CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201102797

Total Synthesis of Bafilomycin A_1

Florian Kleinbeck, Gabriela J. Fettes, Lee D. Fader, and Erick M. Carreira*[a]

Abstract: A convergent synthesis of bafilomycin A_1, a potent inhibitor of V-type ATPases, is presented. The synthesis relies on the zinc triflate mediated diastereoselective addition of a complex enyne to a sensitive aldehyde as the key fragment coupling. A ruthenium-catalyzed *trans*-reduction of the resulting propargylic enyne efficiently installs the required C10–C13 *trans*,*trans*-diene subunit, implementing an alternative strategy to traditional palladium-catalyzed cross-coupling strategies. A highly selective oxidation of a secondary hydroxyl group in a triol sets the stage for the completion of the synthesis.

Keywords: bafilomycin A_1 · enyne · natural products · polyketide · total synthesis

Introduction

Bafilomycin A_1 (**1**) was first isolated in 1983 by Werner and Hagenmaier from a culture of *Streptomyces griseus* sp. Sulphurus[1] and was classified as a member of the plecomacrolide family, a class of naturally occurring polyketides which also includes the hygrolidines, the concanamycins, formamycin and elaiophyllin.[2] While the connectivity of bafilomycin A_1 could be elucidated by extensive NMR experiments in combination with IR and UV spectroscopy,[1] the relative and absolute configuration of the plecomacrolides was first proposed by Corey using molecular modeling analysis on the basis of NMR studies,[3] and could subsequently be verified for bafilomycin A_1 by X-ray crystallographic analysis.[4] The structure of bafilomycin A_1 is characterized by a 16-membered macrolactone ring with two distinct diene subunits, an acid- and base-sensitive six-membered cyclic hemiketal that is linked to the macrocycle by a three-carbon spacer, and a characteristic hydrogen bonding network between the hydroxyl group of the hemiketal, the C17-hydroxyl group and the carbonyl group of the macrolactone.

The unique hydrogen-bonding network is believed to impose a defined three-dimensional structure on bafilomycin A_1 both in the solid state and in solution,[5] and thus plays a crucial role for its biological activity. Apart from its broad antibacterial and antifungal potency,[1] the ability of bafilomycin A_1 to selectively inhibit V-type ATPases[6] has attracted much attention. V-type ATPases generate proton gradients across vacuolar membranes, a function that is generally important in the pH regulation within cell compartments. As multiple diseases, with osteoporosis being the most prominent one, are associated with pH regulation, the potential of bafilomycin A_1 and related analogs as drug candidates was demonstrated by development of structure-activity relationships.[7]

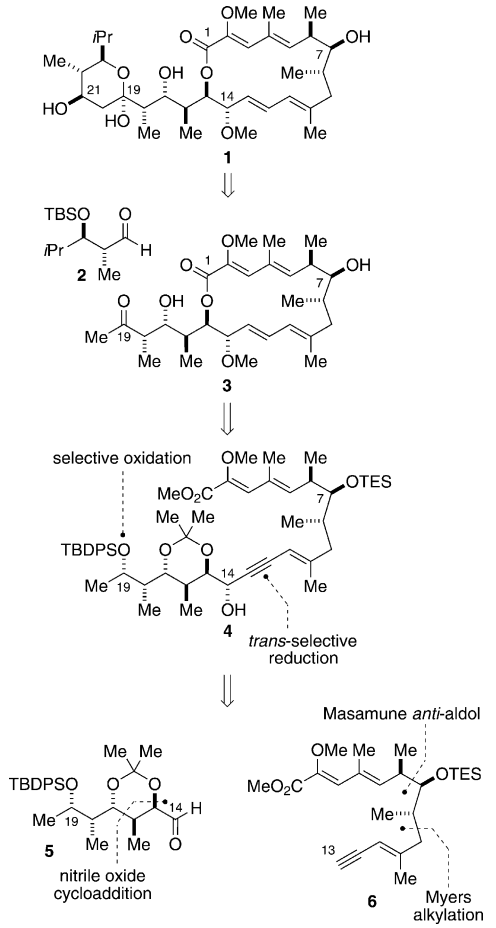
The unique biological and structural properties of bafilomycin A_1 have attracted significant attention from the synthetic community. Since its discovery, total syntheses have been reported by the groups of Evans,[8] Toshima,[9] Roush,[10] and Hanessian.[11] The Marshall group published a synthesis of bafilomycin V_1,[12] a derivative obtained by methanolysis of the natural product, and numerous approaches to fragments have been described.[13] While the four previously published syntheses of bafilomycin A_1 differ in the methodologies used to assemble the aldol-type structures of the respective fragments, they all rely on a common palladium-catalyzed Stille or Suzuki cross-coupling strategy to join the two major fragments under mild conditions by formation of the C11−C12 bond, at the same time installing the challenging *trans*,*trans*-diene portion of the molecule.

Our interest in bafilomycin A_1 was stimulated by the opportunity to explore and evaluate new reaction methodology in the context of the synthesis of a complex polyketide. A preliminary report of our synthesis of bafilomycin A_1 was published in 2009.[14] Specifically, we intended to take advantage of the magnesium-mediated diastereoselective nitrile oxide cycloaddition[15] to establish the four contiguous stereogenic centers at C15 to C18 with their challenging *syn*-*anti*-*syn* relationship, and the stereoselective zinc triflate mediated addition of terminal alkynes to aldehydes as the key step for fragment coupling.[16] In combination with the development of conditions for an efficient enyne semireduction of the resulting enyne to access the *trans*,*trans*-1,3-diene motif corresponding to the C10–C13 portion of the molecule, this approach would introduce a novel and alternative strategy to the Pd-catalyzed coupling reactions commonly used for the installation of *trans*,*trans*-diene units.

[a] F. Kleinbeck, G. J. Fettes, Dr. L. D. Fader, Prof. Dr. E. M. Carreira
ETH Zürich HCI H335, Wolfgang-Pauli-Strasse 10
8093 Zürich (Switzerland)
Fax: (+41) 44-632-1328
E-mail: carreria@org.chem.ethz.ch

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201102797.

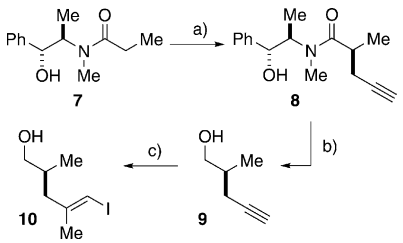
In our retrosynthetic analysis of bafilomycin A_1 (Scheme 1), the C21–C25 portion of bafilomycin A_1 would be introduced by a Mukaiyama aldol reaction, related to the approach developed by Roush.[10] The methyl ketone **3** could be accessed from linear enyne **4** in a sequence consisting of *trans*-selective semireduction, macrolactonization and oxidation of the C19 hydroxyl group. Propargylic enyne **4** could be assembled using the zinc triflate-mediated addition of C1–C13 fragment **6** to aldehyde **5**. A nitrile oxide cycloaddition would provide aldehyde **5**, and the stereogenic centers of the enyne fragment **6** could be set using a Myers alkylation and a Masamune *anti*-aldol addition.



Scheme 1. Retrosynthetic analysis of bafilomycin A_1 (**1**).

Results and Discussion

Synthesis of the C1−C13 enyne fragment: In the first-generation synthesis of the C1−C13 fragment **6**, the stereogenic center at C8 was set using a diastereoselective Myers alkylation[17] of (−)-pseudoephedrine-derived propionylamide **7** with propargyl bromide at −78 °C, providing the alkylation product **8** as a 94:6 mixture of diastereomers[18] in combined 65 % yield (Scheme 2). Attempts to recrystallize the oily alkyne **8** and thus increase the diastereomeric purity of the alkylation product failed. Reductive cleavage of the (−)-pseudoephedrine auxiliary with lithium amidoborate (LAB)[17d,19] provided alcohol **9**, the isolation of which proved to be a challenging task as a result of its volatility[20] and the formation of small amounts of 1-butanol[21] as a side product under the reaction conditions, formed by reductive opening of THF.[22]

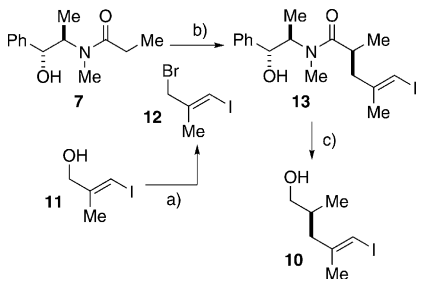


Scheme 2. First-generation synthesis of alcohol **10**. a) LDA, LiCl, THF, −78 °C → RT, 75 min, then propargyl bromide, −78 °C, 4.25 h, d.r. 94:6, 65 %; b) LDA, $BH_3{\cdot}NH_3$, THF, 0 °C → RT, 30 min, then amide **8**, RT, 2 h, 50 %; c) $[Cp_2ZrCl_2]$ (40 mol %), $AlMe_3$, CH_2Cl_2, −10 °C, then alcohol **9**, RT, 12.5 h, then I_2, THF, −40 °C → RT, 30 min, 74 %.

With alcohol **9** in hand, the introduction of the vinyl iodide moiety by a Negishi carboiodination[23] reaction using trimethylaluminum and iodine was performed next.[24] Product **10** could be reliably isolated in about 70 % yield at reaction scales below one millimole, yet yields dropped significantly on scale-up because of incomplete turnover in the initial carboalumination step. Attempts to increase the rate of carbometallation by addition of water according to the modification reported by Wipf and co-workers[25] did not lead to any improvement (Scheme 2).

As a result of the encountered problems, a modified approach to alcohol **10** was developed (Scheme 3). By incorporation of the vinyl iodide moiety into the electrophile used in the Myers alkylation reaction, the troublesome Negishi carboiodination became obsolete, and the increased molecular weight of all intermediates decreased their volatility and therefore facilitated the isolation.

Allylic bromide **12** was identified as suitable alkylating agent, easily accessed on large scale from known alcohol **11**[26] by transformation of the hydroxyl functionality into the mesylate and in situ displacement with bromide.[27] Myers alkylation with excess propionylamide **7** under stan-



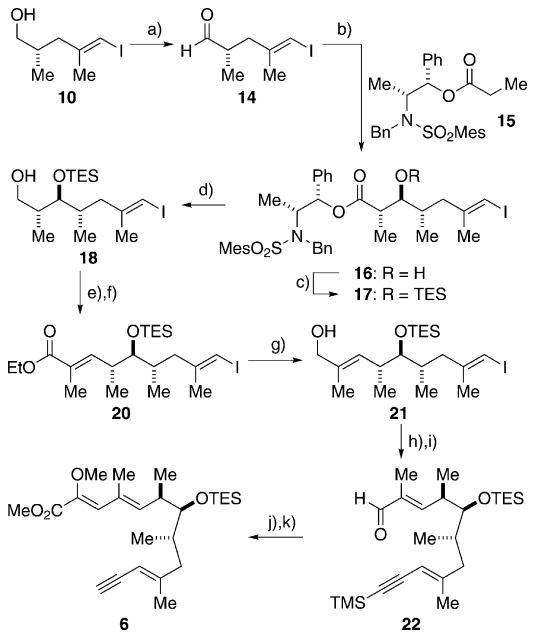
Scheme 3. Second-generation synthesis of alcohol **10**. a) Ms_2O, LiBr, NEt_3, Et_2O, −65 °C → 0 °C, 2 h; b) LDA, LiCl, THF, −78 °C → 0 °C, 1.5 h, then allylic bromide **12** (0.7 equiv), 0 °C, 20 h, d.r. 97:3, 87 % (two steps); c) LDA, $BH_3{\cdot}NH_3$, THF, 0 °C → RT, 30 min, then amide **13**, RT, 3 h, 87 %.

dard conditions furnished the alkylated product **13** with a diastereoselectivity of 97:3 in 87% yield over two steps from alcohol **11**. After removal of excess propionylamide **7** by chromatography on silica gel, the product was obtained as white crystalline solid. Recrystallization from toluene provided essentially a single diastereoisomer in 88% yield. As before, reductive cleavage of the pseudoephedrine auxiliary was performed with lithium amidoborate[17d] to give the previously synthesized alcohol **10** in 87% yield. Determination of the enantiopurity of alcohol **10** by HPLC on a chiral stationary phase[28] showed an enantiomeric excess of >99% *ee*.

Oxidation of alcohol **10** to the corresponding aldehyde **14** was carried out with Dess–Martin periodinane[29] in the presence of pyridine as buffer. Aldehyde **14** was used immediately in the Masamune *anti*-aldol reaction[30] of ester **15** with Cy_2BOTf and NEt_3, giving diastereomerically pure β-hydroxy ester **16** in 90% yield (Scheme 4). The free hydroxyl group of aldol product **16** was subsequently protected with TESCl and catalytic amounts of DMAP to furnish the corresponding silyl ether **17** in 98% yield. Reduction of the ester with DIBAL-H in CH_2Cl_2 provided primary alcohol **18** in 95% yield.[31]

Oxidation of the primary hydroxyl group in alcohol **18** with catalytic amounts of TPAP[32] and NMO as stoichiometric oxidant led to the corresponding aldehyde, which was subjected without previous purification to a Wittig olefination with stabilized ylide **19**[33] in toluene, providing α,β-unsaturated ester **20** with >95:5 diastereoselectivity in 87% yield over two steps. Subsequent reduction of α,β-unsaturated ester **20** with DIBAL-H then led to allylic alcohol **21** in 98% yield, intercepting an intermediate in the synthesis of bafilomycin A_1 published by Hanessian and co-workers.[11,34]

Sonogashira coupling of the vinyl iodide moiety was subsequently carried out to install the enyne portion, using trimethylsilylacetylene in pyrrolidine.[35] The primary alcohol was then oxidized under mild conditions with manganese dioxide to the corresponding α,β-unsaturated aldehyde **22** in 94% yield (Scheme 4). Subsequent Horner–Wadsworth–Emmons reaction with methoxy-substituted phosphonate **23**[36] provided the corresponding ester with >95:5 diastereoselectivity in favor of the desired (*E*)-isomer.[37] Partial deprotection of the TMS group of the alkyne occurred under the reaction conditions, which was inconsequential because of the projected desilylation in the next step. Treatment of the mixture of protected and unprotected enyne with K_2CO_3 in MeOH selectively removed the TMS-protecting groups of the alkyne, providing enyne fragment **6** in 96% yield over two steps (Scheme 4). The absolute configuration of all three stereogenic centers in the C1–C13 enyne fragment could be unambiguously assigned by X-ray crystal structure analysis of *p*-methoxybenzylidene acetal **24**, obtained as a single diastereoisomer in two steps from alcohol **18** (Figure 1, see Supporting Information for details).



Scheme 4. Completion of the enyne fragment **6**. a) DMP, pyridine, CH_2Cl_2, 0°C → RT, 3 h, 99%; b) ester **15**, NEt_3, Cy_2BOTf, −78°C, 4 h, then aldehyde **14**, −78°C, 7 h, 90%; c) TESCl, cat. DMAP, imidazole, DMF, RT, 4.5 h, 98%; d) DIBAL-H, CH_2Cl_2, −78°C, 1.5 h, 95% (96% recovered auxiliary); e) NMO, 4 Å MS, CH_2Cl_2, RT, 30 min, then TPAP (5 mol%), 0°C → RT, 1.5 h; f) $Ph_3P{=}C(Me)CO_2Et$ (**19**), toluene, 65°C, 19 h, d.r. >95:5, 87% (two steps); g) DIBAL-H, CH_2Cl_2, −78°C, 1.5 h, 98%; h) TMS-acetylene, CuI (12 mol%), $[Pd(PPh_3)_4]$ (5 mol%), pyrrolidine, 0°C → RT, 2 h, 96%; i) MnO_2, CH_2Cl_2, RT, 8 h, 94%; j) $(iPrO)_2P(O)CH(OMe)CO_2Me$ (**23**), [18]crown-6, KHMDS, 0°C, 30 min, then aldehyde **22**, 0°C, 2 h, d.r. >95:5; k) K_2CO_3, MeOH, RT, 80 min, 96% (two steps).

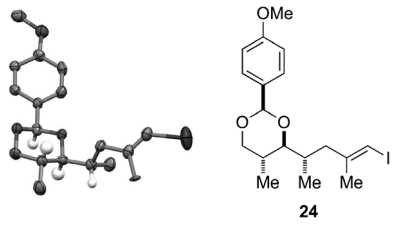
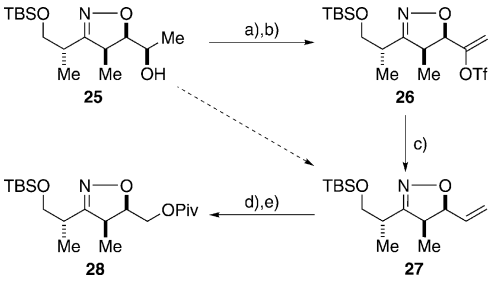


Figure 1. ORTEP representation of the crystal structure of *p*-methoxybenzylidene acetal **24**.

Synthesis of the C14–C20 aldehyde fragment: The magnesium-directed nitrile oxide cycloaddition previously developed in our laboratories seemed to provide a convenient solution to the installation of the challenging *syn-anti-syn* stereotetrad at C15 to C18. Concomitantly, this strategy would provide flexibility in terms of the protecting group pattern, which seemed to be beneficial in light of the potentially delicate zinc-acetylide coupling with the C1–C13 enyne fragment.[38] However, the required use of a chiral allylic alcohol made C–C bond scission necessary in order to access the aldehyde functionality at C14 from the corresponding secondary alcohol. The transformation of the secondary alcohol into the alkene and subsequent oxidative cleavage seemed to be the most promising approach.

The feasibility of such a transformation was examined using known isoxazoline **25** (Scheme 5).[15a] Early attempts

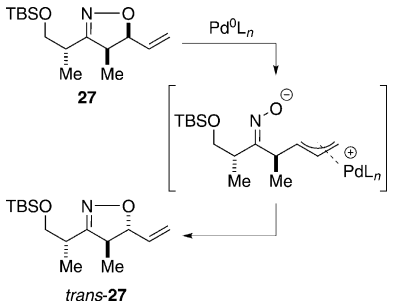
to obtain alkene **27** by base-induced elimination of the corresponding mesylate under a variety of different conditions were not successful. Displacement of the mesylate with phenylselenide and in situ oxidation to the selenoxide furnished alkene **27** in low and varying yields. A three-step sequence proved to be more promising: oxidation of alcohol **25** with TPAP and NMO as stoichiometric oxidant gave the intermediate ketone in 93% yield. Access to vinyl triflate **26** was



Scheme 5. Model studies on C–C bond scission for the synthesis of the C14–C20 aldehyde fragment. a) TPAP, NMO, 4 Å MS, CH_2Cl_2, 0 °C → RT, 2.5 h, 93%; b) KHMDS, THF, −78 °C, 30 min, then $PhNTf_2$, −78 °C, 45 min, 80%; c) $Pd(OAc)_2$ (10 mol%), HCO_2H, NEt_3, DMF, 60 °C, 15 min, 77%; d) O_3, MeOH, −78 °C, 50 min, then $NaBH_4$, −78 °C → RT, 1 h; e) PivCl, pyridine, RT, 11 h, 65% (two steps).

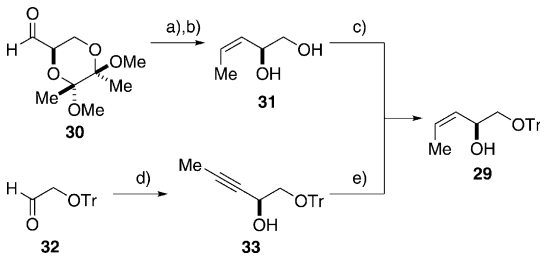
then obtained by regioselective enolate formation using LDA and trapping with $PhNTf_2$, providing the desired product **26** in 80% yield under optimized conditions.[39] Palladium-catalyzed reduction with formic acid as reducing agent then furnished the targeted alkene **27**. However, careful monitoring of the reaction progress in the reduction of vinyl triflate **26** was crucial to prevent partial epimerization of the resulting vinyl isoxazoline **27** on prolonged exposure to the reaction conditions. Mechanistically, the epimerization to the thermodynamically preferred 3,4-*trans*-substituted isoxazoline *trans*-**27** presumably occurs via intermediate formation of the allyl palladium species (Scheme 6). Oxidative cleavage of the double bond in **27** was then accomplished using ozone. After reductive work-up with $NaBH_4$, the intermediate primary alcohol was protected as the pivaloate to give fully protected intermediate **28**.

The failure to access the desired alkene functionality directly from the secondary alcohol led to the modification of the allylic alcohol reaction partner in the nitrile oxide cycloaddition reaction. Instead of an alkene as latent aldehyde functionality, we intended to form the aldehyde in the ultimate step by oxidative cleavage of an appropriate diol.



Scheme 6. Epimerization of vinylisoxazoline **27**.

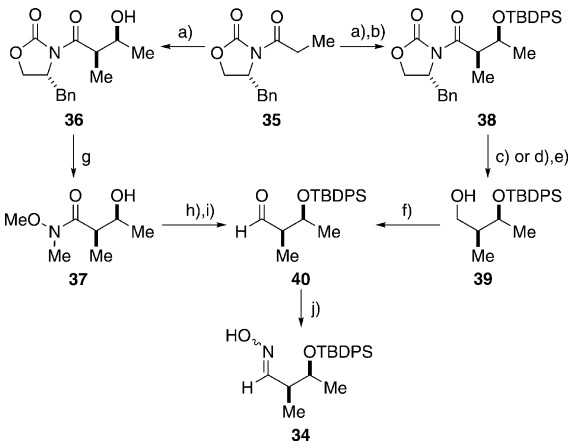
Two routes with similar efficiency to the required chiral allylic alcohol **29** were independently developed (Scheme 7). Wittig olefination of known bis-acetal protected (*R*)-glyceraldehyde **30**,[40] prepared in two steps from D-mannitol, provided the corresponding (*Z*)-alkene with 92:8 d.r. in 65% yield over two steps. Deprotection using a mixture of acetic acid and water liberated diol **31**, the primary hydroxyl group of which was selectively protected as trityl ether, giving allylic alcohol **29** in 88% yield. Alternatively, the same allylic alcohol **29** could be synthesized under the conditions of the zinc triflate mediated addition of terminal alkynes to aldehydes,[16] starting from gaseous propyne and previously described trityl-protected aldehyde **32**.[41] In this transformation, the argon atmosphere above the reaction was simply exchanged for propyne after standard preformation of the catalyst. The generated zinc acetylide then added efficiently to aldehyde **32**, giving propargylic alcohol **33** in 88% yield and 94% *ee*.[42] Carefully monitored Lindlar reduction of the alkyne then efficiently installed the (*Z*)-alkene.



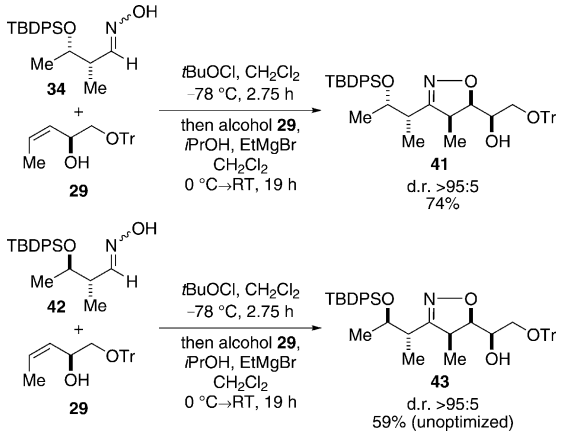
Scheme 7. Synthesis of chiral allylic alcohol **29**. a) Ph_3PEtBr, *n*BuLi, THF, 0 °C, 30 min, then aldehyde **30**, −78 °C → RT, 6.5 h, d.r. 92:8, 65% (two steps); b) AcOH/H_2O 1:1, 60 °C, 6.5 h, 93%; c) TrCl, pyridine, cat. DMAP, CH_2Cl_2, RT, 5 h, 88%; d) $Zn(OTf)_2$, (+)-NME, NEt_3, toluene, RT, 2 h, then propyne, RT, 15 min, then aldehyde **32**, RT, 1 h, 94% *ee*, 88%; e) Lindlar catalyst, H_2, EtOAc, RT, 25 min, 97%.

The oxime reaction partner **34** which served as precursor for the nitrile oxide was assembled using an Evans aldol approach (Scheme 8).[43] Treatment of (*R*)-propionyl oxazolidinone **35** with Bu_2BOTf and NEt_3 and subsequent aldol reaction with acetaldehyde provided multigram quantities of the *syn*-aldol product **36** in 84% yield as a single diastereoisomer. Subsequent silyl protection under standard conditions with TBDPSCl and imidazole in DMF furnished silyl ether **38** in 95% yield.

Removal of the chiral auxiliary proved to be more difficult than expected. Attempted reductive cleavage with $LiBH_4$ in the presence of either EtOH[44] or H_2O[45] afforded the expected alcohol **39**[46] in only 50 and 61% yield, respectively. Under all conditions tested, formation of the corresponding amide, resulting from reductive opening of the isoxazoline auxiliary, could be observed.[47] A two-step approach via the intermediate benzyl ester, originally reported by Evans[48] slightly improved the overall yield of the trans-



Scheme 8. Synthesis of oxime **34**. a) Bu_2BOTf, NEt_3, CH_2Cl_2, 0 °C, then acetaldehyde, −78 °C → RT, 3 h, d.r. >95:5, 84%; b) TBDPSCl, imidazole, DMF, RT, 44 h, 95%; c) $LiBH_4$, EtOH or H_2O, Et_2O, 0 °C → RT, 4 h, 50% or 61%; d) benzyl alcohol, *n*BuLi, THF, 0 °C, 76%; e) DIBAL-H, CH_2Cl_2, −78 °C, 1.5 h, 88%; f) TEMPO (3 mol%), NaOCl, KBr, CH_2Cl_2/pH 8.6 buffer 1:1, 0 °C, 25 min; g) $Me(MeO)NH_2^+Cl^-$, $AlMe_3$, THF, 0 °C, 30 min, then imide **36**, 0 °C, 2.5 h, 84%; h) TBDPSCl, imidazole, cat. DMAP, DMF, RT, 12 h, 98%; i) DIBAL-H, THF, −78 °C, 1.75 h, 89%; j) $HONH_2$·HCl, EtOH/pyridine 6:1, RT, 12 h, 98%.

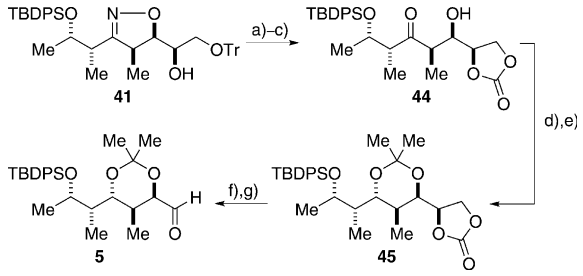


Scheme 9. Nitrile oxide cycloadditions with epimeric oximes **34** and **42**.

formation to 67% yield. Oxidation of primary alcohol **39** to the corresponding aldehyde **40** was finally carried out using catalytic amounts of TEMPO and NaOCl as stoichiometric oxidant.[49] A higher-yielding approach to aldehyde **40** was established by transformation of the initial *syn*-aldol product **36** into Weinreb amide **37**, conveniently achieved in 84% yield under standard conditions using $AlMe_3$ and *N*,*O*-dimethylhydroxylamine hydrochloride. Subsequent protection of the free hydroxyl group as the TBDPS ether using TBDPSCl and DMAP as catalyst was followed by reduction with DIBAL-H.[50,51] The oxime **34** was then synthesized in 98% yield by condensation of aldehyde **40**, prepared according to either route presented in Scheme 8, with hydroxylamine hydrochloride in the presence of pyridine.

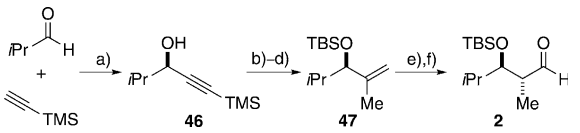
Treatment of oxime **34** with *t*BuOCl in CH_2Cl_2 at −78 °C led to in situ formation of the corresponding hydroximinoyl chloride, from which the nitrile oxide was generated by elimination upon slow addition to a solution of allylic alcohol **29**, *i*PrOH and EtMgBr in CH_2Cl_2 at 0 °C. Magnesium-directed 1,3-dipolar cycloaddition then provided isoxazoline **41** as a single diastereoisomer[52] in 74% yield. The influence of the TBDPS protected hydroxyl group at C19 was shown to be inconsequential for the diastereoselectivity of the reaction. When the epimeric oxime **42**[53] was subjected to the standard reaction conditions, the corresponding isoxazoline **43** was obtained as a single diastereoisomer (Scheme 9).[54] The bulky trityl protecting group proved essential in order to prevent coordination of the protected primary alcohol to magnesium.

The envisaged reductive opening of the isoxazoline necessitated protection of the free secondary hydroxyl group at C14. As the trityl group was incompatible with the reductive conditions of the isoxazoline opening, it was replaced at this stage by a carbonate to mask the 1,2-diol unit. The trityl group was cleaved with *p*-TsOH in methanol to furnish the diol in 92% yield, which was subsequently protected as the carbonate using triphosgene and pyridine in 97% yield. Finally, reductive opening with Raney-nickel in the presence of boric acid under a hydrogen atmosphere cleanly gave β-hydroxy ketone **44** in 88% yield.[55] Installation of the 1,3-*anti*-diol using the conditions reported by Evans[56] proceeded sluggishly and only afforded a 4.3:1 ratio of diastereoisomers in combined 74% yield. Despite extensive efforts to optimize the reaction and attempted use of other methods known to provide 1,3-*anti*-relationships,[57] the diastereoselectivity of the reduction could not be improved. The highly sterically congested environment around both the ketone and the hydroxyl group in combination with the unfavorable impact of the relative configuration of the stereogenic centers are the likely reasons for the low diastereoselectivity and the reduced reactivity of the system. Protection of the diol unit provided acetonide **45** in 99% yield. The carbonate was efficiently hydrolyzed with 1 N LiOH in a mixture of THF, MeOH and H_2O, and subsequent cleavage of the resulting diol with $NaIO_4$ absorbed on silica gel furnished aldehyde **5** in 99% yield (Scheme 10).[58]



Scheme 10. Completion of the C14–C20 aldehyde fragment **5**. a) *p*-TsOH·H_2O (cat.), MeOH, RT, 1.75 h, 92%; b) triphosgene, pyridine, CH_2Cl_2, −78 → 0 °C, 1.5 h, 97%; c) cat. Raney-Ni, $B(OH)_3$, H_2, MeOH/H_2O 5:1, RT, 3 h, 88%; d) $Me_4N^+HB(OAc)_3^-$, AcOH/MeCN 1:1, −10 °C, 5 d, d.r. 4.3:1, 74%; e) *p*-TsOH·H_2O (cat.), 2,2-dimethoxypropane, RT, 20 min, 99%; f) 1 N aq. LiOH, THF/MeOH/H_2O 5:1:1, RT, 25 min, 92%; g) $NaIO_4$ on silica, CH_2Cl_2, RT, 30 min, 99%.

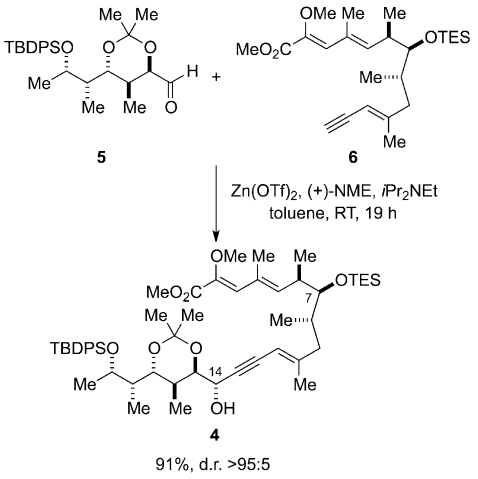
Synthesis of the C21–C25 aldehyde fragment: The C21–C25 aldehyde fragment provided the opportunity to highlight the potential of the asymmetric catalytic version of the zinc triflate mediated addition of terminal alkynes to aldehydes for the straightforward large-scale synthesis of chiral building blocks. Addition of TMS acetylene to isobutyraldehyde in the presence of 20 mol% $Zn(OTf)_2$ provided the corresponding propargylic alcohol **46** in 77% yield and 92% *ee*, as determined by GC on a chiral stationary phase (Scheme 11). Direct removal of the TMS protecting group



Scheme 11. Synthesis of aldehyde **2**. a) $Zn(OTf)_2$ (20 mol%), (+)-NME (22 mol%), NEt_3 (50 mol%), toluene, 60°C, 12 h, 92% *ee*, 77%; b) K_2CO_3, MeOH, RT, 7.5 h; c) $[Cp_2ZrCl_2]$ (20 mol%), $AlMe_3$, CH_2Cl_2, RT, 24 h; d) TBSCl, imidazole, DMF, RT, 18 h, 71% (three steps); e) 9-BBN, THF, −78°C → RT, 13.5 h, then THF/EtOH, 2 M aq. NaOH, 30% aq. H_2O_2, RT, 2 h, d.r. 96:4, 69%; f) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78°C, 70 min, 81%.

gave the intermediate volatile alcohol.[59] A zirconium-catalyzed carboalumination of the alkyne installed the 2-methyl substituted terminal alkene. After extensive optimization, best results were obtained when the reaction was run with 20 mol% of $[Cp_2ZrCl_2]$ and 6.2 equivalents of $AlMe_3$. The use of deoxygenated CH_2Cl_2 proved to be essential for high turnover. The resulting allylic alcohol was directly subjected to silylation with TBSCl, providing silyl ether **47** in 71% yield over three steps. As documented in many cases, the attempted zirconium-mediated carboalumination of the TBS-protected propargylic alcohol failed under a variety of conditions. The subsequent diastereoselective hydroboration of **47** with 9-BBN, previously described by Evans and co-workers,[60] afforded the known *anti*-substituted primary alcohol[61] in 69% yield and 96:4 d.r. Finally, oxidation of the alcohol using Swern conditions gave aldehyde **2** in 81% yield.

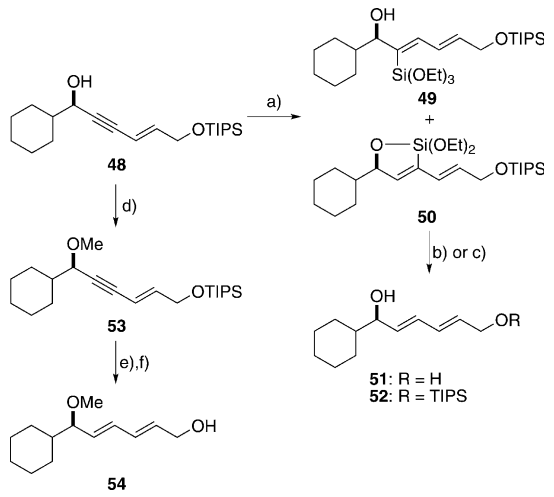
Coupling of the C1–C13 and C14–C20 fragments and macrolactonization: The zinc triflate mediated coupling of enyne **6** with aldehyde **5** constituted the key step in the synthesis of bafilomycin A_1. In the event, formation of the zinc acetylide from enyne **6** in the presence of (+)-NME and subsequent addition to aldehyde **5** proceeded smoothly, providing propargylic alcohol **4** in 91% yield as a single diastereoisomer according to analysis by ^1H NMR spectroscopy [Eq. (1)].[62] Only slight modifications of the standard reaction conditions reported earlier[15] were required: a two-fold excess of dried zinc triflate and 2.3 equivalents of both (+)-NME and amine base were best suited to provide for high reproducibility.[63] The standard base NEt_3 was generally replaced by the bulkier iPr_2NEt to minimize the risk of epimerization at the labile α-stereogenic center of aldehyde **5**. A control experiment with the lithium acetylide derived from enyne **6** revealed complete lack of selectivity in the addition event, affording the product as a 1:1 mixture of diastereoisomers. The excellent reagent control of the zinc triflate mediated addition was further demonstrated by switching to the enantiomeric (−)-NME, forming the epimeric propargylic alcohol as a single diastereoisomer.[64]



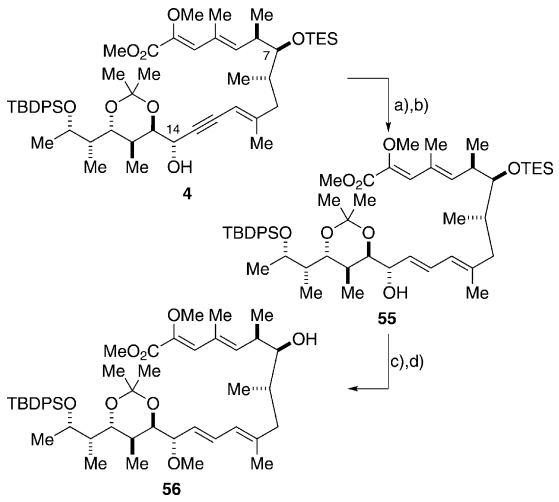
Selective semi-reduction of the enyne moiety to the corresponding *trans*,*trans*-diene constituted the next challenge in the synthetic sequence. Traditional methods for propargylic alcohols frequently used in organic synthesis comprise reduction under dissolving metal conditions in liquid ammonia[65] or directed reduction with Red-Al or $LiAlH_4$.[66] The early installation of the C1–C5 α,β,γ,δ-unsaturated ester unit in **4** excluded these approaches due to lack of chemoselectivity. As the most promising alternative, a hydrosilylation–protodesilylation sequence was chosen instead.[67,68]

As little precedence for the reduction of propargylic enynes has been reported in the literature, a model study on *trans*-reductions via hydrosilylation-protodesilylation was carried out (Scheme 12). Propargylic enyne **48**, easily accessible in one step by addition of TIPS protected (*E*)-pent-2-en-4-yn-1-ol to cyclohexane carbaldehyde, was chosen as a model system. Treatment of **48** with 1.2 equivalents $(EtO)_3SiH$ and catalytic amounts of $[Cp^*Ru(NCMe)_3]PF_6$[69] in CH_2Cl_2 under the reported conditions led to a mixture of isomeric vinylsilanes **49** and **50**.[70] As a result of the sensitivity of the intermediate vinylsilanes, the unpurified reaction product was carried on directly to the next step. Treating the mixture of **49** and **50** with excess TBAF in THF at room temperature led to clean formation of diol **51** in 68% yield. Reducing the amount of TBAF to exactly one equivalent resulted in selective protodesilylation in 71% yield, leaving the TIPS group untouched.

These modifications proved to be crucial for a successful application of the hydrosilylation–protodesilylation sequence in the synthesis of bafilomycin A_1, for which selective protodesilylation of the vinylsilane in the presence of two silyl protected hydroxyl groups was a mandatory condition. Later experiments revealed that the temperature could



Scheme 12. Model study on hydrosilylation-protodesilylation of propargylic enyne **48**. a) $(EtO)_3SiH$, $[Cp^*Ru(NCMe)_3]PF_6$ (4 mol%), CH_2Cl_2, 0°C → RT, 2 h; b) TBAF (3.1 equiv), CuI, THF, RT, 11 h, 68% (two steps); c) TBAF (1.0 quiv.), CuI, THF, RT, 1.25 h, 71% (two steps); d) *t*BuOK, THF, −20°C, 25 min, then MeI, −20°C, 1.5 h, 53% (71% based on recovered **48**); e) $(EtO)_3SiH$, $[Cp^*Ru(NCMe)_3]^+PF_6^-$ (8 mol%), CH_2Cl_2, 0°C → RT, 1.5 h; f) TBAF (3.0 equiv), CuI, THF, RT, 24 h, traces (two steps).



Scheme 13. *Trans*-reduction of propargylic enyne **4**. a) $(EtO)_3SiH$, $[Cp^*Ru(NCMe)_3]PF_6$ (14 mol%), CH_2Cl_2, 0°C → RT, 15 min; b) TBAF (1.05 equiv), CuI, THF, 0°C, 10 min, 72% (two steps); c) MeI, NaH, THF/DMF 1:1, 0°C → RT, 2 h, 89%; d) HF·pyridine, pyridine, THF, 0°C → RT, 7 h, 91%.

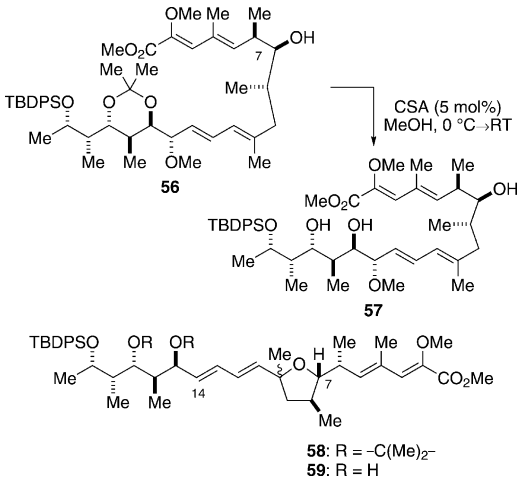
be further reduced to 0°C, with the protodesilylation being essentially complete within 10 min. In order to guarantee high reliability and reproducibility, the TBAF solution was always freshly prepared from solid TBAF·3 H_2O and anhydrous THF.

The synthetic plan required subsequent methylation of the C14-hydroxyl group after *trans*-reduction of the enyne moiety. From a synthetic point of view, the order of these two transformation could be reversed, thus performing the *trans*-reduction of the enyne moiety after methylation of the propargylic hydroxyl group. Hydrosilylation of propargylic ether **53**, however, showed that only sluggish conversion was observed under the developed conditions, leading to formation of multiple products. Subsequent protodesilylation furnished only traces of the corresponding methylated diene **54** (Scheme 12). These results highlight that the availability of a free hydroxyl group is important for efficient hydrosilylation, suggesting that replacement of one alkoxy group of the silane by the propargylic hydroxyl group ideally positions the silane for an intramolecular hydrosilylation.

When the established reaction conditions for the hydrosilylation were applied to enyne **4**, clean conversion of the starting material was observed. Treatment of the intermediate mixture of vinyl silanes with TBAF in the presence of CuI provided the *trans,trans*-diene **55** in excellent 72% yield for the two-step transformation, with none of the isomeric *cis,trans*-diene detected by ^1H NMR (Scheme 13). Most importantly, the TES-protected C7-hydroxyl functionality proved to be stable to the conditions of the protodesilylation of the intermediate vinyl silane. Subsequent treatment of the allylic alcohol with MeI and NaH in a mixture of THF and DMF cleanly afforded the corresponding C14 methyl ether. The TES group on the C7 hydroxyl group was then selectively removed using HF·pyridine in THF to provide alcohol **56**. This deprotection was necessary in the light of previous reports from the Evans and the Roush laboratories, which had shown that efficient macrolactonization did only occur when the C7 hydroxyl group was unprotected, presumably due to higher population of conformations favoring macrolactonization.[71]

Hydrolysis of the acetonide and saponification of the methyl ester were supposed to set the stage for the macrolactonization. Unfortunately, the cleavage of the acetal protecting group posed a significant challenge, with problems arising from the unexpected acid sensitivity of the C10–C13 diene subunit. When acetonide **56** was treated with 5 mol% CSA in MeOH at 0°C for 30 min, the expected triol **57** was obtained in only 25% yield (Scheme 14).

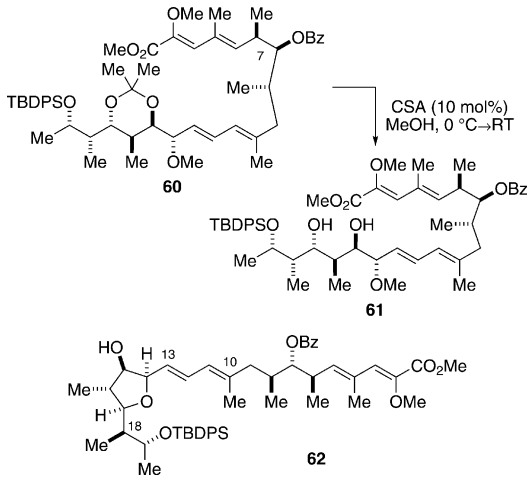
Two additional reaction products were isolated and identified by mass spectroscopy as well as 1D- and 2D-NMR ex-



Scheme 14. Attempted deprotection of acetonide **56**.

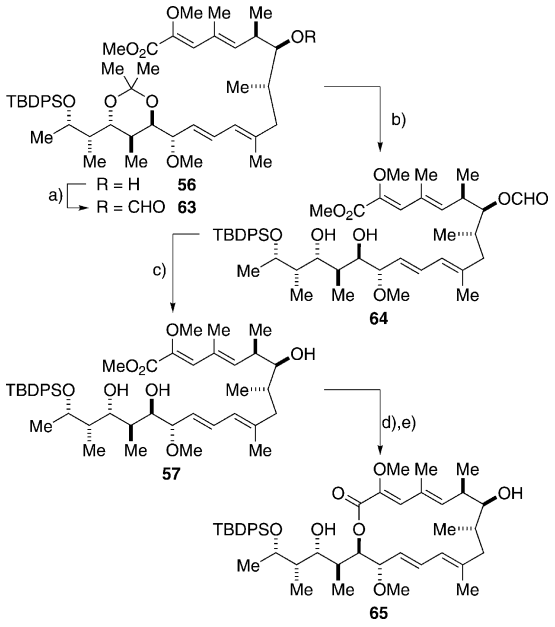
periments as 1.6:1 diastereomeric mixtures of tetrahydrofurans **58** and **59**. Mechanistically, the formation of the tetrahydrofuran moiety can be explained by a conjugate displacement of the methoxy group as a result of the attack of the C7-hydroxyl group onto carbon atom C10 of the diene moiety.[72] Analysis of NOE experiments revealed that the tetrahydrofuran ring of the major diastereomer possessed an *anti*-substitution pattern, while the minor diastereomer was found to be the corresponding *syn*-isomer. When the deprotection reaction was allowed to proceed for several hours, triol **57** and acetonide **58** both converged towards dihydroxytetrahydrofuran **59**.

Despite extensive efforts, reaction conditions preventing this undesired tetrahydrofuran formation could not be identified. Under a wide range of conditions, employing either Brønsted or Lewis acids in the presence or absence of nucleophilic solvents, the formation of **58** and **59** occurred to a significant degree. The decision was therefore taken to temporarily protect the C7 hydroxyl group with an acid-stable, but base-labile protecting group that could be cleaved during saponification of the ester moiety. When the corresponding benzoyl-protected acetonide **60** was subjected to deprotection using 10 mol% CSA in MeOH at 0°C, the desired diol **61** was isolated together with a slightly less polar byproduct **62** that had slowly formed during the course of the reaction (Scheme 15). The structure could be assigned by mass spectroscopy in combination with 1D- and 2D-NMR experiments to be tetrahydrofuran **62**, resulting from S_N2 displacement of the allylic C14 methoxy group by the C17-hydroxyl group.



Scheme 15. Attempted deprotection of acetonide **60**.

Again, extensive attempts to optimize the reaction conditions and suppress formation of tetrahydrofuran **62** were met with no success. However, the observed tetrahydrofuran formation occurred at a significantly slower rate than formation of tetrahydrofurans **58** and **59**. Interestingly, any products resulting from S_N2 displacement of the C14-methoxy group by the C17-hydroxyl group were never observed in the case of acetonide **56**. Best results for deprotection of the acetonide in **60** were obtained by quenching the reaction after approximately 30% conversion and resubmission of the isolated starting material **60** to the reaction conditions. This procedure provided diol **61** in 69% yield (80% yield based on recovered acetonide **60**) after three cycles. Though this approach would have provided access to sufficient amounts of material to continue the synthesis, modification of the protecting group at the C7-hydroxyl group was required, as the benzoyl protecting group turned out to be too stable for removal under the conditions of the saponification. Therefore, the C7-hydroxyl group was protected as the corresponding formate, the sterically least demanding ester protecting group, in 99% yield using the mixed anhydride of formic and acetic acid (Scheme 16). The resulting acetonide



Scheme 16. Formation of triol **57** and macrolactonization. a) AcO(O)CH, DMAP, CH_2Cl_2, RT, 15 min, 99%; b) CSA (0.05 equiv), MeOH, RT, 20 min, three cycles; c) K_2CO_3, MeOH, RT, 20 min, 68% from **63** (79% based on recovered **56**); d) 1N aqueous LiOH, THF/MeOH/H_2O 5:1:1, RT, 12 h; e) 2,4,6-trichlorobenzoylchloride, *i*Pr_2NEt, toluene, RT, 4 h, then diluted with toluene, DMAP, RT → 40°C, 5 h, 60% (two steps).

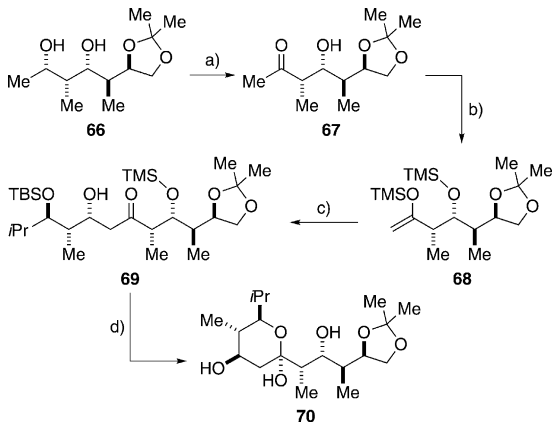
63 was treated under the previously described conditions for the benzoyl protected acetonide **60**, applying the same strategy of quenching the reaction after approximately 30% conversion and resubmission of the isolated starting material **63** to the reaction conditions. After the third cycle, the crude reaction mixture containing remaining acetonide **63** and diol **64** was combined with diol **64** isolated from the two previous cycles, and the formate protecting group was removed under mild conditions employing K_2CO_3 in MeOH. This strategy finally provided triol **57** in 68% yield (79% yield based on recovered acetonide **56**).[73]

With triol **57** in hand, the attention turned to the formation of the 16-membered macrolactone. Inspired by synthetic precedence from Hanessian's approach toward bafilomy-

cin A_1,[11] we attempted selective formation of the macrolactone in the presence of the unprotected C17-hydroxyl group. We anticipated that the bulky TBDPS protecting group on the C19-hydroxyl group would prevent ring closure to the 18-membered macrolactone. In addition, computational studies by Hanessian and co-workers had indicated that the larger ring was also significantly higher in energy.[74] In the event, saponification of the methyl ester using 1 N LiOH in a mixture of THF, MeOH and water at room temperature smoothly provided the corresponding *seco*-acid. Macrolactonization proceeded best using Yonemitsu's modification of the Yamaguchi method,[75] furnishing as expected selectively the 16-membered macrolactone **65** in 60% yield over two steps, without any detectable trace of the larger ring isomer.[76]

Introduction of the C21–C25 fragment and completion of the synthesis: The introduction of the C21–C25 aldehyde fragment via a Mukaiyama aldol reaction required oxidation of the C19-hydroxyl group to the corresponding ketone. A traditional and conservative approach required prior protection of the free hydroxyl groups on C7 and C17, selective removal of the TBDPS-protecting group, and deprotection of the newly introduced protecting groups after the Mukaiyama aldol reaction. Such a strategy would not only increase the total number of steps, but proved also difficult due to protecting group incompatibilities and the required mildness of the conditions for global deprotection imposed by the sensitivity of bafilomycin A_1 toward basic and acidic conditions.[1]

A report on oxidation reactions in natural bafilomycin A_1 encouraged us to attempt the selective oxidation of the C19-hydroxyl group in the presence of the unprotected C7- and C17-hydroxyl groups.[77] We reasoned that the C19-hydroxyl group was the sterically least hindered, and that oxidation systems capable of oxidizing primary alcohols to aldehydes in the presence of free secondary alcohols might also efficiently differentiate between the three secondary alcohols present in the substrate. Most promising seemed to be TEMPO as a particularly bulky oxidant, with $PhI(OAc)_2$ serving as stoichiometric oxidant.[78] Suitable reaction conditions were developed using diol **66** as a model system that closely mimicked the steric environment of the C14–C20 region.[79] When diol **66** was treated with catalytic amounts of TEMPO and $PhI(OAc)_2$, slow but clean transformation to the corresponding methyl ketone **67** was observed in 90% yield (Scheme 17). Oxidation of the C17-hydroxyl group or overoxidation to the diketone was never detected during analysis of the crude reaction mixtures by ^{1}H NMR. To test the influence of the absolute configuration at C19 on the outcome of the selective oxidation, a 2:1 mixture of *syn*-diol **66** and the corresponding *anti*-diol epimeric at C19 was subjected to the reaction conditions. When the reaction was stopped after 90% conversion, the reisolated starting material consisted exclusively of the *anti*-isomer, demonstrating that oxidation of *syn*-diol **66** occurred at a higher reaction rate than oxidation of the epimeric *anti*-diol.



Scheme 17. Model studies on the selective oxidation of the C19-hydroxyl group and the Mukaiyama aldol reaction. a) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, RT, 4 d, 90%; b) NEt_3, TMSCl, LiHMDS, THF, −78 °C, 1.5 h; c) aldehyde **2**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, d.r. >95:5; d) TAS-F, H_2O, DMF, RT, 3 h, 61% (three steps).

Ketone **67** was subsequently used to determine reaction conditions for the Mukaiyama aldol addition. The transformation required formation of the silylenol ether and concomitant protection of all free hydroxyl groups as the corresponding TMS ethers. Adjustment of the conditions previously reported by Paterson for a similar transformation efficiently provided protected silylenol ether **68**, using LiHMDS and the $TMSCl{\cdot}NEt_3$ complex. The silylenol ether **68** then reacted with aldehyde **2** in the presence of $BF_3{\cdot}OEt_2$ as Lewis acid to provide hydroxy ketone **69**.[80] Due to partial deprotection during work-up, removal of all silyl groups was directly carried out with buffered TAS-F on the unpurified reaction mixture, providing hemiketal **70** in 61% yield over three steps (Scheme 17).[81] X-ray crystallographic analysis of the corresponding C21 *p*-nitrobenzoate revealed the correct relative configuration of the newly formed stereogenic centers (Figure 2).

With reaction conditions successfully established, the last steps of the synthesis could be attempted. The TBDPS group in **65** was removed using TAS-F buffered with water, providing the corresponding triol in 90% yield (Scheme 18). Subsequent treatment of the triol with TEMPO and $PhI(OAc)_2$ provided selectively methyl ketone **72** in excellent 71% yield, with no other oxidation products being de-

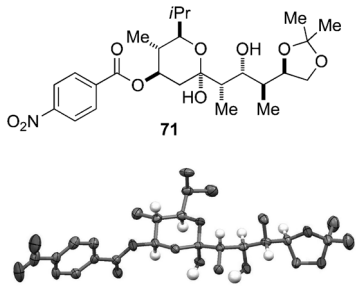
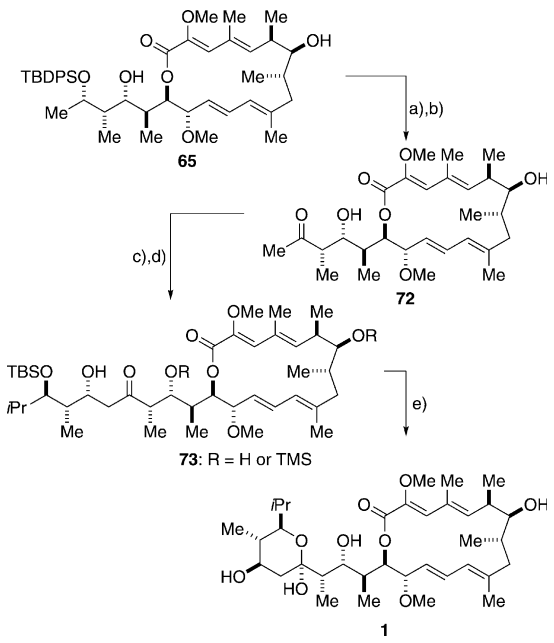


Figure 2. ORTEP representation of the crystal structure of *p*-nitrobenzoate **71**.



Scheme 18. Completion of the synthesis of bafilomycin A_1 (**1**). a) TAS-F, H_2O, DMF, 0 °C → RT, 4 h, 90 %; b) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, RT, 4 d, 71 %; c) NEt_3, TMSCl, LiHMDS, THF, −78 °C, 25 min; d) aldehyde **2**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 30 min; e) TAS-F, H_2O, DMF, RT, 45 min, 35 % (three steps; 76 % based on recovered **72**).

tected. This present example is one of the rare cases in which two secondary hydroxyl groups could be efficiently differentiated in an oxidation reaction.[82]

The silylenol ether for the Mukaiyama aldol reaction was then accessed from ketone diol **72** using LiHMDS, TMSCl and NEt_3 in THF, leading to concomitant protection of both free hydroxyl groups as the TMS ethers. Subsequent treatment with aldehyde **2** and $BF_3{\cdot}OEt_2$ led to a mixture of bis-, mono- and unprotected aldol products **73**. As in the case of the model system, the crude mixture was directly subjected to global removal of all silyl protecting groups using buffered TAS-F, providing directly synthetic bafilomycin A_1 in 35 % yield over three steps, or 76 % based on recovered ketone **72**.[83]

Conclusion

In summary, we have successfully completed a stereoselective, convergent synthesis of bafilomycin A_1 which highlights the potential of two synthetic methodologies developed in our laboratories—the nitrile oxide cycloaddition and the zinc acetylide addition to aldehydes—for the use in the synthesis of complex natural products. The C14–C20 portion with its four contiguous stereogenic centers was assembled in high selectivity using our nitrile oxide cycloaddition methodology. The use of a chiral allylic diol in this transformation provided straightforward access to the C14-aldehyde functionality. The efficient coupling of aldehyde **5** and enyne **6** highlights the mildness and versatility of zinc acetylide mediated addition of terminal alkynes to aldehydes, allowing the stereoselective coupling of complex and highly functionalized fragments. In combination with the semireduction of the enyne using a sequence of hydrosilylation and protodesilylation, the C10–C13 *trans*,*trans*-diene subunit of the target structure was installed. This strategy offers an alternative to classical palladium-catalyzed cross-coupling approaches for the stereoselective installation of 1,3-diene systems and could be applied to the efficient, convergent coupling of complex and densely functionalized fragments in the synthesis of other natural products.

Experimental Section

Full experimental details with complete characterization of all new compounds are given in the Supporting Information.

Acknowledgements

This research was supported by ETH and the Swiss National Science Foundation. We thank the Natural Sciences and Engineering Research Council of Canada for a postdoctoral scholarship (to L.D.F.) and the Fonds der Chemischen Industrie for a pre-doctoral scholarship (to F.K.). We are grateful for generous support of our program from Roche, Eli Lilly, and Boehringer Ingelheim.

[1] a) G. Werner, H. Hagenmaier, K. Albert, H. Kohlshorn, H. Drautz, *Tetrahedron Lett.* **1983**, *24*, 5193–5196; b) G. Werner, H. Hagenmaier, H. Drautz, A. Baumgartner, H. Zähner, *J. Antibiot.* **1984**, *37*, 110–117.
[2] For a review on the plecomacrolide family, see: W.-M. Dai, Y. Guan, J. Jin, *Curr. Med. Chem.* **2005**, *12*, 1947–1993.
[3] E. J. Corey, J. W. Ponder, *Tetrahedron Lett.* **1984**, *25*, 4325–4328.
[4] G. H. Baker, P. J. Brown, R. J. J. Dorgan, J. R. Everett, S. V. Ley, A. M. Z. Slawin, D. J. Williams, *Tetrahedron Lett.* **1987**, *28*, 5565–5568.
[5] G. H. Baker, P. J. Brown, R. J. J. Dorgan, J. R. Everett, *J. Chem. Soc. Perkin Trans. 2* **1989**, 1073–1079.
[6] E. J. Bowman, A. Siebers, K. Altendorf, *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 7972–7976.
[7] a) E. J. Bowman, B. J. Bowman, *J. Bioenerg. Biomembr.* **2005**, *37*, 431–435; b) C. Farina, S. Gagliardi, *Drug Discovery Today* **1999**, *4*, 163–172; c) S. Gagliardi, M. Rees, C. Farina, *Curr. Med. Chem.* **1999**, *6*, 1197–1212; d) C. Farina, S. Gagliardi, *Curr. Pharm. Des.* **2002**, *8*, 2033–2048.
[8] D. A. Evans, A. M. Calter, *Tetrahedron Lett.* **1993**, *34*, 6871–6874.
[9] a) K. Toshima, T. Jyojima, H. Yamaguchi, H. Murase, T. Yoshida, S. Matsumura, M. Nakata, *Tetrahedron Lett.* **1996**, *37*, 1069–1072; b) K. Toshima, H. Yamaguchi, T. Jyojima, M. Noguchi, M. Nakata, S. Matsumura, *Tetrahedron Lett.* **1996**, *37*, 1073–1076; c) K. Toshima, T. Jyojima, H. Yamaguchi, T. Noguchi, H. Yoshida, H. Murase, M. Nakata, S. Matsumura, *J. Org. Chem.* **1997**, *62*, 3271–3284.
[10] a) W. R. Roush, T. D. Bannister, *Tetrahedron Lett.* **1992**, *33*, 3587–3590; b) W. R. Roush, T. D. Bannister, M. D. Wendt, *Tetrahedron Lett.* **1993**, *34*, 8387–8390; c) K. A. Scheidt, A. Tasaka, T. D. Bannister, M. D. Wendt, W. R. Roush, *Angew. Chem.* **1999**, *111*, 1760–1762; *Angew. Chem. Int. Ed.* **1999**, *38*, 1652–1655; d) K. A. Scheidt, T. D. Bannister, A. Tasaka, M. D. Wendt, G. J. Savall, G. J. Fegley, W. R. Roush, *J. Am. Chem. Soc.* **2002**, *124*, 6981–6990; e) W. R. Roush, T. D. Bannister, M. D. Wendt, J. A. Jablonowski, K. A. Scheidt, *J. Org. Chem.* **2002**, *67*, 4275–4283.

[11] a) S. Hanessian, J. Ma, W. Wang, *J. Am. Chem. Soc.* **2001**, *123*, 10200–10206; b) S. Hanessian, J. Ma, W. Wang, Y. Gai, *J. Am. Chem. Soc.* **2002**, *124*, 7249 (erratum).
[12] a) J. A. Marshall, N. D. Adams, *Org. Lett.* **2000**, *2*, 2897–2900; b) J. A. Marshall, N. D. Adams, *J. Org. Chem.* **2002**, *67*, 733–740.
[13] a) I. Paterson, S. Bower, M. D. McLeod, *Tetrahedron Lett.* **1995**, *36*, 175–178; b) B. Breit, S. K. Zahn, *Tetrahedron Lett.* **1998**, *39*, 1901–1904; c) J.-C. Poupon, R. Lopez, J. Prunet, J.-P. Férézou, *J. Org. Chem.* **2002**, *67*, 2118–2124; d) J.-C. Poupon, J. Demont, J. Prunet, J.-P. Férézou, *J. Org. Chem.* **2003**, *68*, 4700–4707; e) R. Lopez, J.-C. Poupon, J. Prunet, J.-P. Férézou, L. Ricard, *Synthesis* **2005**, 644–661; f) F. Eustache, P. I. Dalko, J. Cossy, *Tetrahedron Lett.* **2003**, *44*, 8823–8826; g) F. Eustache, P. I. Dalko, J. Cossy, *J. Org. Chem.* **2003**, *68*, 9994–10002; h) E. Quéron, R. Lett, *Tetrahedron Lett.* **2004**, *45*, 4527–4531; i) E. Quéron, R. Lett, *Tetrahedron Lett.* **2004**, *45*, 4533–4537; j) E. Quéron, R. Lett, *Tetrahedron Lett.* **2004**, *45*, 4539–4543; k) J. S. Yadav, K. B. Reddy, G. Sabitha, *Tetrahedron* **2008**, *64*, 1971–1982.
[14] F. Kleinbeck, E. M. Carreira, *Angew. Chem.* **2009**, *121*, 586–589; *Angew. Chem. Int. Ed.* **2009**, *48*, 578–581.
[15] a) J. W. Bode, N. Fraefel, D. Muri, E. M. Carreira, *Angew. Chem.* **2001**, *113*, 2128–2131; *Angew. Chem. Int. Ed.* **2001**, *40*, 2082–2085; b) J. W. Bode, E. M. Carreira, *Org. Lett.* **2001**, *3*, 1587–1590; c) L. Fader, E. M. Carreira, *Org. Lett.* **2004**, *6*, 2485–2488; d) N. Lohse-Fraefel, E. M. Carreira, *Org. Lett.* **2005**, *7*, 2011–2014; e) N. Becker, E. M. Carreira, *Org. Lett.* **2007**, *9*, 3857–3858; f) N. Lohse-Fraefel, E. M. Carreira, *Chem. Eur. J.* **2009**, *15*, 12065–12081; g) D. Muri, E. M. Carreira, *J. Org. Chem.* **2009**, *74*, 8695–8712; for applications in natural product synthesis, see: h) J. W. Bode, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 3611–3612; i) J. W. Bode, E. M. Carreira, *J. Org. Chem.* **2001**, *66*, 6410–6424; j) D. Muri, N. Lohse-Fraefel, E. M. Carreira, *Angew. Chem.* **2005**, *117*, 4104–4106; *Angew. Chem. Int. Ed.* **2005**, *44*, 4036–4038.
[16] a) D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807; b) D. E. Frantz, R. Fässler, C. S. Tomooka, E. M. Carreira, *Acc. Chem. Res.* **2000**, *33*, 373–381; c) D. Boyall, F. López, H. Sasaki, D. E. Frantz, E. M. Carreira, *Org. Lett.* **2000**, *2*, 4233–4236; d) E. El-Sayed, N. K. Anand, E. M. Carreira, *Org. Lett.* **2001**, *3*, 3017–3020; e) D. Boyall, D. E. Frantz, E. M. Carreira, *Org. Lett.* **2002**, *4*, 2605–2606; for an application in natural product synthesis, see: f) A. M. Szpilman, D. M. Cereghetti, N. R. Wurtz, J. M. Manthorpe, E. M. Carreira, *Angew. Chem.* **2008**, *120*, 4407–4410; *Angew. Chem. Int. Ed.* **2008**, *47*, 4335–4338; g) A. M. Szpilman, J. M. Manthorpe, E. M. Carreira, *Angew. Chem.* **2008**, *120*, 4411–4414; *Angew. Chem. Int. Ed.* **2008**, *47*, 4339–4342; h) A. M. Szpilman, D. M. Cereghetti, J. M. Manthorpe, N. R. Wurtz, E. M. Carreira, *Chem. Eur. J.* **2009**, *15*, 7117–7128.
[17] a) A. G. Myers, B. H. Yang, H. Chen, J. L. Gleason, *J. Am. Chem. Soc.* **1994**, *116*, 9361–9362; b) A. G. Myers, J. L. Gleason, T. Yoon, *J. Am. Chem. Soc.* **1995**, *117*, 8488–8489; c) A. G. Myers, J. L. Gleason, T. Yoon, D. W. Kung, *J. Am. Chem. Soc.* **1997**, *119*, 656–673; d) A. G. Myers, B. H. Yang, H. Chen, L. McKinstry, D. J. Kopecky, J. L. Gleason, *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.
[18] The diastereoselectivity of the Myers alkylation could not unequivocally be determined from the ^{1}H NMR of the unpurified reaction product due to overlap of characteristic signals. Since it has been previously shown that the reductive cleavage of the auxiliary with lithium amidoborate occurs without loss of configurational purity at the newly formed stereocenter, the enantiopurity of the *p*-nitrobenzoate derivative of alcohol **9** was determined.
[19] A. G. Myers, B. H. Yang, D. J. Kopecky, *Tetrahedron Lett.* **1996**, *37*, 3623–3626.
[20] The boiling point of alcohol **9** has been reported to be 67–72 °C at 12 mm Hg; see: a) E. Buchta, H. Schesinger, *Justus Lieb. Ann. Chem.* **1955**, *591*, 1–24; b) J. D. Pettigrew, P. D. Wilson, *Org. Lett.* **2006**, *8*, 1427–1429. Removal of all solvents via a Vigreux column after work-up was required.
[21] The presence of 1-butanol in the reaction product could unequivocally be established by comparison of NMR data with an original sample as well as by NMR and high resolution mass spectroscopic data of the *p*-nitrobenzoate derivative of 1-butanol. The *p*-nitrobenzoate of 1-butanol was obtained by treating an aliquot of the crude reaction mixture with *p*-nitrobenzoyl chloride and NEt_3 in CH_2Cl_2 at 0 °C, followed by purification using chromatography on silica gel. For NMR and mass spectroscopic data of butyl *p*-nitrobenzoate, see: J. McNulty, J. J. Nair, S. Cheekoori, V. Larichev, A. Capretta, A. J. Robertson, *Chem. Eur. J.* **2006**, *12*, 9314–9322.
[22] For reductive opening of THF with lithium di-*tert*-butyldiphenyl (LiDBB), see: a) S. Streiff, N. Ribeiro, L. Désaubry, *J. Org. Chem.* **2004**, *69*, 7592–7598 and references therein. For additional activation by a boron Lewis acid, see: b) B. Mudryk, T. Cohen, *J. Am. Chem. Soc.* **1991**, *113*, 1866–1867.
[23] a) D. E. Van Horn, E.-I. Negishi, *J. Am. Chem. Soc.* **1978**, *100*, 2252–2254; b) C. L. Rand, D. E. Van Horn, M. W. Moore, E.-I. Negishi, *J. Org. Chem.* **1981**, *46*, 4093–4096; c) E.-I. Negishi, *Pure Appl. Chem.* **1981**, *53*, 2333–2356; d) E.-I. Negishi, D. E. Van Horn, T. Yoshida, *J. Am. Chem. Soc.* **1985**, *107*, 6639–6647.
[24] The reaction had been previously described for the enantiomeric bishomopropargylic alcohol *ent*-**9**; see U. Bhatt, M. Christmann, M. Quitschalle, E. Claus, M. Kalesse, *J. Org. Chem.* **2001**, *66*, 1885–1893.
[25] P. Wipf, S. Lim, *Angew. Chem.* **1993**, *105*, 1095–1097; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1068–1071.
[26] a) R. Baker, J. L. Castro, *J. Chem. Soc. Perkin Trans. 1* **1990**, 47–65. For the synthesis of the chloro- and bromoacids analogous to **191**, see: b) A. P. Krapcho, *J. Org. Chem.* **1962**, *27*, 2375–2377.
[27] T. Ritter, P. Zarotti, E. M. Carreira, *Org. Lett.* **2004**, *6*, 4371–4374. Methanesulfonic acid anhydride was preferentially chosen to prevent formation of the less reactive corresponding allylic chloride. Any byproducts resulting from S_N2' substitution were not detected, highlighting complete selectivity for the S_N2 pathway.
[28] Vinyl iodide **10** was sufficiently UV active to be used without further derivatization. The maximum of the absorption was determined by UV spectroscopy to be around $\lambda = 248$ nm.
[29] a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156; b) D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287; c) S. D. Meyer, S. L. Schreiber, *J. Org. Chem.* **1994**, *59*, 7549–7552.
[30] a) A. Abiko, J.-F. Liu, S. Masamune, *J. Org. Chem.* **1996**, *61*, 2590–2591; b) A. Abiko, J.-F. Liu, S. Masamune, *J. Am. Chem. Soc.* **1997**, *119*, 2586–2587; c) J.-F. Liu, A. Abiko, Z. Pei, D. C. Buske, S. Masamune, *Tetrahedron Lett.* **1998**, *39*, 1873–1876; d) T. Inoue, J.-F. Liu, D. C. Buske, A. Abiko, *J. Org. Chem.* **2002**, *67*, 5250–5256.
[31] Additionally, the auxiliary could be easily recovered in 96% yield. The intermediate secondary silyl ether **18** was found to be prone to migration of the silyl protecting group even at −20 °C, leading to a mixture of all four possible non-, mono- and diprotected isomers after two weeks.
[32] a) W. P. Griffith, S. V. Ley, W. P. Whitcombe, A. D. White, *J. Chem. Soc. Chem. Commun.* **1987**, 1625–1627; b) W. P. Griffith, S. V. Ley, *Aldrichimica Acta* **1990**, *23*, 13–19; c) S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639–666.
[33] H.-J. Bestmann, H. Hartung, *Chem. Ber.* **1966**, *99*, 1198–1207.
[34] The decision to reduce the ester prior to Sonogashira coupling was taken to avoid intricacies from potential deactivation of the palladium catalyst by trace impurities present after the Wittig olefination.
[35] A. R. De Lera, B. Iglesias, J. Rodríguez, R. Alvarez, S. López, X. Villanueva, E. Padrós, *J. Am. Chem. Soc.* **1995**, *117*, 8220–8231.
[36] A. G. Schultz, J. J. Napier, R. Ravichandran, *J. Org. Chem.* **1983**, *48*, 3408–3412.
[37] It had been previously shown by Roush and co-workers for a similar system that the use of the diisopropoxyphosphonate **23** proved to be crucial to obtain high (*E*)-selectivity; see reference [10c,d] for details.
[38] For an alternative, more conventional entry to the C14–C20 fragment of bafilomycin A_1, see: F. Kleinbeck, PhD thesis, Diss. ETH No. 17777, ETH Zurich (Switzerland), **2008**.
[39] The reaction proved to be highly sensitive to the addition order, the type of base and both the amounts of base and $PhNTf_2$ used.

[40] a) P. Michel, S. V. Ley, *Angew. Chem.* **2002**, *114*, 4054–4057; *Angew. Chem. Int. Ed.* **2002**, *41*, 3898–3901; b) P. Michel, S. V. Ley, *Synthesis* **2003**, 1598–1602; for general reviews on 1,2-diacetals, see: c) S. V. Ley, D. K. Baeschlin, D. J. Dixon, A. C. Foster, S. J. Ince, H. W. M. Priepke, D. J. Reynolds, *Chem. Rev.* **2001**, *101*, 53–80; d) S. V. Ley, A. Polara, *J. Org. Chem.* **2007**, *72*, 5943–5959.

[41] A. N. Röhrle, H. Schmidhammer, *Helv. Chim. Acta* **1998**, *81*, 1070–1076.

[42] The correct absolute configuration was confirmed by analysis of the corresponding Mosher ester of **33**. See: a) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512–519; b) G. R. Sullivan, J. A. Dale, H. S. Mosher, *J. Org. Chem.* **1973**, *38*, 2143–2147; c) I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.

[43] a) J. R. Gage, D. A. Evans, *Org. Synth.* **1990**, *68*, 83–87. For a general review, see: b) D. A. Evans, *Aldrichimica Acta* **1982**, *15*, 23–32.

[44] a) T. D. Penning, S. W. Djuric, R. A. Haack, V. J. Kalish, J. M. Miyashiro, B. W. Rowell, S. S. Yu, *Synth. Commun.* **1990**, *20*, 307–312; for a study on the reactivity of saline borohydrides, see: b) H. C. Brown, S. Narasimhan, Y. M. Choi, *J. Org. Chem.* **1982**, *47*, 4702–4708.

[45] These conditions were used to reductively cleave the oxazolidinone auxiliary from a similar TBDPS-protected Evans *syn*-aldol product; see: D. R. Williams, D. C. Ihle, S. V. Plummer, *Org. Lett.* **2001**, *3*, 1383–1386.

[46] *ent*-**39** and *ent*-**40** have been previously reported, however, without experimental details; see: M. Toyota, N. Yamamoto, Y. Nishikawa, K. Fukumoto, *Heterocycles* **1995**, *40*, 115–117.

[47] The amide could be isolated in greater than 30% yield. The significant steric shielding of the amide moiety in **38** exerted by the bulky TBDPS protecting group apparently counterbalanced the inherently higher reactivity of this carbonyl group. For a report on the reductive opening of oxazolidinone auxiliaries using $LiBH_4$, see: a) G. E. Keck, G. D. Lundquist, *J. Org. Chem.* **1999**, *64*, 4482–4491; for the more commonly observed hydrolytic opening of isoxazoline auxiliaries using LiOH or $LiOH/H_2O_2$, see: b) D. A. Evans, T. C. Britton, J. A. Ellman, *Tetrahedron Lett.* **1987**, *28*, 6141–6144.

[48] a) D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129; b) D. A. Evans, M. DiMare, *J. Am. Chem. Soc.* **1986**, *108*, 2476–2478; c) D. A. Evans, R. L. Dow, T. L. Shih, J. M. Takacs, R. Zahler, *J. Am. Chem. Soc.* **1990**, *112*, 5290–5313.

[49] a) P. L. Anelli, C. Biffi, F. Montanari, S. Quici, *J. Org. Chem.* **1987**, *52*, 2559–2562; b) P. L. Anelli, F. Montanari, S. Quici, *Org. Synth.* **1990**, *69*, 212–217.

[50] For a DIBAL-H reduction on a closely related system, see: D. E. Cane, W. Tan, W. R. Ott, *J. Am. Chem. Soc.* **1993**, *115*, 527–535.

[51] a) A. Basha, M. Lipton, S. M. Weinreb, *Tetrahedron Lett.* **1977**, *18*, 4171–4174; b) J. I. Levin, E. Turos, S. M. Weinreb, *Synth. Commun.* **1982**, *12*, 989–993; for examples of the direct transformation of acyloxazolidinones into Weinreb amides, see: c) D. A. Evans, S. L. Bender, J. Morris, *J. Am. Chem. Soc.* **1988**, *110*, 2506–2526; d) D. A. Evans, A. M. Ratz, B. E. Huff, G. S. Sheppard, *J. Am. Chem. Soc.* **1995**, *117*, 3448–3467.

[52] For a rationale of the observed diastereoselectivity, see: a) K. N. Houk, S. R. Moses, Y.-D. Wu, N. G. Rondan, V. Jäger, R. Schohe, F. R. Fronczek, *J. Am. Chem. Soc.* **1984**, *106*, 3880–3882; b) K. N. Houk, H.-Y. Duh, Y.-D. Wu, S. R. Moses, *J. Am. Chem. Soc.* **1986**, *108*, 2754–2755. For a more general discussion, see: c) M. N. Paddon-Row, N. G. Rondan, K. N. Houk, *J. Am. Chem. Soc.* **1982**, *104*, 7162–7166.

[53] See Supporting Information for experimental details.

[54] As the hydroxyl group at C19 was later oxidized to the ketone, the absolute configuration of this stereogenic center was inconsequential. The reason for which the (*S*) configuration at C19 was finally chosen will be discussed later in the text.

[55] a) D. P. Curran, *J. Am. Chem. Soc.* **1982**, *104*, 4024–4026; b) D. P. Curran, *J. Am. Chem. Soc.* **1983**, *105*, 5826–5833; c) D. P. Curran, S. A. Scanga, C. J. Fenk, *J. Org. Chem.* **1984**, *49*, 3474–3478.

[56] D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.

[57] a) I. Paterson, O. Delgado, G. J. Florence, I. Lyothier, M. O'Brien, J. P. Scott, N. Sereinig, *J. Org. Chem.* **2005**, *70*, 150–160; b) G. E. Keck, C. A. Wager, T. Sell, T. T. Wager, *J. Org. Chem.* **1999**, *64*, 2172–2173; c) D. A. Evans, A. H. Hoveyda, *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449; d) D. A. Evans, P. H. Carter, E. M. Carreira, A. B. Charette, J. A. Prunet, M. Lautens, *J. Am. Chem. Soc.* **1999**, *121*, 7540–7552; e) Y. Jiang, J. Hong, S. D. Burke, *Org. Lett.* **2004**, *6*, 1445–1448.

[58] The stereochemical integrity of the potentially labile stereogenic center α to the carbonyl group under the conditions of the diol cleavage could be established by transformation of a sample of aldehyde **5** into the corresponding alcohol and comparison of its spectroscopic data with material previously synthesized via an independent route.

[59] Due to its volatility, the alcohol was conveniently used as a 75% w/w solution in CH_2Cl_2. The concentration of the substrate was determined by integration of the signals at δ 5.30 ppm (CH_2Cl_2) and δ 4.68 ppm ((HO)C**H**) by ^{1}H NMR spectroscopy.

[60] D. A. Evans, G. C. Fu, A. H. Hoveyda, *J. Am. Chem. Soc.* **1992**, *114*, 6671–6679.

[61] a) R. Baker, J. C. Head, C. J. Swain, *J. Chem. Soc. Perkin Trans. 1* **1988**, 85–97; b) L. C. Dias, L. J. Steil, V. D. Vasconcelos, *Tetrahedron: Asymmetry* **2004**, *15*, 147–150.

[62] The correct absolute configuration of the newly set stereogenic center at C14 could be determined by Mosher ester analysis for a closely related addition product.

[63] Similar observations have been reported, see reference [16c]. The $Zn(OTf)_2$ was generally dried at 120 °C at 0.5 mbar for 2 h under vigorous stirring to provide a finely ground powder.

[64] The diastereomeric mixture could be conveniently determined in C_6D_6 by integration of the signals corresponding to the proton at the propargylic center. Separation of the diastereoisomers by column chromatography proved to be feasible.

[65] For an overview, see: L. Brandsma, W. F. Nieuwenhuizen, J. W. Zwikker, U. Maeeorg, *Eur. J. Org. Chem.* **1999**, 775–779 and references therein.

[66] a) S. E. Denmark, T. K. Jones, *Org. Synth.* **1985**, *64*, 182–188; b) T. Tsuda, T. Yoshida, T. Kawamoto, T. Saegusa, *J. Org. Chem.* **1987**, *52*, 1624–1627.

[67] a) B. M. Trost, Z. T. Ball, T. Jöge, *J. Am. Chem. Soc.* **2002**, *124*, 7922–7923; b) A. Fürstner, K. Radkowski, *Chem. Commun.* **2002**, 2182–2183; c) B. M. Trost, Z. T. Ball, T. Jöge, *Angew. Chem.* **2003**, *115*, 3537–3540; *Angew. Chem. Int. Ed.* **2003**, *42*, 3415–3418; d) F. Lacombe, K. Radkowski, G. Seidel, A. Fürstner, *Tetrahedron* **2004**, *60*, 7315–7324; e) B. M. Trost, Z. T. Ball, *J. Am. Chem. Soc.* **2005**, *127*, 17644–17655; for the application of a hydrosilylation-protodesilylation reaction sequence in a natural product synthesis, see: f) A. Fürstner, M. Bonnekessel, J. T. Blank, K. Radkowski, G. Seidel, F. Lacombe, B. Gabor, R. Mynott, *Chem. Eur. J.* **2007**, *13*, 8762–8783.

[68] Attempts to use chromium(II) salts for the reduction of enynes to *trans*,*trans*-dienes were met with no success, resulting in no reaction under various reaction conditions. For some early reports on simple systems, see: a) C. E. Castro, R. D. Stephens, *J. Am. Chem. Soc.* **1964**, *86*, 4358–4363; b) C. E. Castro, R. D. Stephens, S. Mojé, *J. Am. Chem. Soc.* **1966**, *88*, 4964–4969; c) J. R. Hanson, *Synthesis* **1974**, 1–8; for reductions of ynones, see: d) A. B. Smith III, P. A. Levenberg, J. Z. Suits, *Synthesis* **1986**, 184–189; e) E. M. Carreira, J. Du Bois, *J. Am. Chem. Soc.* **1995**, *117*, 8106–8125.

[69] For the preparation of $[Cp^*Ru(NCMe)_3]PF_6$ in gram quantities, see: a) T. D. Tilley, R. H. Grubbs, J. E. Bercaw, *Organometallics* **1984**, *3*, 274–278; b) B. Steinmetz, W. A. Schenk, *Organometallics* **1999**, *18*, 943–946.

[70] Purification of the crude mixture of vinylsilanes **49** and **50** by chromatography on florisil led to the isolation of only the minor isomer. Analysis of the ^{1}H NMR data revealed an acyclic triethoxysilane, in which the silyl substituent had been transferred to the carbon atom in α-position to the alcohol, in agreement with structure **49**. An IR

spectrum taken from the crude reaction product displayed only a small peak around 3500 cm^{-1}, indicative of a free hydroxy group. This observation may hint at a cyclic structure **50** for the major diastereomer. The formation of a cyclic vinylsilane on transfer of the silyl atom to the carbon atom in β-position to the alcohol has been previously described in the literature; see reference [67e].

[71] In Evans' synthesis of bafilomycin A_1, an intermediate with a TBS-protected C7-hydroxy group required seven times longer for cyclization than the corresponding unprotected *seco*-acid. Roush had reported that their C7 TBS-protected cyclization precursor provided less than 10% yield or no product at all under a variety of conditions; see references [8] and [10d] for details.

[72] A similar addition of the C7-hydroxyl group onto the diene system was observed when natural bafilomycin A_1 was treated with $HgCl_2$ and $CaCO_3$ in a mixture of MeCN and H_2O; see: S. Hanessian, J. Pan, Y. Gai, *Molecules* **1998**, *3*, 97–99. However, the same authors remove silyl protecting groups in high yield at a late stage of their synthesis of bafilomycin A_1 using superstoichiometric amounts of $TsOH{\cdot}H_2O$ in MeOH at RT for 4 h. In the light of this report, the sensitivity of intermediate **56** to the mildly acidic conditions comes as a surprise.

[73] A base-labile protecting group for the C7-hydroxyl group was initially chosen to allow its concomitant removal during saponification of the methyl ester. As the macrolactonization step required material of high purity, and purification at the stage of the *seco*-acid was difficult to perform, high purity of the starting material for the saponification was crucial. It was found that purification of formate protected diol **64** to a level that would provide the *seco*-acid in sufficient purity for the macrolactonization was less straightforward and efficient than purification of triol **57**. Therefore, the strategy to combine deprotection and saponification in one synthetic step was abandoned in the end, and removal of the formate protecting group was performed prior to saponification.

[74] S. Hanessian, Y. Meng, E. Olivier, *Tetrahedron Lett.* **1994**, *35*, 5393–5396.

[75] a) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993; b) M. Hikota, Y. Sakurai, K. Horita, O. Yonemitsu, *Tetrahedron Lett.* **1990**, *31*, 6367–6370.

[76] Formation of the symmetrical anhydride, as reported by Roush (see reference [10d]), was never observed. See also: K. Makino, N. Nakajima, S.-I. Hashimoto, O. Yonemitsu, *Tetrahedron Lett.* **1996**, *37*, 9077–9080.

[77] P. A. Gatti, S. Gagliardi, A. Cerri, M. Visconti, C. Farina, *J. Org. Chem.* **1996**, *61*, 7185–7188.

[78] A. De Mico, R. Margarita, L. Parlanti, A. Vescovi, G. Piancatelli, *J. Org. Chem.* **1997**, *62*, 6974–6977.

[79] Diol **66** was easily accessible in two steps from an advanced intermediate in an earlier generation synthesis of aldehyde **5**.

[80] I. Paterson, C. Watson, K.-S. Yeung, P. A. Wallace, R. A. Ward, *J. Org. Chem.* **1997**, *62*, 452–453.

[81] K. A. Scheidt, H. Chen, B. C. Follows, S. R. Chemler, D. S. Coffey, W. R. Roush, *J. Org. Chem.* **1998**, *63*, 6436–6437.

[82] For an example of efficient differentiation of two secondary hydroxy groups in an oxidation reaction using TPAP, see: I. Paterson, C. Watson, K.-S. Yeong, R. A. Ward, P. A. Wallace, *Tetrahedron* **1998**, *54*, 11955–11970.

[83] It is interesting to note that deprotection of the C7 TMS ether required only 45 min, as compared to up to 5 h for the corresponding TES ether, as reported by Roush (see reference [10d]).

Received: September 7, 2011
Published online: February 16, 2012

