Total Synthesis of Bafilomycin A_1 Relying on Iterative 1,2-Induction in Acyclic Precursors

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Abstract: The macrolide bafilomycin A_1 was synthesized starting from D-valine and D-mannitol as chiral progenitors of propionate units. Acyclic subunits corresponding to different parts of the molecule were constructed based on an iterative 1,2-asymmetric induction protocol as a distinctive feature of the synthesis. The assembly of two segments encompassing the entire carbon framework of the macrolide was achieved by using a Stille coupling. The resulting seco-ester was further manipulated to provide crystalline bafilomycin A_1 via a conventional carbodiimide-mediated Keck-type macrolactonization.

Introduction

The bafilomycins, concanamycins, and hygrolidins are a small subset of a family of 16-membered and 18-membered tetraenic macrolactones respectively that belong to the hygrolide group of macrolide antibiotics.[1] Bafilomycin A_1, **1** (Figure 1) was isolated in 1983 from cultures of *Streptomyces griseus* sp. sulfuru by Werner and Hagenmeier.[2] It exhibited inhibitory activity against G.positive bacteria and fungi.[2] It has also shown immunosuppressive activity,[3] and selective potent inhibition of vacuolar H^+-ATPases,[4] with potential applications in the treatment of osteoporosis. The structure and absolute configuration of bafilomycin A_1, **1** were established by X-ray crystallographic analysis,[5] which confirmed the earlier assignments made by Corey and Ponder[1] based on NMR data and molecular modeling. Inspection of the fine functional features in **1** reveals a unique H-bonding network involving the lactone carbonyl, the hemiacetal hydroxyl group, and an intervening C-17 hydroxyl group, which confer upon its three-dimensional structure topological features that may have important biological implications at the molecular level. Indeed, a single-crystal X-ray analysis of a Grob fragmentation product[6] in which the macrolactone remained intact and the pseudosugar unit was transformed into an ester maintained a H-bonding network similar to **1** between the C_{17} hydroxyl group and the lactone carbonyl. This product retained substantial H^+-ATPase inhibitory activity.[7] On the other hand, a ring-expanded 18-membered lactone analogue,[8] *iso*-bafilomycin A_1, in which the hemiacetal-lactone carbonyl H-bond was present, was inactive possibly due to the altered topology of the macrocycle.

The first total synthesis of bafilomycin A_1 was reported by Evans and Calter.[9] Two other syntheses have been disclosed since then by Toshima[10] and Roush,[11] and their respective groups. The synthesis of segments of bafilomycin A_1 has been reported by Paterson,[12] Roush,[13] and Marshall[14] and their respective co-workers. Total syntheses of concanamycin F[15] have been disclosed by Paterson[16] and Toshima,[17] respectively. Yonemitsu and co-workers[18] have also described the total synthesis of hygrolidin.[19]

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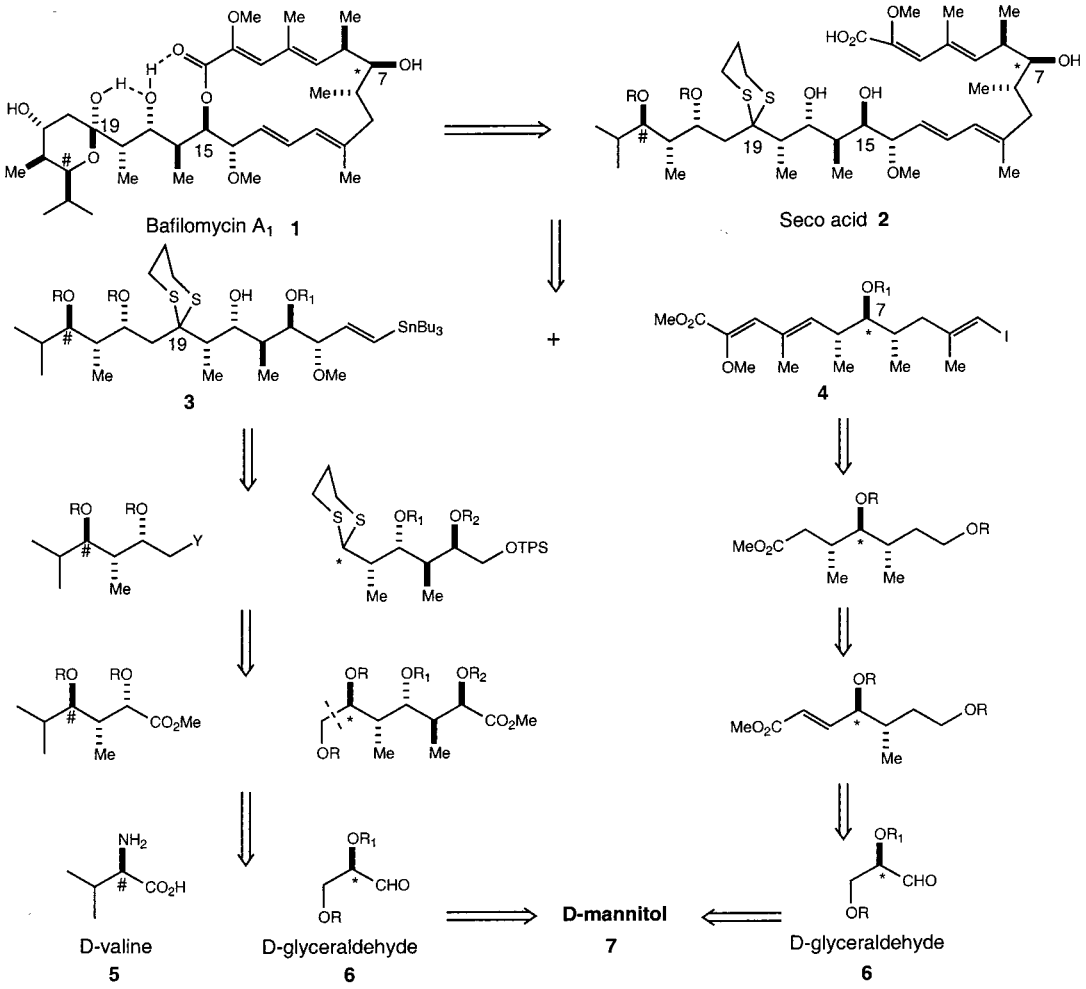

Figure 1.

The structure of **1** presents a number of challenges that must be considered as part of the synthesis plan, which we enumerate as follows: (a) four propionate units must be generated with high stereochemical control, (b) the linking of these subunits to the tetraenic portion must be based on mild C−C coupling methods, maintaining the integrity of stereogenic centers and olefin geometries, (c) once assembled, the acyclic seco-acid must be successfully converted to the macrolactone, (d) the hemiacetal function in the pseudosugar unit must be protected from β-elimination, and (e) orchestration of final steps in which the judiciously selected protective groups should uneventfully liberate the intact product. In their original paper, Werner and Hagenmeier[2] had alluded to the instability of bafilomycin A_1 under even mildly acidic or basic conditions, thus heightening the challenge of a total synthesis. The above considerations were dealt with in often elegant ways in the previously reported syntheses. Evans and Calter[9] relied on aldol constructs for the polypropionate segments, and a Stille coupling[20] to generate an intermediate macrocyclic lactone, which they engaged in a final aldol coupling to create the pseudosugar unit en route to **1**. Toshima and co-workers[10] relied on a combination of strategies, utilizing enantiopure building blocks such as (*S*)-3-hydroxy 2-methyl propionic acid, ethyl (*S*)-lactate, sugars, and aldol/Stille methodologies as in the Evans and Calter synthesis to reach the target. Roush and co-workers[11] capitalized on crotylboration as a key step for propionate triad synthesis, and assembled an intermediate macrolactone based on the Kishi modification of a Suzuki-type coupling.[21] The compatibility of protective groups and their ultimate removal have loomed as potential stumbling blocks at various stages in the previously reported syntheses. For example, silyl ethers were extensively used since their removal under mild fluoride-ion catalyzed conditions as a final step was considered "safe".[22] However, deprotection of silyl ethers at various positions proved to be problematic, and the nature of the silyl protective group was also critical.

Our disconnective analysis is shown in Figure 1 where the target structure **1** would be generated by macrolactonization of the seco-acid **2**. This was envisaged to arise from vinyl stannane **3** and vinyl iodide **4** subunits via a Stille coupling[20] followed by protective group adjustments. Subunit **3** would arise from propionate triads[23] having the required absolute stereochemistry, originating from D-valine **5** and D-glyceraldehyde **6** as chiral nonracemic starting materials. Subunit **4** would also find its stereochemical progeny in D-glyceraldehyde, thus capitalizing on a common precursor approach that originates with D-mannitol, **7**. The asterisk and pound signs designating the stereogenic centers in D-glyceraldehyde and D-valine respectively can be traced back to individual fragments, and eventually

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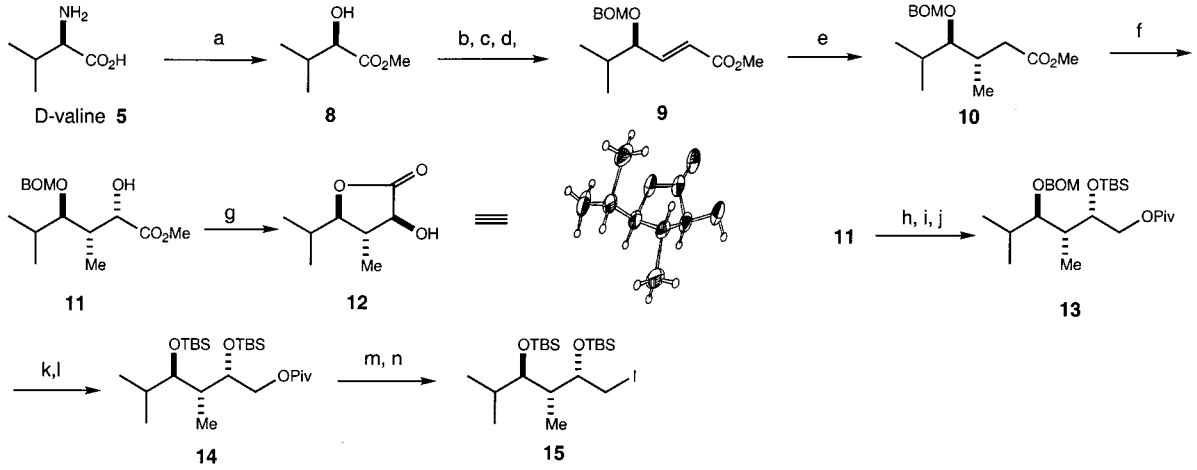
Scheme 1[a]



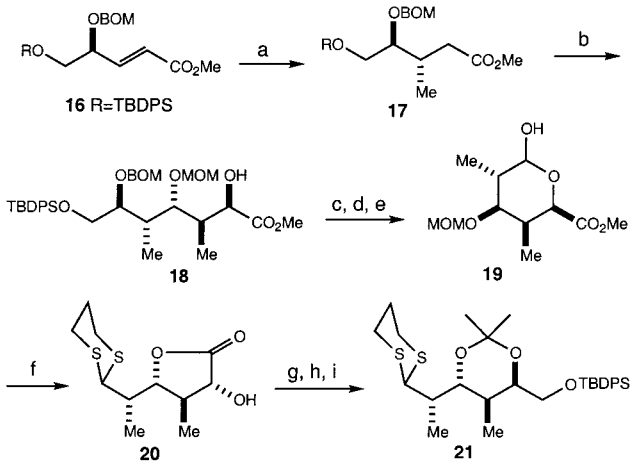
[a] Conditions: (a) $NaNO_2$, H_2SO_4, then CH_2N_2, 53%; (b) BOMCl, *i*-Pr_2NEt, CH_2Cl_2, 85%; (c) Dibal-H, toluene, 87%; (d) Swern oxidation, then $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 86%; (e) Me_2CuLi, TMSCl, THF, −78 °C, 90%; (f) KHMDS, then Davis oxaziridine, THF, 80%; (g) H_2, $Pd(OH)_2$/C, MeOH; (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 94%; (i) Dibal-H, toluene, 86%; (j) PivCl, Pyr., 88%; (k) H_2, $Pd(OH)_2$/C, MeOH; (l) TBSOTf, 2,6-lutidine, CH_2Cl_2, overall 95% for two steps; (m) Dibal-H, toluene, 91%; (n) I_2, imidazole, PPh_3, toluene, 84%.

located at C-7 and C-23 respectively of bafilomycin A_1 (Figure 1). Paramount to this strategy was the successful construction of the required propionate triads in a highly stereocontrolled manner. As an added challenge, we sought to achieve this objective by utilizing a strategy that relies on a series of iterative 1,2-inductions[24] in one- and two-directional[25,26] protocols.

Scheme 1 summarizes the synthesis of the $C_{21}-C_{25}$ subunit from D-valine. Conversion to the selectively protected γ-alkoxy-α,β-unsaturated ester **9** based on standard methodology was achieved in good overall yield. Conjugate addition of lithium dimethylcuprate as in analogous cases[27] led to the *anti*-adduct **10** as the major product in 90% yield. We have previously shown that 1,2-induction in related cuprate additions proceeded with very high stereoselectivity, regardless of the nature of the terminal carbon atom (alkoxy,[27] alkyl,[24b] or aryl[28]). Treatment of the corresponding potassium enolate with the Davis oxaziridine reagent[29] afforded the *anti/syn* adduct **11** in excellent yield and stereoselectivity. Hydrogenolysis led directly to the crystalline lactone **12**, which was suitable for single-crystal X-ray analysis, thus confirming the stereochemical outcome of the cuprate and hydroxylation reactions arising from two consecutive and highly stereocontrolled 1,2-inductions. Protection of the hydroxyl group in **11** and functional group adjustments led to the intended $C_{21}-C_{25}$ subunit as the primary iodide **15**.

The elaboration of the $C_{19}-C_{24}$ subunit as a nucleophilic dithian chiron is shown in Scheme 2. The readily available γ-alkoxy-α,β-unsaturated ester **16** prepared from D-mannitol[27] was subjected to a stereocontrolled cuprate addition to give **17** as the major product.[24,27] Consecutive cycles of enolate hydroxylation[24a] and cuprate addition afforded **18** harboring a *syn/anti/syn* propionate triad with the desired stereochemistry

Scheme 2[a]



[a] Conditions: (a) ref 27; (b) ref 24a; (c) TBAF-HOAc/THF, 95%; (d) $Pd(OH)_2$/C, MeOH, H_2; (e) NaIO4, MeOH-H_2O; (f) 1,3-propanedithol, BF_3-Et_2O, 83%; (g) $NaBH_4$, THF-H_2O, 95%; (h) TBDPSCl, imidazole, THF, 88%; (i) 2, 2-dimethoxypropane, PPTS, CH_2CI_2, 95%.

at the α-hydroxy ester site. Stereochemical confirmation was ascertained through X-ray analysis.[24a] It should be recalled that the four new stereogenic centers comprising the equivalent of two biosynthetic propionate units in **18** originate from a single center in **16** by a series of stereocontrolled sequential 1,2-inductions. We have previously commented on the remarkably stereocontrolled consecutive 1,2-inductions in growing acyclic chains comprising conjugate cuprate additions and enolate hydroxylations.[24,27] Possible transition states accounting for *anti* and *syn* groups were suggested based on preferred trajectories of approach, stereoelectronic factors, and 1,2-allylic strain. It is difficult to speculate to what extent the local conformation of the growing chain can influence the stereochemical outcome of the conjugate addition reactions. X-ray crystal structures of compounds harboring *anti*-C-methyl and hydroxyl combinations as found in C_5-C_6 of **18** reveal an antiperiplanar orientation on an extended carbon backbone. Insights into the conformational preferences of propionate triads have been recently reviewed by Hoffmann.[23] Conversion of **18** to the hemiacetal **19** was followed by treatment with 1,3-propanedithiol in the presence of BF_3-Et_2O which afforded the lactone dithiane

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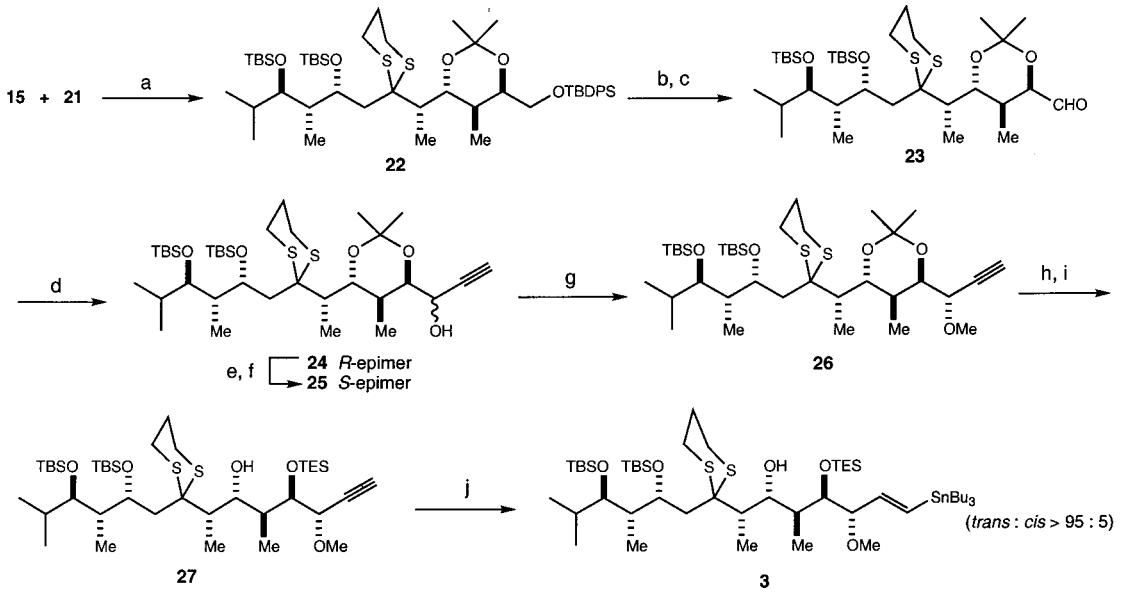
Scheme 3[a]



[a] Conditions: (a) **21**, *t*-BuLi, THF-HMPA, −78 °C, then **15**, 84%; (b) TBAF-HOAc, THF, 91%; (c) DMSO, Et_3N, SO_3·Py, toluene, room temperature, 89%; (d) ethynylmagnesium bromide, THF, −10 °C, 89%; (e) Dess-Martin, CH_2Cl_2, 92%; (f) Super-Hydride, CH_2Cl_2, −78 °C, 93%; (g) *t*-BuOK, CH_3I, THF, 86%; (h) MeOH, CSA, 86% based on 40% of recovered starting material; (i) TESCI, DMAP, THF-DMF (3:1), 89%; (j) Bu_3SnH, $PdPh_2CI_2$(cat.), THF, 87%.

intermediate **20** in excellent overall yield. Further manipulation and functional group adjustment led to the desired $C_{19}-C_{24}$ chiron **21**, ready to be coupled to the iodide **15**.

The elaboration of the entire vinyl stannane subunit **3** (Figure 1) is shown in Scheme 3. Thus, generation of the dithian anion from **21** with *tert*-butyllithium in a mixture of THF and HMPA and condensation with the iodide **15** proceeded in 84% yield. The installation of the vinyl stannane group required the introduction of an acetylenic alcohol having an *S*-configuration at C_{14}. The TBDPS ether was selectively cleaved and the resulting alcohol was oxidized to the aldehyde **23** with use of the Doering−Parikh reagent,[30] which proved to be the most efficient. The mixture of acetylenic alcohols **24** and **25** could be easily obtained by reaction of **23** with ethynylmagnesium bromide. Oxidation of the readily separated undesired *R*-isomer was done with use of the Dess−Martin reagent[31] in excellent yield, since Swern and Doering−Parikh oxidations were curiously unsuccessful. On the other hand, oxidation with MnO_2 resulted in an 80% yield of the corresponding ketone but the reaction was slow. Reduction of the ketone with Super hydride[32] led to the desired *S*-isomer, **25**, thus allowing the use of the two epimers of the acetylenic alcohols in a productive way. Methylation of **25** with t-BuOK as base gave the ether **26**. That the oxidation/reduction sequence leading to **25** had indeed proceeded with the desired stereochemical outcome would be ascertained later through completion of the synthesis of **1**. On the basis of numerous model studies in this series, it was necessary to remove the C_{15}/C_{17} isopropylidene acetal at this juncture and to use protective groups that would be removed without affecting the final target structure or intermediates leading to it. For example, cleavage of the acetal under acidic conditions in the presence of a C_{19} carbonyl led invariably to cyclic hemiacetals. In the event that the C_{23} hydroxyl group were also to become free, then the resulting dioxaspiro bisacetals would definitely hamper further progress toward the synthesis.[33] Thus, mild hydrolysis of **26** led to the corresponding diol, which was selectively converted into the C_{15} TES ether **27** in excellent yield. Finally, treatment with tributyltin hydride in the presence of a catalytic quantity of bistriphenylphosphine palladium(II) chloride[34] led to the desired vinyl stannane subunit **3** in a highly stereocontrolled manner starting from D-valine and D-mannitol and proceeding via acyclic precursors.

The construction of the vinyl iodide subunit **4** involved the use of a common chiron **17** that was transformed to **28** through a series of high-yielding steps (Scheme 4). Oxidation to the aldehyde and chain extension led to the γ-alkoxy-α,β-unsaturated ester **29**. We were now in position to extend the potential of these stereocontrolled conjugate cuprate additions and to test their efficacy in a two-directional mode.[25] Indeed, treatment of **29** with lithium dimethyl cuprate afforded a 90% yield of **30** in which the requisite (and arduously accessible)[25,35] *anti/anti* orientation was secured. Conversion of **30** to the triol **31** followed by oxidative cleavage and treatment with the propylidene phosphorane in refluxing benzene[36] led, after protection, to the *trans*-olefin **32**, which was further transformed to the pivalate ester **33** in high yield. It is of interest that an analogous olefination reaction with diethyl 2-ethoxycarbonyl phosphonopropionate in the presence of NaH in THF led to a 2:1 mixture of inseparable *trans/cis*-α,β-unsaturated esters. To further elaborate this chiron into **4**, we needed to extend the chain at both extremities. To that end, we chose to introduce the vinyl iodide functionality first. The MOM protective group in **30** was selectively removed with B-bromocatecheborane[37] to afford **35**,

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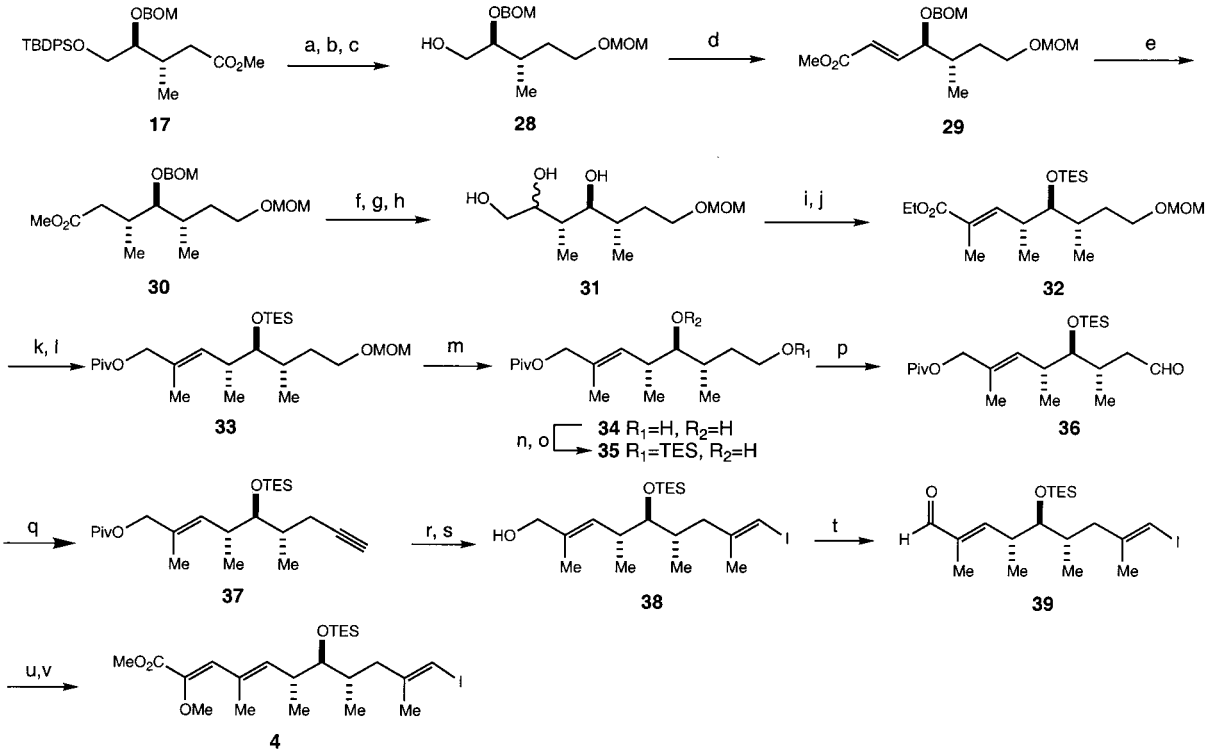
Scheme 4[a]



[a] Conditions: (a) Dibal-H, toluene, −78 °C, 89%; (b) MOMCI, Hunig's base, CH_2CI_2, 92%; (c) TBAF, THF, 92%; (d) Swern oxidation, then $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 87%; (e) Me_2CuLi, TMSCI, THF, −78 °C, 90%; (f) KHMDS, Davis' reagent, THF, 84%; (g) $LiBH_4$, MeOH, 92%; (h) H_2, $Pd(OH)_2/C$, MeOH, 90%; (i) $NaIO_4$, CH_2Cl_2(with 2% H_2O), then $Ph_3P{=}C(CH_3)CO_2Et$, benzene, reflux, 18 h, 85%; (j) TESCI, 2, 6-Lutidine, THF, 95%; (k) Dibal-H, toluene, −78 °C, 89%; (l) PivCI, Pyr., CH_2Cl_2, 95%; (m) *B*-bromocatecholborane, CH_2CI_2, −78 °C, 30% for **35**, 60% for **34**; (n) TESOTf, 2,6-lutidine, CH_2Cl_2, 95%; (o) PPTS, CH_2CI_2-CH_3OH (3:1), 93%; (p) Dess-Martin, CH_2Cl_2, 93%; (q) dimethyl (1-diazo-2-oxopropyl)phosphonate, K_2CO_3, MeOH, 91%; (r) $Cp2ZrCI_2$, Me3AI, H_2O(cat.), −30 °C, then I_2, 78%; (s) Dibal-H, toluene, −78 °C, 92%; (t) MnO_2, CH_2Cl_2, 90%; (u) methyl methoxyacetate, LiHMDS, THF, 86%; (v) MsCl, Pyr., DBU, 80%.

accompanied by a major quantity of diol **34** that was converted to **35** in a two-step procedure (Scheme 4). Oxidation to the aldehyde **36** under Dess−Martin conditions and chain-elongation to the acetylenic intermediate **37** occurred in high yield, especially with use of the diazophosphonate method[38] (97%) as compared to the venerable Corey−Fuchs procedure (72%).[39] Iodination utilizing the versatile Negishi protocol[40] followed by deesterification with Dibal-H led to the allylic alcohol **38**, which was efficiently oxidized to the corresponding α,β-unsaturated aldehyde **39** with MnO_2. Initial attempts to introduce the vinylic α-methoxy ester utilizing 2-methoxy trimethylphosphonoacetate in the presence of different bases (NaH, NaHMDS, DBU/LiBr in THF) led to equal amounts of *cis*- and *trans*-olefins which could not be separated. The desired *trans*-dienic geometry was achieved through a simple aldol condensation with lithium 2-methoxyacetate, followed by mesylation of the resulting alcohol and β-elimination. Much to our satisfaction the resulting subunit **4**, obtained in 83% yield, was stereochemically pure within the limits of our detection.[41]

With chirons **3** and **4** in hand, we were now poised to engage them in a Stille coupling[20] to produce the protected seco-ester related to **2** (Figure 1). Previous syntheses of bafilomycin A_1[9,10] relied on a Stille cross-coupling protocol to append appropriate subunits and produced segments which were further elaborated en route to bafilomycin A_1. While operationally similar, our Stille cross-coupling presented the uncertainty of having larger fully assembled reacting partners **3** and **4**, with a potentially problematic dithian group.[42] A successful coupling to produce the entire seco-ester of type **2** would still require the completion of a number of unprecedented steps comprising selective deprotections, marcrolactonization, and hemiacetal formation, without undue side reactions (ex. β-elimination, dioxaspiro bis-acetal formation, etc.). Preliminary reactions intended to survey palladium reagents to effect the catalytic Stille cross-coupling proved discouraging. Thus, no coupling or decomposition was observed with $PdCl_2(MeCN)_2$, $PdCl_2(PPh_3)_2$, or $Pd(dppf)Cl_2$. Utilizing $PdCl_2(PPh_3)_2$ or $Pd(dppf)Cl_2$ in the presence of Hunig's base afforded the desired product in 10% and 35% yields, respectively. However, using ($Pd(dppf)Cl_2$ *and* triphenylarsine[43] provided the seco-ester **40** in 60% yield.

At this juncture, it is of interest to comment on the cross-coupling reaction. It is surprising that the coupling failed with $PdCl_2(dppf)$ in DMF at 50 °C, conditions that were successful in the case of smaller vinyl iodide and vinyl stannane partners.[17a] Only after the addition of triphenylarsine[43] and Hunig's base[44] did we succeed in achieving efficient coupling of subunits **3** and **4**. Our plan to include the dithian group on the vinyl

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(41) The TBS ether variant of intermediate **4** has been synthesized by Evans and Calter utilizing asymmetric aldol and Stille coupling methodology: Calter, M. A. Ph.D. Dissertation, Harvard University, 1993; see ref 9.
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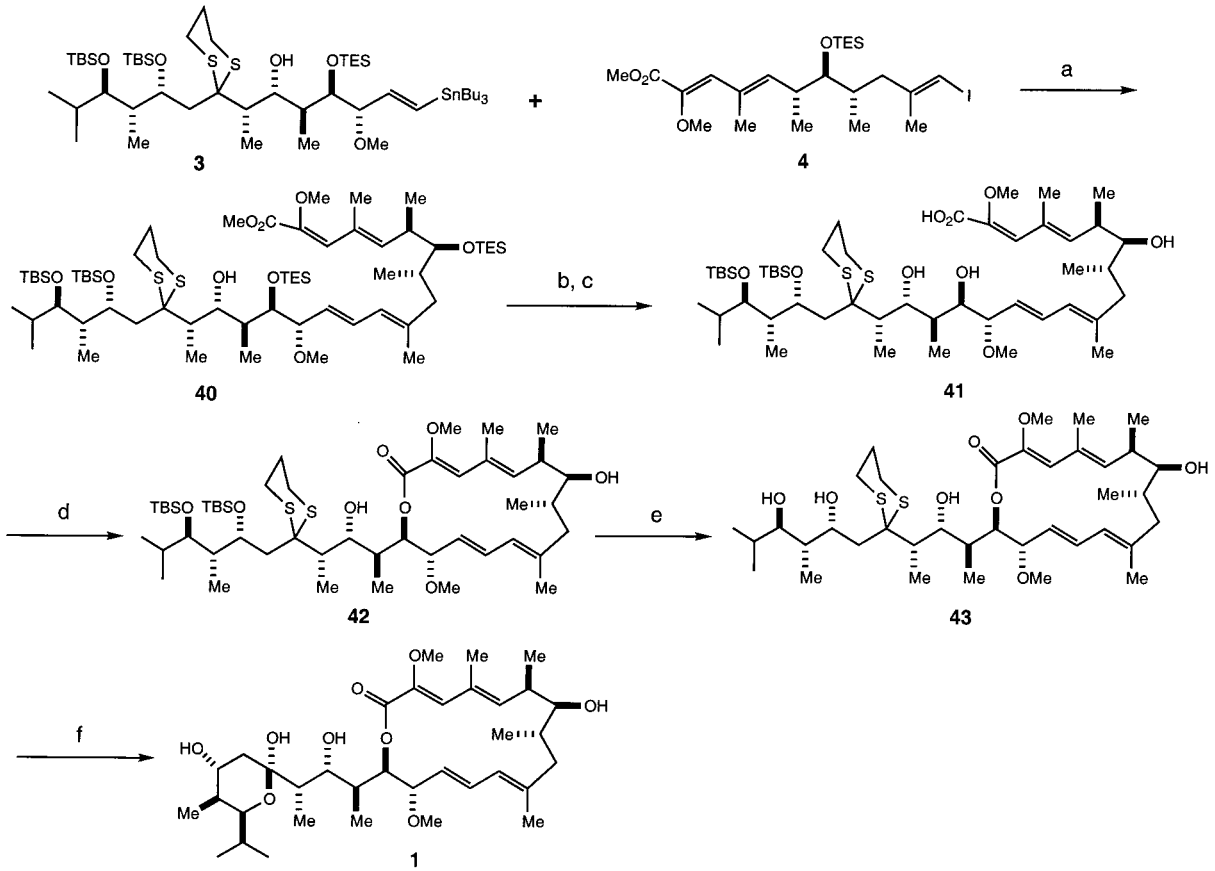
Scheme 5[a]



[a] Conditions: (a) $Pd(dppf)CI_2$, Hunig's base, $AsPh_3$, 50 °C, THF-DMF (1:1), 60%; (b) TBAF-AcOH (1:1), THF, 87%; (c) KOH, 80 °C, dioxane, 88%; (d) EDC, DMAP, reflux, CH_2CI_2, 65%; (e) TsOH, MeOH, 86%; (f) $HgCl_2$, $CaCO_3$, CH_3CN-H_2O (3:1), 85%.

stannane subunit **3** was fortuitous, since Smith and co-workers[42] have shown that ligation of a proximal dithian group in a vinyl iodide can affect the outcome of the cross-coupling reaction.

With the first of three major hurdles overcome, we proceeded onward to the target molecule, with the daunting macrolactonization in sight. To this end, we had to generate a partially deprotected seco acid **41** from its precursor **40**, which meant selective cleavage of the C_7 and C_{15} TES ethers in the presence of the C_{21} and C_{23} TBS ethers, not to mention the base-induced hydrolysis of the methyl ester to the carboxylic acid. In this event, we found that a mixture of TBAF and acetic acid was highly effective in the above-mentioned selective desilylations, and the task was rendered even easier when basic hydrolysis of the ester, even at 80 °C in aqueous dioxane, afforded the desired seco-acid **41** in excellent overall yield.

Previous syntheses[9,10] of shorter subunits of **1** have succeeded in the macrolactonization reaction adopting the Yamaguchi protocol[45] to give the desired 16-membered lactone. The macrolactonization of a *seco*-acid consisting of the entire bafilomycin A_1 carbon framework in this series was unprecedented. Model studies in the macrolactonization of bafilomycin A_2 (the methyl glycoside) *seco*-acid utilizing EDC as described by Boden and Keck[46] led to a mixture of the desired lactone, bafilomycin A_1, and the corresponding glycal resulting from elimination, in 30% yield. However, application of the same protocol to the *seco*-acid derivative **41** led to the desired 16-membered macrolactone **42** in 65% yield with no detectable amounts of the 18-membered lactone (iso-bafilomycin A_1).[8] The latter, shown to be energetically less favored by some 20−25 kcal/mol compared to bafilomycin A_1,[8] has been obtained indirectly by ring expansion via an orthoacid intermediate in the presence of an organocopper reagent, and its structure was ascertained by X-ray crystallography.[8] Fortunately, the EDC, DMAP coupling protocol developed by Boden and Keck[46] afforded the lactone **42** with no trace of *iso*-bafilomycin A_1.

There now remained to deprotect the two TBS ethers to afford the penultimate intermediate **43**, which was accomplished in the presence of methanolic *p*-toluenesulfonic acid in 86% yield. Finally, treatment of **43** with mercuric chloride and calcium carbonate in aqueous acetonitrile effected smooth dethioacetalization to afford crystalline bafilomycin A_1, identical in all respects with an authentic sample.

The fourth total synthesis of bafilomycin A_1 reported in this account highlights the power of stereochemical control in 1,2-inductions in acyclic systems. In fact, a common chiral progenitor with a single stereogenic center derived from D-mannitol was the original "inducer", eventually leading to four consecutive enantiopure centers in the C_{15}−C_{18} subunit. The three contiguous stereogenic centers in the C_6−C_8 subunit were generated from enantiopure *R*-2-hydroxy 3-methyl butyric acid, easily prepared from *R*-valine. The installation of vicinal methyl and hydroxy groups as part of four (or five) contiguous and skipped propionate subunits with high stereochemical control demonstrates the generality of the cuprate addition and enolate hydroxylation protocol through a series of 1,2-inductions starting with a single stereogenic center.[24,25] Finally, the successful application of the immensely useful Stille coupling, with highly

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functionalized units such as **3** and **4**, further attests to the great versatility of the method as a means of assembling complex natural products through vinylic intermediates.

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Supporting Information Available: Complete experimental procedures, selected ^{1}H, ^{13}C spectra,, and an X-ray structure (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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