# Total Synthesis of Bafilomycin $V_1$: A Methanolysis Product of the Macrolide Bafilomycin $C_2$

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A synthesis of bafilomycin $V_1$, a methanolysis product of the macrolide natural product bafilomycin $C_2$, is described. The route utilizes chiral nonracemic allenylzinc reagents, prepared in situ from propargylic mesylates, to access key segments of this methyl ester. The acetylenic moieties of the derived homopropargylic alcohol adducts play an important role in further elaboration of these subunits. Final assemblage of the 25-carbon chain, containing 12 stereocenters, an α-methoxy *Z,E* 1,3-dienic ester, and an additional *E,E* 1,3-diene, was achieved through Stille coupling of an acetylene-derived vinyl stannane and vinyl iodide of approximate equal complexity. Attempted cyclization of several C15 hydroxy acid derivatives to the 16-membered lactone bafilomycin $A_1$, a potent inhibitor of vacuolar ATPases, could not be achieved.

Bafilomycin $A_1$, a polyketide isolated from the fermentation broth of *Streptomyces griseus* by Werner et al. in 1984,[1] is a member of a macrolide family, which includes the bafilomycins (Figure 1), the concanamycins,[2] and the hygrolidins.[3] Structural features of the bafilomycins include a 16-membered macrolide with a tetraene core, an α-methoxy *Z,E* dienoate, 12 stereocenters, and a *β*-hydroxy hemiacetal appendage.

The bafilomycins differ in substitution on the C21-oxygen. Accordingly, bafilomycin $A_1$ is unsubstituted while bafilomycin $B_1$ contains a flavensomycinic ester and bafilomycin $C_1$ has a fumaric ester appendage (Figure 1). Bafilomycins $A_2$, $B_2$, and $C_2$ possess a methoxy substituent at C19. The stereochemistry of bafilomycin $A_1$ 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] The X-ray crystal structure revealed an interesting hydrogen-bonding network between the C17-hydroxyl and both the lactone carbonyl and the C19-hydroxyl of the hemiacetal. The solution conformation has been shown to be indistinguishable from that in the solid state.[5b]

The bafilomycins are structurally related to the concanamycins and hygrolidins, differing mainly in the C22-substituent. Accordingly, the bafilomycins are substituted with a C22-isopropyl group, the hygrolidins are substituted with an ethyl group, and the concanamycins contain a 2-propenyl appendage. The concanamycins are 18-membered lactones incorporating a "biosynthetic" butyrate moiety at C8−C9 of the carbon backbone. All of these macrolides share the hydrogen bonding motif.

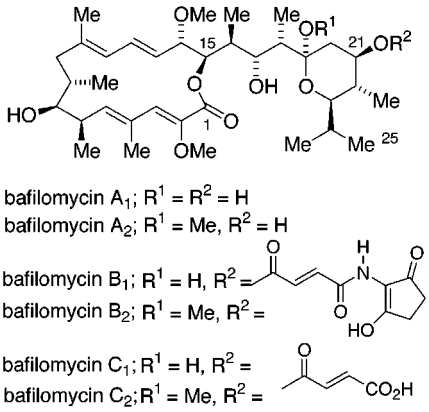


**Figure 1.** Structures of the bafilomycins.

**Biological Activity.** Bafilomycin $A_1$ is a potent and specific inhibitor of vacuolar ATPases (V-ATPases) in vitro and in vivo.[6] Given that V-ATPases are known to participate in bone resorption (i.e, the loss of bone),[6a] inhibitors of such enzymes may serve as potential treatments for osteoporosis. Structure−activity relationships (SAR) of bafilomycin $A_1$ have shown that derivatization of the C21-hydroxyl through acylation or alkylation has no effect, while the C7-hydroxyl is essential in preserving activity.[6b] The tetraene core of the lactone ring is also essential for activity as both partial and complete hydrogenation result in marked loss of activity. Several functional group modifications on the hemiacetal ring did not have a major effect on activity, but replacing the ring with an acyclic side-chain resulted in complete loss of activity. Several degradation products of bafilomycin $A_1$

(1) Werner, G.; Hagenmaier, H.; Drautz, H.; Baumgartener, A.; Zähner, H. *J. Antibiot.* **1984**, *37*, 110.

(2) (a) Kinashi, H.; Someno, K.; Higashijima, T.; Miyazawa *Tetrahedron Lett.* **1981**, *22*, 3857. (b) Westley, J. W.; Liu, C.-M.; Sello, L. H.; Evans, R. H.; Troup, N.; Blount, J. F.; Chiu, A. M.; Todaro, L. J.; Miller, P. A. *J. Antibiot.* **1984**, *37*, 1738.

(3) Seto, H.; Tajima, I.; Akao, H.; Furihata, K.; Otake, N. *J. Antibiot.* **1984**, *37*, 610.

(4) Corey, E. J.; Ponder S. W. *Tetrahedron Lett.* **1984**, *25*, 4325.

(5) (a) Baker, G. H.; Brown, P. J.; Dorgan, R. J. J.; Everett, J. R.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron Lett.* **1987**, *28*, 5565. (b) Baker, G. H.; Brown, P. J.; Dorgan, R. J. J.; Everett, J. R. *J. Chem Soc., Perkin Trans. 2* **1989**, 1073.

(6) (a) Sundquist, K. T.; Marks, S. C. *J. Bone Miner. Res.* **1994**, *9*, 1575. (b) Gagliardi, S.; Gatti, P. A.; Belfiore, P.; Zocchetti, A.; Clarke, G. D.; Farina, C. *J. Med. Chem.* **1998**, *41*, 1883.

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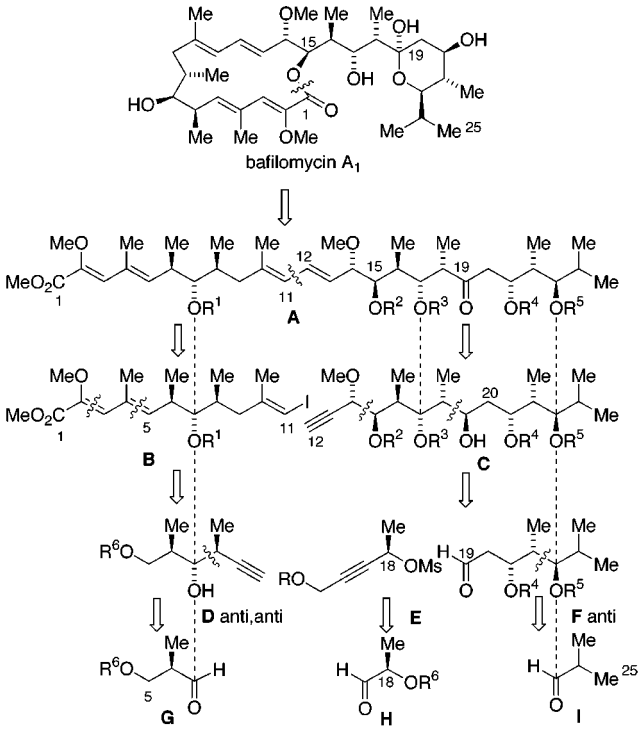


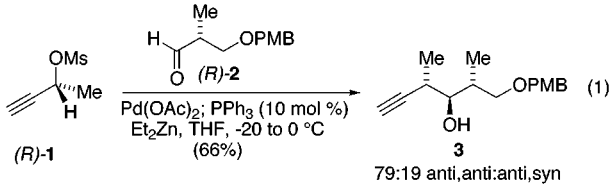

**Figure 2.** Synthetic plan for bafilomycin $A_1$.

have also been prepared; however, their SAR has not been reported to our knowledge.[7]

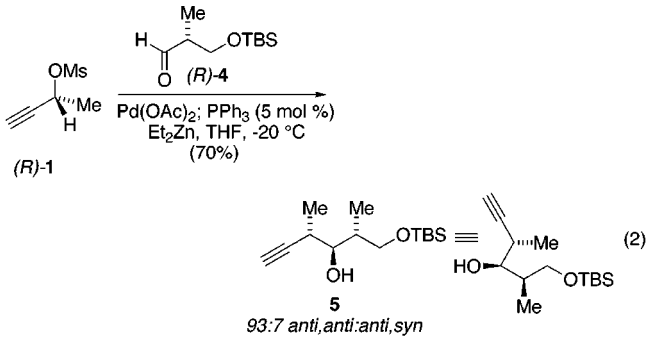
**Synthesis.** To date, three total syntheses of bafilomycin $A_1$ have been reported. The first, by Evans and Calter in 1993, took advantage of the versatility of the aldol reaction to introduce stereocenters of subunits and a Stille coupling to join key fragments.[8] The second, by Toshima and co-workers, employed Stille and aldol reactions, analogous to those of Evans and Calter, as major coupling events.[9] They assembled the subunits in a linear fashion from chiral pool materials. The third and most recent total synthesis of bafilomycin $A_1$ was achieved by Roush and co-workers in 1999.[10] They effected a stereoselective aldol condensation for fragment coupling and diastereoselective aldehyde crotylboration methodology to set subunit stereocenters.

**Synthetic Approach.** Our synthetic approach, illustrated in Figure 2, utilizes stereoselective additions of chiral nonracemic allenylzinc reagents to aldehydes **F**, **G**, and **I** for assembly of the anti,anti stereotriad **D** and the anti subunits **C** and **F**. The acetylenic moiety plays a key role in elaborations to segments **B** and **C** as well as the joining of these segments, or their equivalents, through Stille coupling of iodide **B** with a C12 vinylstannane derived from an analogue of **C**.

**Synthesis of the C1−C11 Subunit.** Our synthesis of the C1−C11 segment began with formation of the elusive anti,anti stereotriad. It was desirable to adopt an orthogonal protecting group strategy to permit an eventual selective deprotection. For this, we envisioned an addition of the allenylzinc reagent derived from mesylate *(R)*-**1** to *(R)*-α-methyl-*β*-OPMB (PMB = *p*-methoxybenzyl) propanal (**2**),[11] an aldehyde that had yet to be examined in allenylzinc stereotriad synthesis (eq 1).[12] The PMB protecting group seemed appropriate because it can be selectively cleaved in the presence of several other protecting groups such as silyl ethers and esters. Surprisingly, the addition was extremely sluggish and additional catalyst and warming to 0 °C were necessary for product formation. A disappointing 79:19 mixture of anti,anti and anti,syn isomers **3** was formed as an inseparable mixture. The selectivity of this addition is considerably lower than that involving the previously examined *β*-ODPS (DPS = diphenyl-*tert*-butylsilyl) aldehyde.[12] The anti,syn isomer derives from partial racemization of the allenylzinc intermediate, a consequence of the unreactivity of aldehyde **2**, which necessitates higher temperatures and additional catalyst for adduct formation.




Formation of a significant amount of the anti,syn diastereomer with the *β*-OPMB aldehyde prompted us to substitute an alternative protecting group in an effort to increase the selectivity. Accordingly, we examined the α-methyl-*β*-OTBS (TBS = *tert*-butyldimethylsilyl) aldehyde *(R)*-**4**[13] (eq 2). Addition of the allenylzinc reagent derived from mesylate *(R)*-**1** to aldehyde *(R)*-**4** proceeded at −20 °C to give the anti,anti triad **5** in 70% yield along with a small amount of the anti,syn isomer, which was separated by silica gel chromatography.




The resulting hindered alcohol was protected as the TBS ether **6** with TBSOTf in the presence of 2,6-lutidine in near quantitative yield (Scheme 1). At this stage, we wanted to perform a one carbon homologation of the terminal alkyne. For this we employed a two-step hy-

(7) Deeg, M.; Hagenmaier, H.; Kretschmer, A. *J. Antibiot*. **1987**, *40*, 320.

(8) (a) Evans, D. A.; Calter, M. A. *Tetrahedron Lett*. **1993**, *34*, 6871. (b) Only the late stage aldol and subsequent conversion to the natural product have been reported (ref 8a). The details of the remainder of the synthesis were taken from the Ph.D. Thesis of Michael A. Calter, Harvard University, Cambridge, Massachusetts, 1993.

(9) Toshima, K.; Jyojima, T.; Yamaguchi, H.; Noguchi, Y.; Yoshida, T.; Murase, H.; Nakada, M.; Matsumura, S. *J. Org. Chem*. **1997**, *62*, 3271 and references therein.

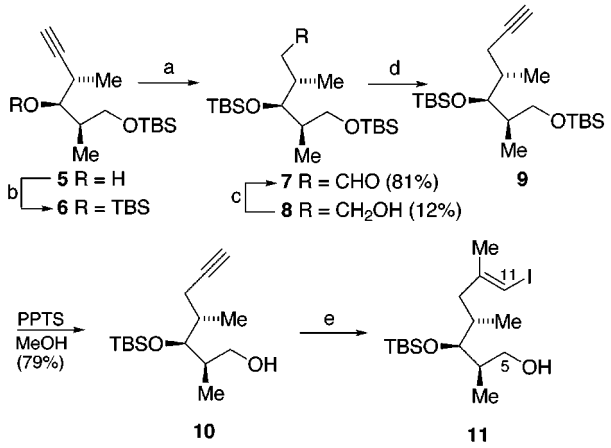
(10) Total synthesis: (a) Scheidt, K.; Tasaka, A.; Bannister, T. D.; Wendt, M. D.; Roush, W. R. *Angew. Chem., Int. Ed*. **1999**, *38*, 1652. Subunit synthesis: (b) Roush, W. R.; Bannister, T. D. *Tetrahedron Lett*. **1992**, *33*, 3587. (c) Roush, W. R.; Bannister, T. D.; Wendt, M. D. *Tetrahedron Lett*. **1993**, *34*, 8387.

(11) Smith, A. B., III; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett*. **1998**, *1*, 1823.

(12) Marshall, J. A.; Adams, N. D. *J. Org. Chem*. **1999**, *64*, 5201.

(13) Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. J. *J. Org. Chem*. **1987**, *52*, 316.

**Scheme 1**[a]

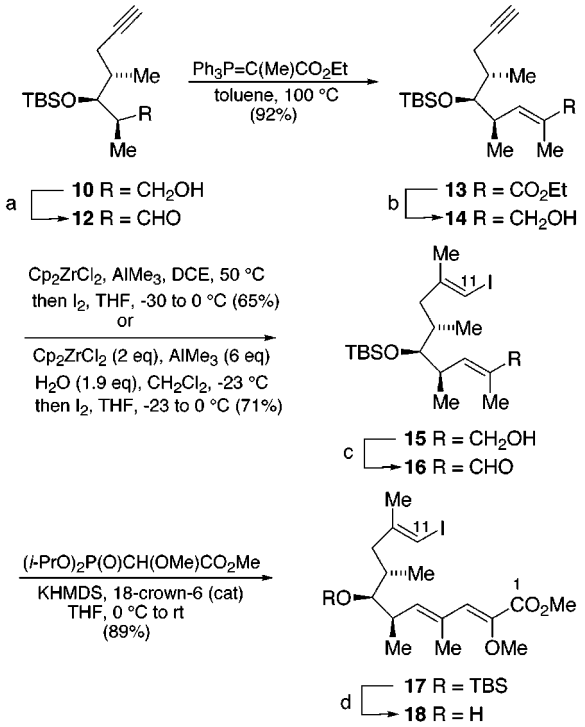



[a] Key: (a) $(c\text{-}C_6H_{11})_2BH$, DME, 0 °C to room temperature, and then $H_2O_2$, NaOH; (b) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C (96%); (c) Dess−Martin periodinane, $CH_2Cl_2$, room temperature (95%); (d) $(EtO)_2P(O)CHN_2$, KO*t*-Bu, THF, −78 to 0 °C (96%); (e) $Cp_2ZrCl_2$, $AlMe_3$, DCE, 60 °C, and then $I_2$, THF, −30 to 0 °C (37−48%).

droboration−homologation sequence. Several reagents and conditions were examined, including borane and catecholborane, and it was found that dicyclohexylborane was the most effective. Accordingly, treatment of alkyne **6** with freshly prepared $(c\text{-}C_6H_{11})_2BH$ in 1,2-dimethoxyethane from 0 °C to room temperature followed by treatment with basic $H_2O_2$ provided aldehyde **7** in 81% yield along with 12% of alcohol **8**.[14] Formation of the alcohol was somewhat surprising and is presumably a result of reduction of the aldehyde by a borohydride species (formally $R_2B(H)OH^-$) that may be formed during the oxidation step.[14b] Alcohol **8** could be recycled through oxidation with the Dess−Martin periodinane reagent[15] to give aldehyde **7** in near quantitative yield. Attempts to convert this aldehyde to alkyne **9** by utilizing either the Corey−Fuchs[16] protocol or Savignac's dichlorophosphonate reagent[17] were unsuccessful due to extensive decomposition and cleavage of the TBS ethers. However, homologation occurred cleanly with the Seyferth−Gilbert diazophosphonate reagent[18] to provide alkyne **9** in 96% yield.

The primary TBS ether was then removed chemoselectively with catalytic PPTS in MeOH to give alcohol **10** in 79% yield (95% based on recovered starting material). With alcohol **10** in hand, we turned our attention to the formation of the vinyl iodide, which we envisioned obtaining by Negishi carbozirconation.[19] Accordingly, alkyne **10** was treated with $Cp_2ZrCl_2$ and $AlMe_3$ in dichloroethane at 60 °C and the resultant vinylalane was quenched by addition of an $I_2$ solution in THF at −30 °C. Unfortunately, conversion to vinyl iodide **11** was inefficient (37−48% yield) despite several attempts at optimization. Given the low yield of the Negishi carbozirconation/iodination of alkyne **10** and the potential instability of the vinyl iodide product, we decided to further functionalize alcohol **10** and carry out the vinyl iodide transformation at a later stage.

**Scheme 2**[a]




[a] Key: (a) $(COCl)_2$, DMSO, TEA, $CH_2Cl_2$, −78 °C (91%); (b) DIBAL-H, $CH_2Cl_2$, −78 °C (92%); (c) $MnO_2$, $CH_2Cl_2$, room temperature (95%); (d) TBAF, THF, room temperature (81%).

Oxidation of alcohol **10** under Swern conditions[20] and treatment of the resulting aldehyde **12** with the triphenylphosphorylidene propionate Wittig reagent in toluene provided ester **13** in high yield (Scheme 2). It is noteworthy that a high temperature (100−110 °C) was necessary for complete reaction within a reasonable time. Reactions were incomplete in refluxing $CH_2Cl_2$ or 1,2-dichloroethane, presumably due to the steric environment at the α-position of the aldehyde. A small amount of the *Z* isomer (∼5%) was formed as evidenced by the appearance of a vinylic proton doublet at 6.7 ppm (vs 6.9 ppm for **13**) in the $^1H$ NMR spectrum of the conjugated ester. Ester reduction with DIBAL-H gave the requisite allylic alcohol **14** in high overall yield. Stereoselective installation of the C10−C11 trisubstituted olefin was accomplished under Negishi's carbozirconation conditions, which provided vinyl iodide **15** in 65% yield. We later found that the yield of the Negishi carbozirconation could be increased to 71% by the addition of water to the reaction mixture, a modification developed by Wipf and Lim.[21]

Allylic alcohol **15** was oxidized with $MnO_2$ in $CH_2Cl_2$. The resulting aldehyde **16** was treated with an α-OMe phosphonate reagent[22] in the presence of KHMDS and a catalytic amount of 18-crown-6 in THF from 0 °C to room temperature, which afforded a 94:6 2*Z*/2*E* mixture of

(14) (a) Hoffmann, R. W.; Dresely, S. *Synthesis* **1988**, 103. (b) Cf.: Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **2000**, *65*, 1501.

(15) (a) Dess, B. D.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) The Dess−Martin reagent in this study was prepared by a modified procedure using oxone; Cf.: Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.

(16) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *12*, 3769.

(17) Marinetti, A.; Savignac, P. *Org. Syn.* **1974**, 108.

(18) (a) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379. (b) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997. (c) Cf.: Kabat, M. M.; Kiegiel, J.; Cohen, N.; Toth, K.; Wovkulich, P. M.; Uskokovi′c, M. R. *J. Org. Chem.* **1996**, *61*, 118.

(19) Negishi, E.-i.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639.

(20) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

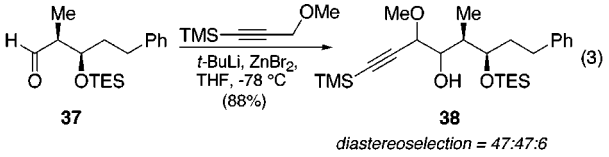
(21) Wipf, P.; Lim, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068.

(22) Paterson, I.; McLeod, M. D. *Tetrahedron Lett.* **1997**, *38*, 4183.

isomers. These esters could be distinguished by signals at 5.8 (major) and 5.6 ppm (minor) for the $\beta$-vinylic proton in the $^1$H NMR spectrum. The hindered TBS ether was removed with TBAF to complete the synthesis of the C1−C11 subunit **18**.

**Synthesis of the C15−C25 Subunit 36.** We have previously described the assembly of this segment, so a detailed discussion is not required.[23] However, it is worth pointing out that the stereochemically defining steps involving addition of the allenylzinc reagent derived from mesylate **19**[24] to isobutyraldehyde (**20**), Sharpless epoxidation[25] of the derived allylic alcohols **22** and **31**, as well as the methylcuprate addition leading to alcohol **33** all proceed with excellent diastereoselectivity. The one exception, addition of the allenylzinc reagent derived from mesylate **19** to the unbranched aldehyde **27**, is of no consequence as the alcohol product is converted to ketone **29**, the precursor of glycoside **30**. The structure of triol **33** was confirmed through single-crystal X-ray structure analysis.[23]

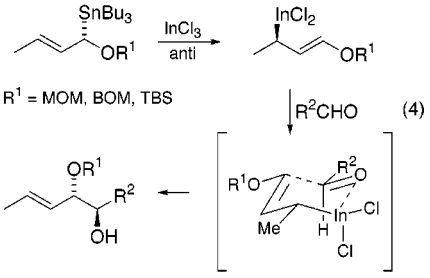
With aldehyde **36** in hand, we turned our attention to the anti-1,2-diol array. A direct approach would simultaneously install the differentially protected anti-1,2-diol and the alkyne, the latter of which could be hydrometalated prior to coupling to the vinyl iodide partner. At the time, there were no methods for the formation of enantioenriched methoxy-substituted allenylmetal reagents.[26] Racemic or achiral reagents of this type can be formed by deprotonation of propargylic ethers with *s*- or *t*-BuLi and subsequent transmetalation with $ZnBr_2$.[26,27] Following this procedure, we prepared the allenylzinc reagent from TMS-propargyl methyl ether,[28] which was allowed to react with a model aldehyde, **37**,[12] affording a 47:47:6 inseparable mixture of diastereomers in high yield (eq 3). As these additions are known to occur through a cyclic transition state, the major isomers are presumed to be the anti adducts and the minor is presumed to be a syn isomer. The addition of external chiral additives such as (−)-sparteine[29] or (−)-*N*-methylephedrine[30] resulted in lower yields and exerted no beneficial effect on the selectivity.



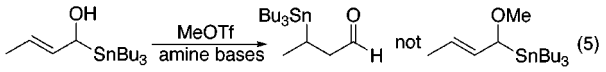

**37** **38**

*diastereoselection = 47:47:6*

Unable to effect a kinetic resolution, we decided to pursue an alternative strategy. Some years ago, we reported a method for the synthesis of differentially protected anti-1,2-diols by treatment of enantioenriched α-oxygenated allylic stannanes with $InCl_3$ to form an intermediate allylic indium reagent through an anti $S_E2'$ transmetalation process (eq 4).[31]




These reagents undergo highly anti-selective additions to aldehydes, presumably through a six-membered chair transition state. In principle, the MeO substituent could be installed prior to the addition reaction through the use of a chiral α-OMe allylic stannane (eq 4, $R^1$ = Me). In an attempt to access this unknown reagent, hydroxy stannane **39** was prepared as previously reported by addition of $Bu_3SnLi$ to crotonaldehyde. Unfortunately, all attempts to methylate the derived alkoxide with MeI resulted in extensive decomposition of the hydroxy stannane. Typical etherifications of α-hydroxy stannanes utilize MOM or BOM chloride in the presence of an amine base (i.e., *i*-$Pr_2NEt$ or $Et_3N$). These reactions are believed to proceed through an $S_N1$ pathway. In an attempt to prevent decomposition of the hydroxy stannane, we employed MeOTf in the presence of pyridine-type bases for this methylation. However, none of the expected methyl ether **41** was detected. Instead, an isomerized product whose $^1$H NMR spectrum is consistent with aldehyde **40** was produced as the sole product. Interestingly, this isomerization could also be effected with 10 mol % MeOTf or $Yb(OTf)_2$.[31]




**39** **40** **41**

With the synthesis of an α-OMe allylic stannane looking unfeasible, we decided to pursue an alternative method for installation of the anti-1,2-diol. The use of an α-OMOM or α-BOM stannane was considered. However, we foresaw protecting group orthogonality problems. Given the prior results of Roush[10] and Toshima[9] with Takai's in situ generated $\gamma$-methoxyallylchromium reagent[33] we decided to follow this approach. Accordingly,

(23) Marshall, J. A.; Adams, N. D. *Org. Lett*. **2000**, *2*, 2897.

(24) Cf.: Marshall, J. A.; Yanik, M. M. *J. Org. Chem*. **2001**, *66*, 1373.

(25) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. For the catalytic asymmetric epoxidation, see: (b) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem*. **1986**, *51*, 1922.

(26) Recently, Poisson and Normant have reported a kinetic resolution of racemic allenylzinc bromides through selective reaction with 0.5 equiv of the *N*-benzyl imine of lactic or mandelic aldehyde to consume the "matched" allenylzinc reagent as the homopropargylic amine adduct. Subsequent addition of pivalic aldehyde to the reaction mixture afforded the homopropargylic alcohol adduct of the less reactive ("mismatched") allenylzinc enantiomer: Poisson, J.-F.; Normant, J.-F. *J. Am. Chem. Soc.* **2001**, *123*, 4639. These workers have also shown that racemic MOMO-substituted allenylzinc reagents, which can be formed from the TMS derivative of propargyl methoxymethoxy ether by treatment with *s*-butyllithium at −40 °C followed by addition of $ZnBr_2$ at 0 °C, react with the same imines to afford homopropargylamine adducts of the matched allenylzinc pairing. However, they have not determined if the unreactive residual mismatched allenylzinc reagent will afford adducts of aldehydes with useful diastereoselectivity. The addition of the racemates of such reagents to a silyl derivative of mandelic aldehyde proceeds with low diastereoselectivity: Poisson, J.-F.; Normant, J.-F. *Org. Lett*. **2001**, *3*, 1889.

(27) Poisson, J.-F.; Normant, J.-F. *J. Org. Chem*. **2000**, *65*, 6553.

(28) Labaudiniere, L.; Hanaizi, J.; Normant, J.-F. *J. Org. Chem*. **1992**, *57*, 6903.

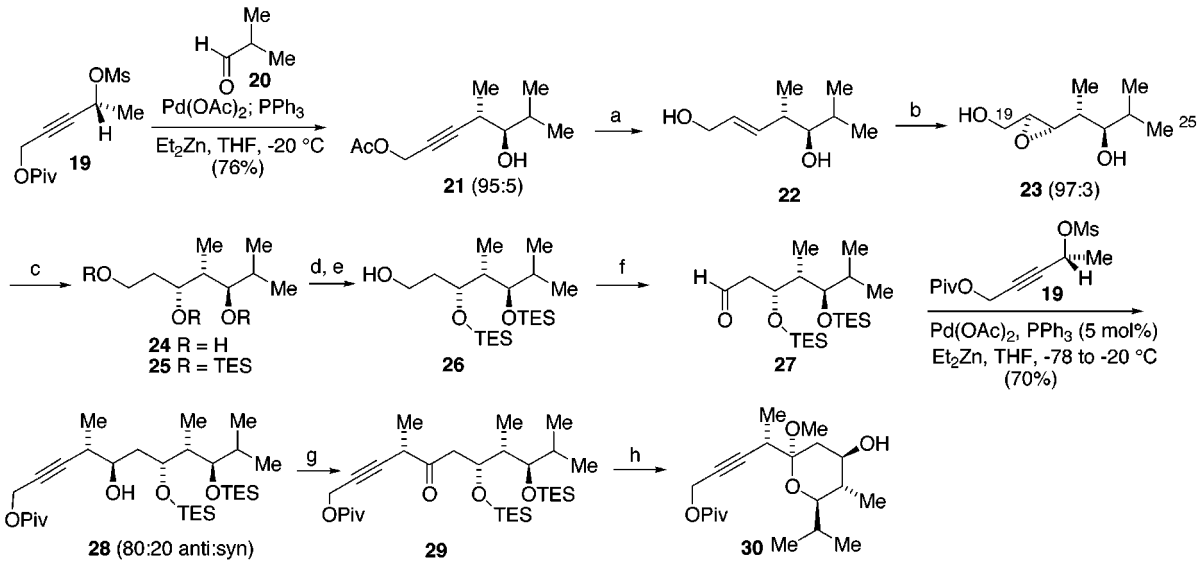
(29) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708.

(30) For recent reports utilizing *N*-methylephedrine in enantioselective additions of zinc acetylides to aldehydes, see: (a) Frantz, D. E.; Fässler, R.; Carriera, E. M. *J. Am. Chem Soc.* **2000**, *122*, 1806. (b) Boyall, D.; López, F.; Frantz, D. E.; Carriera, E. M. *Org. Lett*. **2000**, *2*, 4233.

(31) (a) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem*. **1996**, *61*, 105. (b) For a recent review on additions of allylic indium reagents to aldehydes, see: Marshall, J. A. *Chemtracts-Organic Chemistry* **1997**, 481.

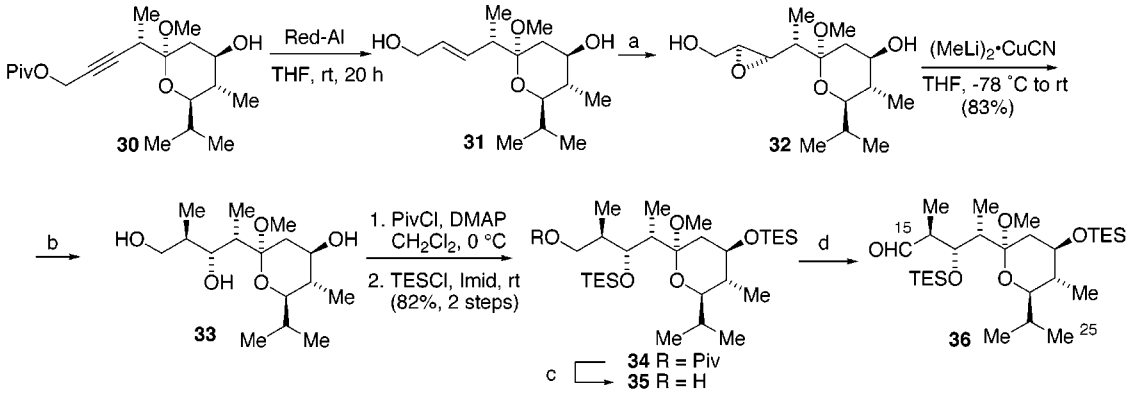
(32) For a recent mechanistic study on the 1,3-isomerization of allylic stannanes promoted by $BF_3{\cdot}OEt_2$, see: Marshall, J. A.; Gill, K. *J. Organomet. Chem*. **2001**, *624*, 294.

**Scheme 3**[a]



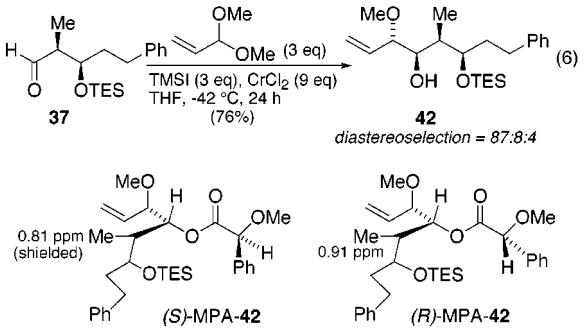

[a] Key: (a) $LiAlH_4$, THF (87%); (b) (+)-DIPT, TBHP, TIP (86%); (c) Red-Al, THF (93%); (d) TESOTf, 2,6-lutidine (99%); (e) $H_2O$, HOAc, THF (95%); (f) Swern (99%); (g) Dess−Martin; (h) PPTS, MeOH, room temperature, 1 h (84%, 2 steps).

**Scheme 4**[a]




[a] Key: (a) L-(+)-DIPT, TBHP, TIP, 4 Å MS, $CH_2Cl_2$, −20 °C, (80%, 2 steps); (b)TESOTf, 2,6-lutidine, $CH_2Cl_2$, −78 °C, (92%); (c) DIBAl-H, $CH_2Cl_2$, −78 °C (92%); (d) Dess−Martin, $NaHCO_3$, $CH_2Cl_2$, (quant).

the model aldehyde **37** was treated with $CrCl_2$ and acrolein dimethyl acetal in the presence of TMSI at −42 °C in THF to provide alcohol **42** in 76% yield along with two minor diastereomers with an overall selectivity of 87:8:4 (eq 6). The absolute configuration of the carbinyl center of the major isomer was confirmed by conversion to the *(S)*- and *(R)*-mandelic esters (MPA).[34]



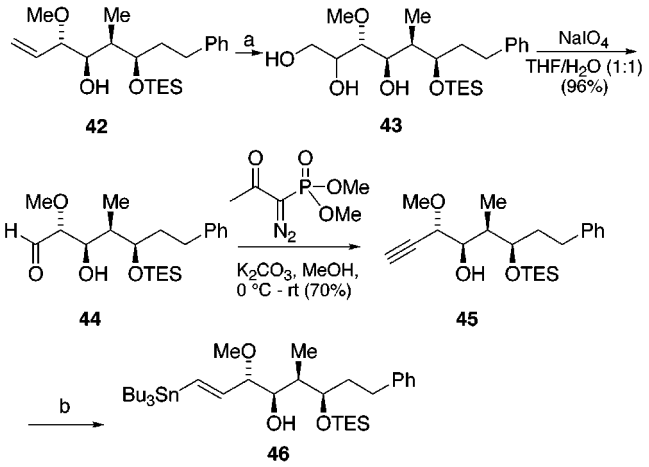

Before applying this methodology to our aldehyde intermediate **36**, we decided to test the proposed conversion of the allylic ether adduct to the vinylstannane and carry through to the Stille coupling of this model system. To that end, hydroxylation of alkene **42** with a catalytic amount of $OsO_4$ in the presence of NMO and cleavage of the resultant 1,2-diol with $NaIO_4$ provided aldehyde **44** in 83% yield for the two steps (Scheme 5). Oxidative cleavage of alkene **42** with $O_3$ and ozonide reduction with $PPh_3$ or $Me_2S$ was less efficient. Conversion of aldehyde **44** to the terminal alkyne was best accomplished with the Ohira diazophosphonate reagent[35] in the presence of $K_2CO_3$ in MeOH. Cleavage of the TES ether was minimized to 10% by employing 1.5 equiv of both the phosphonate reagent and $K_2CO_3$ as compared to Ohira's original conditions (2.0 equiv) which resulted in ca. 20% of the desilated adduct. Use of the Seyferth−Gilbert reagent resulted in the formation of several unidentifiable side products. Palladium-catalyzed hydrostannation

(33) Takai, K.; Nitta, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5263.

(34) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. D. *J. Org. Chem.* **1986**, *51*, 2370.

(35) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.

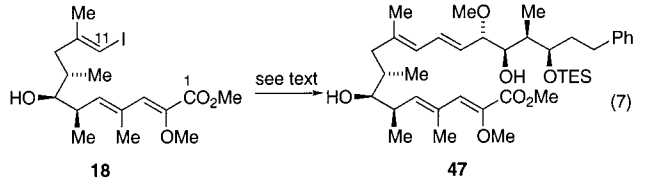
**Scheme 5**[a]




[a] Key: (a) $OsO_4$ (5 mol %), NMO, THF/pH 7 buffer (4:1) (86%); (b) $Bu_3SnH$, $Pd(PPh_3)_2Cl_2$, $CH_2Cl_2$ (73%).

of alkyne **45** provided vinyl stannane **46** with >90:10 *E*/*Z* selectivity.[36]

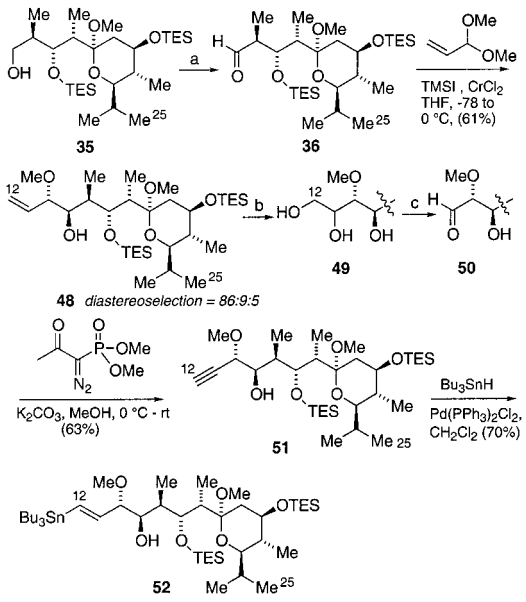
For the Stille coupling, we initially tried Liebeskind's copper(I) thiophene catalyst.[37] However, this method led only to recovered starting materials after several hours at room temperature (eq 7). The use of $Pd_2dba_3$ in the presence of $AsPh_3$ in *N*-methylpyrrolidinone (NMP) at 55 °C produced only a small amount of product.[38,39] Some homocoupling of the iodide was observed, which could be attributed to the sluggishness of the cross coupling reaction. We reasoned that if the transmetalation process could be accelerated, the cross coupling rate would increase. Added LiCl provided the requisite acceleration as the reaction proceeded to completion in 5 h at 55 °C.




With the Stille coupling seemingly in control, the fully elaborated C12−C25 subunit was assembled along the same lines as our model system. Accordingly, alcohol **35** was oxidized with the Dess−Martin periodinane reagent and the resultant aldehyde **36** was subjected to the Takai methoxyallylation conditions (Scheme 6).

The allylation reaction on this substrate was significantly slower than on the model aldehyde, taking several days at −42 °C, which ultimately led to epimerization of the aldehyde. However, if the reaction mixture was stirred at −78 °C with gradual warming to 0 °C over the course of 1 h, the reaction rate significantly increased with a corresponding decreased epimerization of the aldehyde (Scheme 6). Furthermore, the diastereoselectivity was comparable to that of the model system. Alkene **48** was converted to aldehyde **50** in high yield by treatment with $OsO_4$ and cleavage of the resultant diol **49** with $NaIO_4$. Homologation of aldehyde **50** to alkyne **51** and hydrostannation completed the synthesis of the C12−C25 subunit **52**.[40] Stille coupling between stannane **52** and iodide **18** was effected with $Pd_2dba_3$ (0.25 equiv) in the presence of $AsPh_3$ (2.0 equiv) and dry LiCl (3.0 equiv) in freshly distilled NMP (Scheme 7). The coupling reaction proceeded in only 5 h at room temperature to give diene **53** in 76% yield. Elevated temperatures were not required.

**Scheme 6**[a]




[a] Key: (a) Dess−Martin, $NaHCO_3$, $CH_2Cl_2$,(99%, crude); (b) $OsO_4$ (5 mol %), NMO, THF, pH 7 buffer (4:1) (85%); (c) $NaIO_4$, $THF/H_2O$ (1:1) (99%).

For the macrolactonization, we were attracted to the Yamaguchi method[41] in view of the previously reported successful lactonization of a C1−C17 seco acid by this mixed anhydride approach.[8] Following the precedent of Evans and Calter,[8] we saponified the methyl ester **53** with potassium trimethylsilanolate[42] to give hydroxy acid **54** in quantitative yield (crude) (Scheme 7). Formation of the mixed anhydride was found to be slow with 3 equiv of the 2,4,6-trichlorobenzoyl chloride reagent. However, as previously reported by Calter,[8] increasing the amount of this reagent to 10 equiv resulted in complete consumption of the acid within 6 h at room temperature. Unfortunately, the resulting mixed anhydride decomposed upon treatment with DMAP in refluxing in toluene. None of the lactone adduct was observed as judged by TLC and NMR analysis of the crude product.

We believe that the mixed anhydride was formed but that lactonization was the problematic step, possibly

(36) Zhang, H. X.; Gaubé, F.; Balavoine, G. *J. Org. Chem*. **1990**, *55*, 1867.

(37) (a) Allred, G.; Liebeskind, L. S. *J. Am. Chem. Soc*. **1996**, *118*, 2748. (b) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem*. **1994**, *59*, 5905.

(38) Farina, V.; Krishnan, B. *J. Am. Chem. Soc*. **1991**, *113*, 9585.

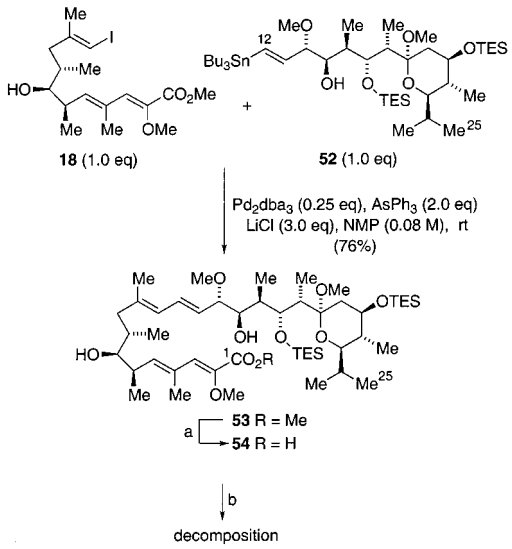
(39) Cf.: Toshima, K.; Jyojima, T.; Miyamoto, N.; Katohno, M.; Nakata, M.; Matsumura, S. *J. Org. Chem*. **2001**, *66*, 1708.

(40) After completion of this work, a more direct approach to propargyl methyl ethers involving addition of a chiral methoxyallenylstannane reagent to aldehydes was reported: Savall, B. M.; Powell, N. A.; Roush, W. R. *Org. Lett*. **2001**, *3*, 3057.

(41) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 1989. (b) For a selected application, see: Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem*. **1990**, *55*, 7.

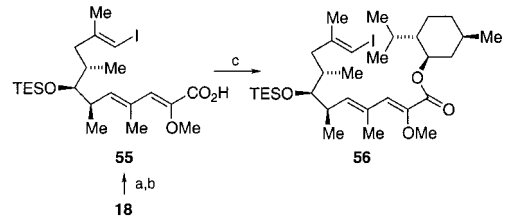
(42) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett*. **1984**, *51*, 5831.

**Scheme 7**[a]




[a] Key: (a) KOTMS, THF (quant, crude); (b) 2,4,6-trichlorobenzoyl chloride, *i*-$Pr_2NEt$, THF (0.01 M), room temperature, and then DMAP, toluene, 110 °C.

**Scheme 8**[a]




[a] Key: (a) KOTMS, THF, room temperature; (b) TESCl, imid, $CH_2Cl_2$, room temperature (65%, 2 steps); (c) 2,4,6-trichlorobenzoyl chloride, TEA, (−)-menthol, THF (0.01 M), room temperature, and then DMAP, toluene, 110 °C (34%).

because the C15−OH was unreactive. We reasoned that activation of the this OH might be achieved with a proximal basic site. One of the more commonly employed of the so-called "double activation" methods utilizes commercially available 2,2′-dipyridyl disulfide, which is activated by $PPh_3$.[43] Unfortunately, acid **54** underwent rapid decomposition under the thioester forming conditions.

To evaluate the effect of the C12−C25 ketal segment, acid **55** was converted to the mixed anhydride and condensed with (−)-menthol under the previously noted modified Yamaguchi conditions (Scheme 8). The reaction occurred with minimal decomposition as evidenced by TLC analysis. The low yield (34%) of menthyl ester **56** actually isolated can be attributed to a premature quenching of the reaction mixture. This result, together with the successful lactonization of Calter,[8] suggests that the C18−C25 (pyranoside) portion of the molecule is responsible for the failure of the lactonization step and the eventual decomposition of the substrate.

We then considered a reversal of the coupling steps by attempting an intermolecular esterification followed by an intramolecular Stille coupling. This strategy would

(43) (a) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614. (b) Corey, E. J.; Brunelle, D. J.; Stork, P. J. *Tetrahedron Lett.* **1976**, *38*, 3405. (c) Corey, E. J.; Brunelle, D. J. *Tetrahedron Lett.* **1976**, *38*, 3409.

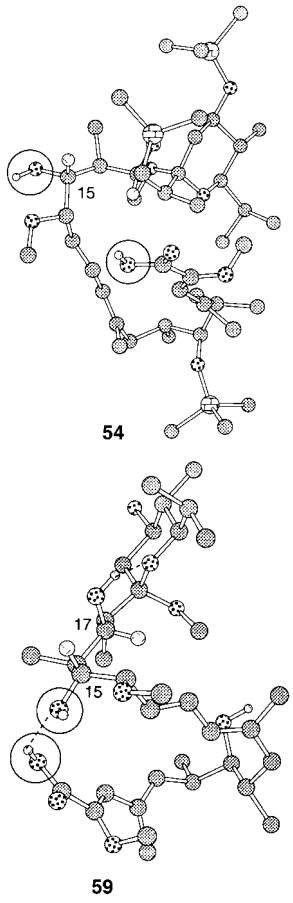
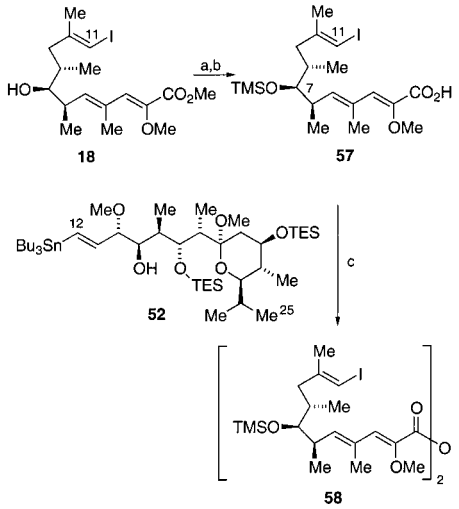



**Figure 3.** Calculated structures for the TES-protected seco acid **54** and the derived triol **59** (MacroModel 5.5) showing the relationship between the C15−OH and the carboxylic group. Only relevant hydrogen atoms are shown.

allow for the formation of the mixed anhydride in the absence of the ketal fragment and thus circumvent the decomposition. Accordingly, acid **57** was treated with 2,4,6-trichlorobenzoyl chloride and TEA in the absence of the stannane **52**. Upon complete consumption of starting material, the anhydride solution was cannulated into a mixture of hydroxy stannane **52** and DMAP in toluene. After 18 h at room temperature, none of the desired ester had been formed. In fact, most of the hydroxy stannane **52** was recovered unchanged. A majority of the acid starting material was converted to a less polar product with a $^1H$ NMR spectrum consistent with symmetrical anhydride **58**. Attempted esterification of acid **57** and alcohol **52** with DCC and DMAP also resulted in the formation of anhydride **58**. An analogous anhydride was produced in several of Calter's abortive attempts at macrolactonization.[8] Esterification between stannane **52** and the symmetrical anhydride **58** in the presence of DMAP under thermal conditions was also examined to no avail.

At this point, we began to suspect that conformational factors might be responsible for the lack of success in attempted macrolactonizations of seco acid **54**. In fact, molecular mechanics calculations (MacroModel 5.5) indicated that the C15−OH and the carboxylic group were on "opposite sides of the fence" (Figure 3). Suspecting that the bulky TES groups might be responsible, at least in part, for this conformational incompatiblity, we carried out analogous calculations on the free seco acid tetrol **59**

**Scheme 9**[a]



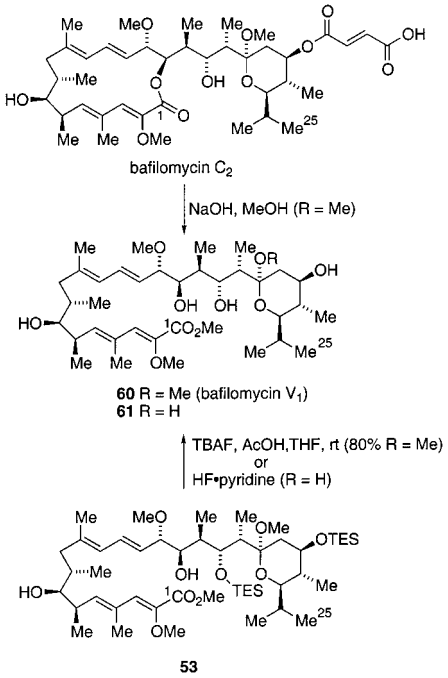
[a] Key: (a) TMSCl, imid, $CH_2Cl_2$, room temperature; (b) KOTMS, THF, room temperature, (64%, 2 steps); (c) 2,4,6-trichlorobenzoyl chloride, TEA, THF (0.01 M), room temperature, and then **52**, DMAP, toluene, room temperature.

(Figure 3). The results were quite astounding! Not only were the C15−OH and the acid moiety in close (hydrogen bonding) proximity, the structure also showed a potentially beneficial hydrogen bond between the C17−OH and the pyranoside ring oxygen. This interaction could serve to disfavor an alternative cyclization pathway at the C-17 OH to afford an 18-membered lactone. Accordingly, the TES protecting groups were removed by treatment with buffered TBAF and the resulting seco acid tetrol was subjected to the modified Yamaguchi cyclization conditions. Unfortunately, the promise of the calculated structure was not fulfilled by the experiment. TLC analysis of the cyclization reaction mixture showed no spot attributable to the lactone product.

Some years following the published isolation and structure elucidation of the bafilomycins, a group from SmithKline-Beecham reported structure−activity relationships of several derivatives.[6b] One such derivative, designated bafilomycin $V_1$ (**60**), was prepared through methanolysis of bafilomycin $C_2$ to the open chain seco ester (Scheme 10). Remarkably, this compound retained biological activity as an inhibitor of vacuolar ATPases, although with less potency than bafilomycin $A_1$.

Because the final lactonization step to complete the synthesis of bafilomycin $A_1$ was evidently unfeasible, we turned our attention to a synthesis of bafilomycin $V_1$. This was achieved in 80% yield through treatment of the Stille adduct **53** with buffered TBAF in THF at room temperature. It is worth noting that the use of HF·pyridine for

**Scheme 10**



the deprotection resulted in hydrolysis of the methyl pyranoside leading to **61**. The $^1$H NMR spectrum of our synthetic bafilomycin $V_1$ was identical to that of the spectrum provided to us by the SmithKline-Beecham group with the exception of additional −OH signals at 2.93 and 2.45 ppm in our spectrum. The $^{13}$C NMR spectrum, optical rotation, and melting point of this substance were not available. However, the close agreement of the $^1$H NMR spectrum and the ample stereochemical precedent for our stereodefining steps, not to mention the X-ray crystal structure determination for triol **33**, leave little doubt as to the structural integrity of our synthetic material.

**Acknowledgment.** Support for this research was provided by NIH Grant RO1 CA 90383 and NSF Grant CHE-9901319. We thank Dr. Carlo Farina, SmithKline-Beecham SpA, for providing detailed $^1$H NMR spectra of bafilomycin $V_1$ derived from natural sources. We gratefully acknowledge Dr. Brian A. Johns for insightful discussions and suggestions.

**Supporting Information Available:** Complete experimental procedures and $^1$H NMR spectra for key intermediates and the final product, except for the compounds in Schemes 3 and 4, which can be found in the Supporting Information for ref 23. This material is available free of charge via the Internet at http://pubs.acs.org.

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