner and modified Julia coupling sequences.
(57) Attempts to cyclize seco acids **9** and **33** were performed using the following conditions: trichlorobenzoyl chloride, Et_3N, DMAP, benzene, reflux; 2-chloro-*N*-methylpyridinium iodide, Et_3N, CH_3CN or CH_2Cl_2; BOP−Cl, Et_3N, CH_2Cl_2 or toluene; DCC, DMAP; and DCC, DMAP·HCl, CH_2Cl_2.
(58) Examples of DDQ oxidation of allylic PMB ethers that give enone products: (a) Kanda, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1993**, *115*, 6451. (b) Trost, B. M.; Chung, J. Y. *J. Am. Chem. Soc.* **1985**, *197*, 4586.
(59) Arase, A.; Hoshi, M.; Mijin, A.; Nishi, K. *Synth. Commun.* **1995**, *25*, 1957.
(60) Hanessian, S.; Meng, Q.; Olivier, E. *Tetrahedron Lett.* **1994**, *35*, 5393.
(61) Paterson, I.; Watson, C.; Yeung, K.-S.; Wallace, P. A.; Ward, R. A. *J. Org. Chem.* **1997**, *62*, 452.

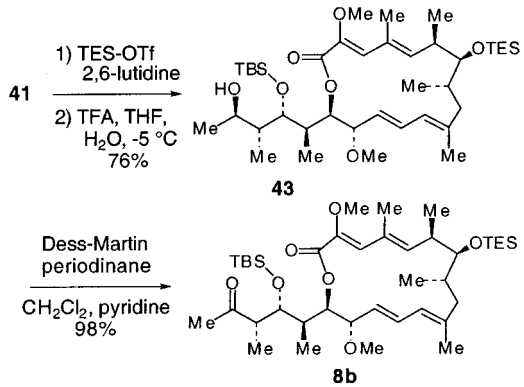




catechol borane and catalytic 9-BBN[59] then provided vinyl boronic acid **39** in 65% overall yield from **34**. The Suzuki cross coupling of **39** (1.0 equiv) and vinyl iodide **12** (1.0 equiv) using the TlOH modified conditions introduced by Kishi provided seco ester **40** in 65% yield.[54] The carboxylic ester of this intermediate was hydrolyzed, and the resulting seco acid cyclized to lactone **41** (52% overall) by application of the Yamaguchi mixed anhydride protocol.[55] Because we hoped to avoid further protecting group manipulations of C(7)-OH, and because it has been reported that the C(21) hydroxyl of bafilomycin A_1 can be oxidized selectively in the presence of C(7)-OH,[30] we removed the C(19)-TES ether under acidic conditions and then attempted to oxidize C(19)-OH of the resulting macrocycle (**38**) selectively by using the Swern protocol (the conditions that had been employed by Gatti in the selective oxidation noted above).[30] However, this two-step sequence provided the C(7)-keto−C(19)-alcohol **42** as the major product, along with the C(7),C(19)-diketone.

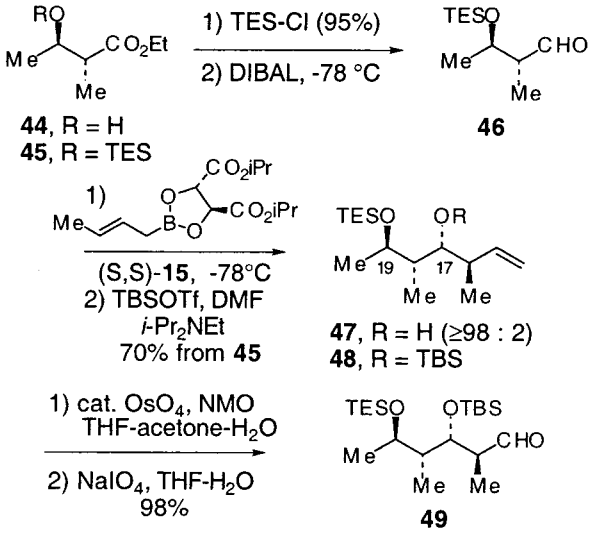
Accordingly, it was necessary to protect C(7)-OH before unmasking C(19)-OH. This was accomplished by treatment of **41** with triethylsilyl triflate (TES−OTf) and 2,6-lutidine in CH_2Cl_2 to protect C(7)-OH, followed by selective hydrolysis of the less hindered C(19)-OTES ether by exposure to trifluoroacetic acid in THF−H_2O at −5 °C.[62] This two-step sequence provided the C(19) alcohol **43** in 76% yield. Finally, oxidation of **43** using the Dess−Martin reagent[63] provided the targeted methyl ketone **8b** in near quantitative yield (98%).

Second-Generation Synthesis of Vinylboronic Acid 39. Although we had developed a successful synthesis of methyl ketone **8b**, it was disappointing that a considerable number of protecting group manipulations were required in order to orchestrate carefully the functionality at C(7), C(15), and C(19) to facilitate both the macrolactonization and the ultimate deprotection of C(19)-OH prior to the oxidation step that delivered methyl ketone **8b**. The synthesis of vinylboronic acid **39**, although highly stereoselective, required seven steps from intermediate **28**, which in turn was synthesized by a 10-step sequence starting from methyl (2*R*,3*R*)-2-methyl-2-hydroxybutyrate (**44**).[33] While it was readily apparent that replacement of the C(19)-DMPM ether by a C(19)-TES ether could be accomplished at the beginning of the synthesis, thereby saving two steps in the overall sequence, we also wanted to minimize manipulations of C(15)-OH and especially to avoid the vinyl to alkynyl conversion employed in the elaboration of **28** to **30**. We suspected that the latter two issues could be confronted simultaneously if we used a γ-methoxy-substituted allenylmetal reagent for the synthesis of these intermediates, rather than the γ-methoxyallylchromium reagent employed in the synthesis of **28**.[33,64]

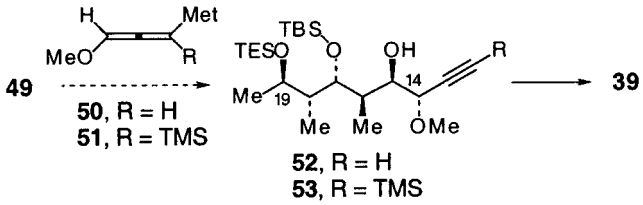


(62) Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031.
(63) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

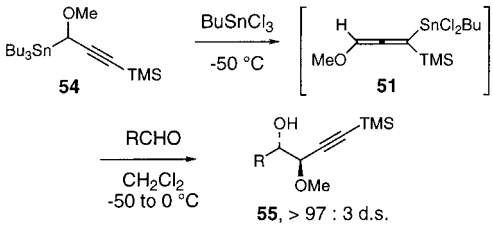
The synthesis of aldehyde 49 with a C(19)-TES ether protecting group was performed starting from the known ethyl ester **44**.[65] Thus, protection of the free hydroxyl group of **44** as a TES ether provided **45** in 95% yield. Controlled reduction of the methyl ester by using DIBAL in CH_2Cl_2 at −78 °C then provided aldehyde **46**, which was used immediately in the subsequent (*E*)-crotylboration reaction with (*S*,*S*)-**15** and provided the expected 16,17-anti homopropargyl alcohol **47**.[44] However, protection of the C(17)-hydroxyl of this intermediate was surprisingly difficult. When standard conditions were employed for this step (e.g., TBS−Cl, imidazole, DMF or TBS−OTf, CH_2Cl_2, *i*-Pr_2NEt), the C(17,19)-bis-TBS ether corresponding to **48** was obtained as the major product. However, when the silylation of **47** was performed by using TBS−OTf and *i*-Pr_2NEt in DMF,[66] the trans-silylation of the C(19)-OTES ether was suppressed and the mono-TBS ether **48** was obtained in good yield. Finally, two-step oxidative cleavage of the vinyl group delivered aldehyde **49** in near-quantitative yield.



The reactions of aldehydes with allenylmetal reagents have been extensively studied in recent years.[67−69] Especially noteworthy are Marshall's elegant studies and synthetic applications of chiral allenyltin reagents, with which homopropargyl alcohols are obtained with excellent selectivity in reactions with chiral aldehydes.[67,68,70,71] Accordingly, we were interested in developing the reaction of chiral aldehyde **49** with a suitable alkoxy-substituted allenylmetal reagent **50** as a means of synthesizing *anti*-α-methoxy homopropargyl alcohol **52**, the immediate precursor to vinyl boronic acid **39**. The literature reveals examples of reactions of aldehydes with γ-alkoxyallenyl zinc and α-alkoxypropargyl titanium reagents that proceed with modest (≤4:1)[72] to good (7:1 to 19:1)[73] selectivity for the targeted *anti*-diol mono ether units, respectively. However, this level of stereoselectivity is less than what we hoped to achieve in the synthesis of **52**. Moreover, scant information was available to enable us to judge the potential of the *racemic* allenyl zinc and titanium reagents of type **50** to react with good selectivity with chiral aldehydes such as **49**.[74] Accordingly, we sought to prepare an allenylstannane reagent **50**, since we anticipated that it might be possible to devise a route to the nonracemic reagent, if needed to achieve good results in the reaction with **49**.[75]



Because existing methods for synthesis of γ-alkoxy allenylmetal reagents are incompatible with R = H in **50**, we elected to employ the TMS-substituted allenylmetal reagent **51** as a surrogate. After examining a number of possibilities, we settled on the choice of Met = $SnBuCl_2$ in **51**.[76] Key to our synthesis of **51** is the facility with which propargylstannanes isomerize to allenylstannanes under Lewis acidic conditions.[71,77] Accordingly, the α-methoxyprogargyl stannane **54** serves as a stable, isolable precursor to **51**, which is generated in situ by treatment with $BuSnCl_3$. Subsequent addition of a range of simple aldehydes provided the targeted *anti*-diol monoethers **55** with ≥97:3 selectivity.[76]



A literature report indicates that racemic **54** can be synthesized by treatment of propargyl methyl ether **56** with *t*-BuLi and then addition of Bu_3SnCl.[78] However we were not able to obtain isomerically pure **54** by using this method; a mixture of the allenylstannane and propargylstannane was obtained from this procedure. Accordingly, we prepared **54** by transmetalation of the intermediate progaryllithium species with zinc chloride.[79] The resulting allenylzinc reagent was then treated with Bu_3SnCl to give the α-methoxy propargylstannane **54** in 97% yield and with only traces of the allenylstannane regioisomer. However, attempts to prepare a highly enantioenriched version of **54** thus far have eluded us.[80]

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(74) A recent report by Normant indicated that a 48:33:19 mixture of diastereomers is obtained in the reaction of an alkoxyallenylzinc reagent with α-(*tert*-butyldimethylsilyloxy)phenyl acetaldehyde: Poisson, J.-F.; Normant, F. H. *Org. Lett.* **2001**, *3*, 1889.
(75) A recent report by Normant indicted that nonracemic allenylzinc reagents can be prepared by kinetic resolution: Poisson, J.-F.; Normant, F. H. *J. Am. Chem. Soc.* **2001**, *123*, 4639.
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(78) Anies, C.; Lallemand, J.-Y.; Pancrazi, A. *Tetrahedron Lett.* **1996**, *37*, 5519.
(79) Zweifel, G.; Hahn, G. *J. Org. Chem.* **1984**, *49*, 4565.
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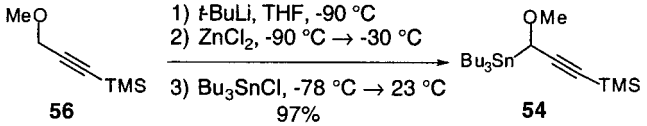
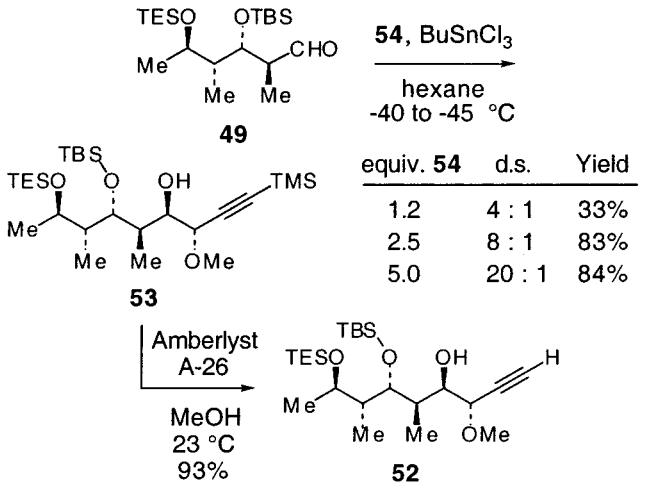


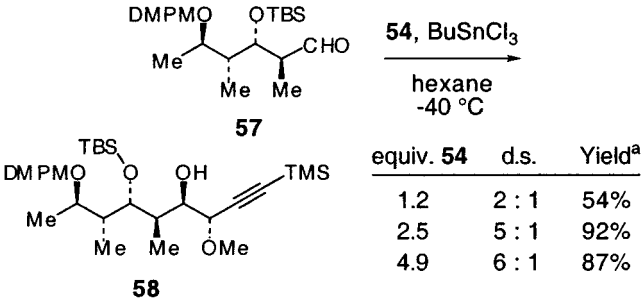
56 54

Even though we were unable to develop an enantioselective synthesis of **54**, it was apparent that an opportunity existed for kinetic resolution of racemic **54** in the reaction with chiral aldehyde **49**:[75,81] if the rates of reaction of the two enantiomers of the derived allenylstannane **51** with **49** are sufficiently distinct, it should be possible to obtain homopropargyl alcohol **53** with excellent diastereoselectivity. In the event, treatment[76] of aldehyde **49** with 1.2 equiv of α-methoxyprogargyl stannane **54** in hexane at −40 to −45 °C provided **53** with 4:1 diastereoselectivity, but in only 33% yield. The selectivity increased to 8:1 when 2.5 equiv of the propargylstannane reagent was used, and impressively, 20:1 selectivity was achieved when 5 equiv of the propargylstannane reagent was employed. By using the latter set of conditions, the targeted homopropargylic alcohol **53** was obtained in 84% yield after chromatographic purification. These data are strongly suggestive of a kinetic resolution, with the (*S*)-enantiomer of the intermediate allenylstannane **51** reacting with **49** at a faster rate than the (*R*)-enantiomer. Finally, treatment of **53** with K_2CO_3 in MeOH at 23 °C (1 h), or better still with Amberlyst A-26 resin in MeOH,[82] then provided the targeted terminal alkyne **52** in 89−93% yield. Homopropargylic alcohol **52** prepared by this sequence was identical to the same intermediate prepared by the selective triethylsilylation of **34** described previously.



This synthesis of **52** constitutes a significant improvement over the previous route to the same intermediate. This second-generation synthesis of **52** ultimately allows the vinylboronic acid **39** to be prepared in only nine steps from the β-hydroxy-α-methyl butyrate **44**, vs 17 steps for the first-generation sequence (also starting from **44**) via intermediate **28**.[33]

Studies are currently in progress to define the full scope and synthetic utility of the reactions of racemic **54** with chiral aldehydes. We have observed kinetic resolutions with other chiral aldehydes, but the results with **49** remain the most impressive and significant that we have achieved to date. For example, use of the related aldehyde **57**[33] in reactions with **54** results in a maximum 6:1 selectivity for the desired isomer **58**. We presume that the intrinsic diastereofacial selectivity of the chiral aldehyde contributes to the magnitude of the observed diastereoselectivity of these kinetic resolution−diastereoselective aldehyde addition processes, but additional studies must be performed in order to probe this hypothesis more fully.



(a) Isolated yield of diastereomer mixture.

Completion of the Total Synthesis of Bafilomycin A_1. Completion of the total synthesis required that we perform a stereoselective aldol reaction between an appropriately protected 2,3-*anti*-aldehyde (cf., **5**) and methyl ketone **8b**. In our previous studies, we had optimized the aldol reactions of lithium enolates of methyl ketones and had found that the best selectivity was achieved when the 2,3-*anti*-aldehyde **5** was protected as a PMB ether.[27,28,33] We had also surmized that the chlorotitanium enolate aldol technology[83] would be better suited for use with the highly functionalized methyl ketone **8**, owing to the strict requirements for chelating functionality at C(15) in the lithium enolate aldol reactions of **6**.[27,28,33] However, our inability to remove a DMPM protecting group at the stage of macrocycle **32** established that we would not be able to complete the synthesis by using the PMB-protected aldehyde **5** for the final aldol coupling with **8**. Clearly, a different protecting group strategy for the aldehyde fragment was required.

In an effort to discover a compatible β-hydroxy protecting group for the aldehyde component, a series of aldol reactions was performed using model methyl ketone **59** and variously protected aldehydes **60**. We chose to use the titanium enolate because of the high stereoselectivity of the reaction of **59** and aldehyde **5**, as we have disclosed previously.[27,28,33] Unfortunately, the aldol reactions of the chlorotitanium enolate of **59** and aldehydes **60a**−**c** provided only modest levels of diastereoselectivity, favoring the desired stereoisomer **61**. Of these aldehydes, **60c** with a TBS ether protecting group is the most desirable for use in completing the synthesis. However, an alternative tactic for coupling of **8** and the TBS-protected aldehyde would be required if **60c** were to be used in the synthesis.

Studies by Evans[84] and Paterson[85] and unpublished work from our laboratory[86] have demonstrated that 2,3-*anti*-β-hydroxy

(81) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1990**, *55*, 6246.
(82) Bach, J.; Berenguer, R.; Garcia, J.; Loscertales, T.; Vilarrasa, J. *J. Org. Chem.* **1996**, *61*, 9021.
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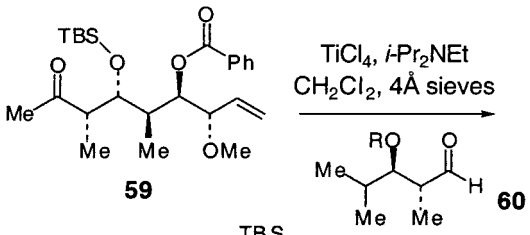
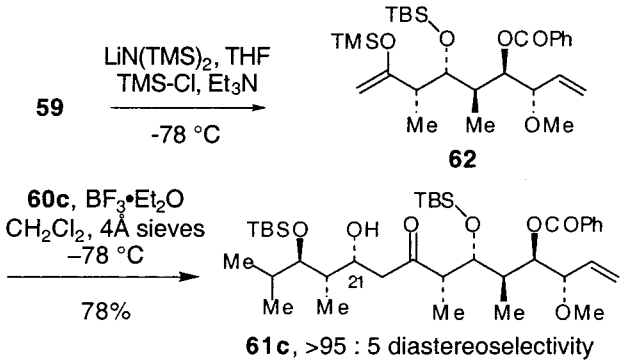


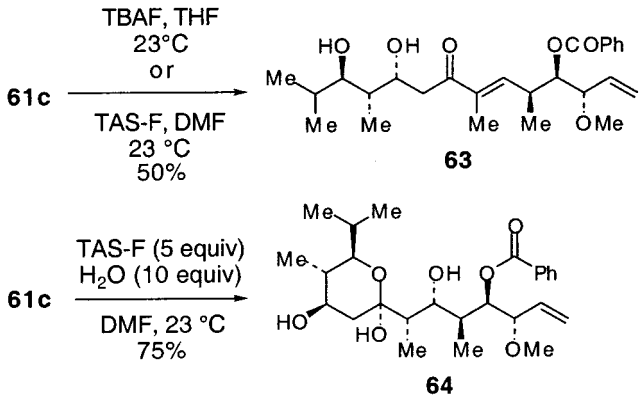
Aldehyde Protecting Aldehyde Group	Selectivity 61 : C(21)-epimer
PMB (**5**)	15 : 1
MTM (**60a**)	7 : 1
MOM (**60b**)	3 : 1
TBS (**60c**)	2 : 1

aldehydes undergo highly Felkin selective Mukaiyama aldol reactions.[87,88] Accordingly, exposure of model methyl ketone **59** to a premixed solution of TMS−Cl and Et_3N (1:1, v: v) in CH_2Cl_2 at −78 °C followed by addition of LiHMDS generated the TMS enol silane **62** in >99% yield.[61] A −78 °C solution of the crude silyl enol ether and freshly prepared aldehyde **60c**[33] was then treated with $BF_3{\cdot}Et_2O$ to provide a >95:5 mixture of aldol products favoring the desired C(21)-(*R*) isomer **61c** in 78% yield. The stereochemistry of the aldol product was assigned by using the characteristic ^{1}H NMR analysis of the ABX pattern for the protons at C(20) and C(21).[89]



Confident that the final carbon−carbon bond of the bafilomycin A_1 could be formed with excellent control over the C(21)-aldol stereochemistry, we turned our attention to finding conditions for the final deprotection sequence. It is known that *iso*-bafilomycin A_1 undergoes ring contraction when treated with TBAF,[60] and it is also known that hemiketals in the bafilomycin series are sensitive even to mild acidic conditions, especially when C(17)-OH is protected as a TBS or TES ether.[26,33] There was also concern that the hindered C(7)-OTES ether of the advanced macrocycle might be difficult to deprotect.[13,17] It was obvious, therefore, that a very mild set of conditions would be required for global deprotection of the penultimate bafilomycin synthetic intermediate.

We utilized the model aldol **61c** to probe the conditions necessary to remove the C(17)- and C(23)-TBS protecting groups. Exposure of **61c** to HF−pyridine in THF did not effect any reaction after 24 h at ambient temperature. However, treatment of **61c** with either 1.0 M TBAF in THF or tris-(dimethylamino)sulfonium difluorosilicate (TAS-F) in DMF generated the enone **63** in 50% yield.[90,91] In an attempt to moderate the basicity of the TAS-F reagent, aldol **61c** was treated with 5 equiv of TAS-F and 10 equiv of water in DMF. Remarkably, this reaction provided hemiketal **64** in 75% yield. Although the exact constitution of the reagent generated from TAS-F and water remains to be determined, this combination as well as TAS-F alone (in DMF, CH_3CN or CH_2Cl_2) has been used in our laboratories to remove silyl ether protecting groups from a variety of acid- and base-sensitive molecules.[92]



Armed with these insights, the bafilomycin A_1 total synthesis was completed as follows. Methyl ketone **8b** was converted to the corresponding TMS enol silane by treatment with LiHN-$(SiMe_3)_2$ in THF at −78 °C in the presence of TMS−Cl and Et_3N. Treatment of a −78 °C solution of the enol silane and aldehyde **60c** in CH_2Cl_2 with $BF_3{\cdot}Et_2O$ in the presence of 4 Å molecular sieves for 45 min (0.3 M final concentration) generated the penultimate bafilomycin precursor **65** with a diastereoselectivity of >95:5 (72% yield; 85% based on recovered methyl ketone **8b**). Reactions performed at lower concentrations required much longer reaction times and gave diminished yields of aldol **65**. Finally, removal of the C(17)- and C(23)-TBS ethers and the C(7)-TES ether was accomplished as planned by treatment of **65** with large excesses of TAS-F and water in DMF, thereby providing synthetic (−)-bafilomycin A_1 (**1**) in 93% yield. It is of interest to note that the deprotection of the C(17)- and C(23)-TBS ethers occurred in less than 0.5 h, but the hindered C(7)-OTES required 4−5 h for complete deprotection. Synthetic (−)-bafilomycin A_1 was identified by comparison to a natural sample by ^{1}H and ^{13}C NMR spectroscopy, IR, optical rotation, and TLC mobility in several solvent systems.

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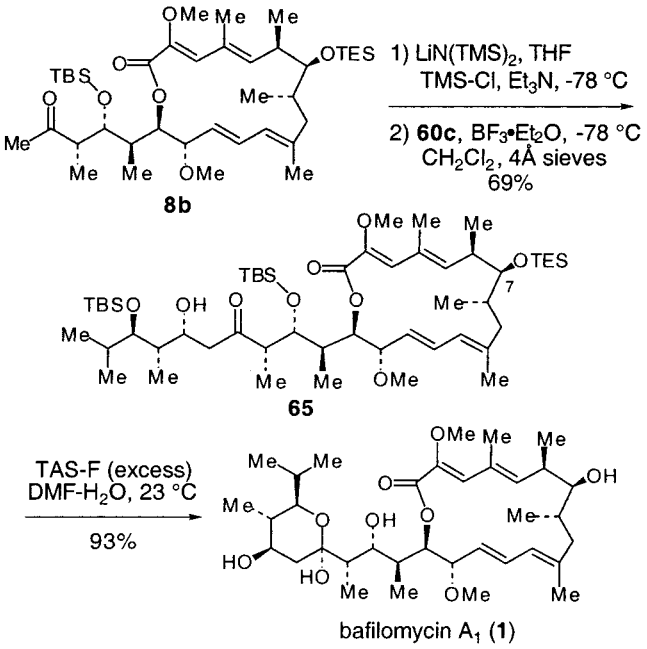
(92) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436.



Conclusion

This synthesis of bafilomycin A_1 illustrates a practical application of the asymmetric (*E*)-crotylboration and diastereoselective α-alkoxypropargylation technology developed in this laboratory. Among the number of stereocenters established using these reagents, the difficult C(6)−C(8) anti−anti dipropionate of bafilomycin was constructed in high yield with 85:15 selectivity, and the α-methoxypropargylation of **49** with the new reagent **54** set the C(14) and C(15) stereocenters with 20:1 selectivity. Furthermore, the use of the Suzuki cross-coupling reaction allowed for the convergent union of two highly functionalized intermediates. The methyl ketone aldol reaction that was utilized as the last key bond formation proceeded in high yield and excellent diastereoselectivity for the newly formed C(21) alcohol. Use of TAS-F for the final deprotection is also a noteworthy development. The synthetic strategy outlined here should be applicable to the synthesis of bafilomycin analogues not available from manipulations of the naturally available material, as well as to syntheses of related macrolide antibiotics (e.g., formamicin (**3**)).[93]

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Supporting Information Available: Complete experimental details and summaries of efforts to synthesize (*E*,*E*)-diene precursors to **9** via the Horner−Emmons and modified Julia olefination strategies (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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