Natural Product Synthesis

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Total Synthesis of Bafilomycin A_1**

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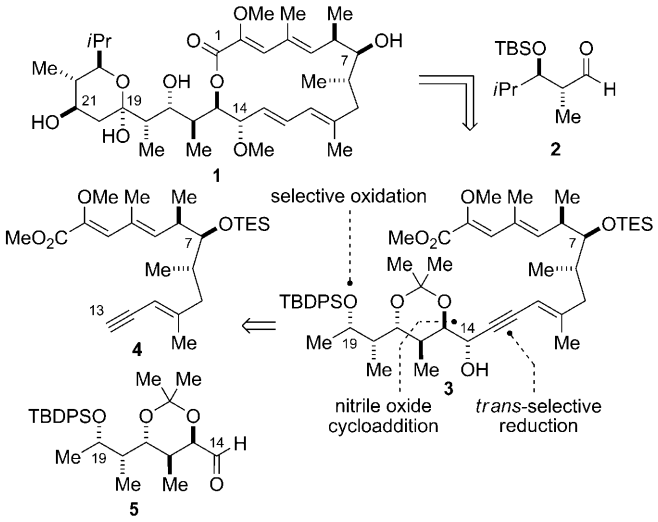
Bafilomycin A_1 (**1**; Scheme 1) was first isolated in 1983 from a culture of *Streptomyces griseus* sp. *sulphurus*[1] and classified as a member of the plecomacrolide family of natural products.[2–4] In addition to its broad antibacterial and antifungal activity,[1b] the ability of bafilomycin A_1 to selectively inhibit V-type ATPases[5] has attracted the most attention, leading to SAR studies and evaluation of its potential for the treatment of diseases, such as osteoporosis.[6] The continued interest in this class of molecules and the need for biologically active analogues demand new synthetic approaches. Moreover, a compex structure such as bafilomycin A_1 provides a forum to examine new methods and consequently implement novel tactics. Herein, we disclose an efficient synthesis that showcases the convergent coupling of complex fragments **4** and **5** (Scheme 1) through a zinc-mediated acetylide addition reaction, and stereoselective reduction of the ensuing enyne moiety by a sequence consisting of a ruthenium-catalyzed *trans*-hydrosilylation and subsequent protodesilylation.



Scheme 1. Retrosynthetic analysis of bafilomycin A_1. TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

Several total syntheses of bafilomycin A_1 have been reported,[7–11] as well as related methodology studies.[12] These generally showcase the application of established methods for polyketide synthesis. We were motivated to craft a different, complementary strategy to bafilomycin A_1 through the implementation of recently developed methods. These include diastereoselective, magnesium-mediated nitrile oxide cycloadditions with chiral allylic alcohols,[13] diastereoselective aldehyde addition reactions of zinc-enealkynilides,[14] and alkyne semireduction (Scheme 1).[15] We envisioned that a successful enyne + RCHO addition reaction would enable a highly efficient fragment–coupling step. However, this approach would only be relevant to the success of the larger synthesis objective if the densely functionalized product enyne could be used to access the *trans*,*trans*-1,3-diene system found in **1**.

The synthesis of the C1–C13 fragment (**4**; Scheme 2) commenced with the allylation reaction[16] of **6** with bromide **7**[17] to afford **8** in 87% yield and 97:3 d.r. Reductive cleavage of the auxiliary[16d,18] provided an intermediate alcohol (87% yield), which after Dess–Martin oxidation furnished aldehyde **9** in 99% yield. An *anti*-selective Masamune aldol addition of **9** with **10**[19] led to β-hydroxy ester **11** as a single diastereoisomer (90% yield). After silylation (98% yield) and ester reduction (95% yield), oxidation of the resulting primary alcohol was followed by Wittig olefination to provide enoate **13** (87%, over 2 steps). Conversion of ester **13** into aldehyde **14** was accomplished by a sequence involving reduction of the ester group to give an intermediate alcohol (98% yield), Sonogashira cross-coupling with TMSC≡CH (96% yield),[20] and oxidation (94% yield). Subsequent Horner–Wadsworth–Emmons condensation involving **14** gave an intermediate dienoate (>95:5 d.r.), which after chemoselective alkyne desilylation (96% yield, over 2 steps) afforded the targeted C1–C13 fragment **4**.

The synthesis of the C14–C20 fragment (**5**; Scheme 3) centered on the use of a nitrile oxide cycloaddition directed by a hydroxy group,[13] which involved the nitrile oxide derived from oxime **15** and dipolarophile **16**. After in situ generation of the nitrile oxide, its cycloaddition with **16** furnished isoxazoline **17** in 74% yield and >95:5 d.r. Removal of the trityl protecting group (92% yield) and protection of the resulting diol as the carbonate using triphosgene (97% yield) was followed by reductive cleavage of the isoxazoline with Raney-Ni/$B(OH)_3$,[21] to furnish hydroxy ketone **18** in 88% yield. Its subsequent reduction[22] with $Me_4NBH(OAc)_3$ resulted in the *anti* relationship of the alcohols at C15 and C17. Formation of the acetonide was

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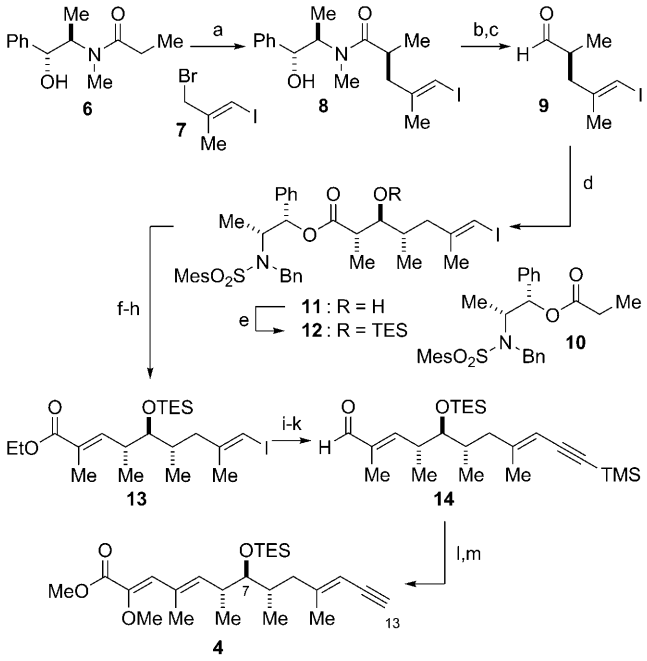
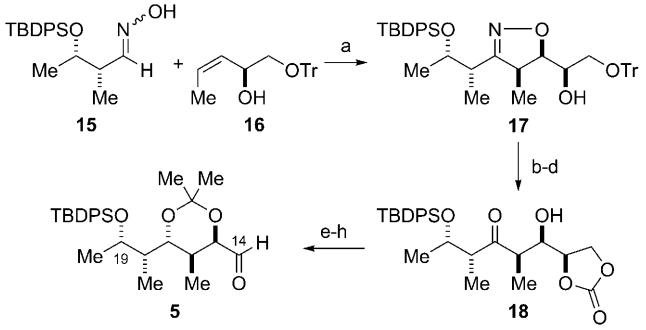


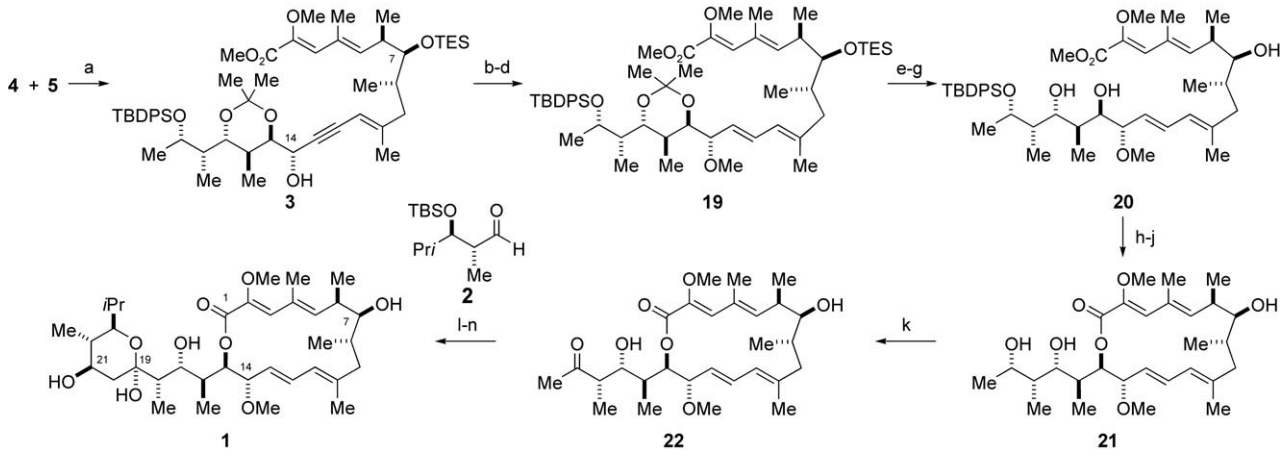
Scheme 2. a) LDA, LiCl, THF, −78 °C to 0 °C, 87%, 97:3 d.r.; b) LDA, $BH_3{\cdot}NH_3$, THF, 87%; c) Dess–Martin periodinane, py, CH_2Cl_2, 99%; d) **10**, Cy_2BOTf, NEt_3, CH_2Cl_2, −78 °C, 90%, >95:5 d.r.; e) TESCl, DMAP, imidazole, DMF, 98%; f) DIBAL-H, CH_2Cl_2, −78 °C, 95%; g) TPAP, NMO, M.S. (4 Å), CH_2Cl_2; h) $Ph_3PC(Me)CO_2Et$, toluene, 65 °C, 87% (over 2 steps), >95:5 d.r.; i) DIBAL-H, CH_2Cl_2, −78 °C, 98%; j) TMSC≡CH, CuI, $[Pd(PPh_3)_4]$, pyrrolidine, 96%; k) MnO_2, CH_2Cl_2, 94%; l) KHMDS, [18]crown-6, $(iPrO)_2P(O)CH(OMe)CO_2Me$, THF, >95:5 d.r.; m) K_2CO_3, MeOH, 96% (over 2 steps). Bn = benzyl, Cy = cyclohexyl, DIBAL-H = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, HMDS = hexamethyldisilazane, LDA = lithium diisopropylamide, Mes = 2,4,6-trimethylphenyl, M.S. = molecular sieves, NMO = 4-methylmorpholine *N*-oxide, py = pyridine, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl, TPAP = tetra-*n*-propylammonium perruthenate.



Scheme 3. a) *t*BuOCl, CH_2Cl_2, −78 °C; then **16**, *i*PrOH, EtMgBr, 0 °C to RT, 74%, >95:5 d.r.; b) $TsOH{\cdot}H_2O$, MeOH, 92%; c) triphosgene, py, CH_2Cl_2, −78 °C to 0 °C, 97%; d) Raney-Ni, $B(OH)_3$, H_2, $MeOH/H_2O$ (5:1), 88%; e) $Me_4NBH(OAc)_3$, AcOH/MeCN (1:1), −5 °C, 74%, 4.3:1 d.r.; f) $TsOH{\cdot}H_2O$, 2,2-dimethoxypropane, 99%; g) aq. LiOH (1 N), 92%; h) $NaIO_4$ on silica gel, CH_2Cl_2, 99%. Tr = trityl, Ts = 4-toluenesulfonyl.

followed by hydrolysis of the carbonate. The resulting 1,2-diol was cleaved with $NaIO_4$/silica gel to provide aldehyde **5** in 90% yield (over 3 steps).

With the two key subunits in hand, our attention turned to the zinc-mediated addition of enyne **4** to aldehyde **5** (Scheme 4).[14] Treatment of **13** with $Zn(OTf)_2$, (+)-NME, and iPr_2NEt in toluene led to the formation of propargylic alcohol **3** in 91% yield as a single diastereomer, as determined by ^1H NMR spectroscopy.[23] This report constitutes the first example of an enyne/aldehyde coupling reaction in the context of complex fragment assembly. Conversion of the enyne into the *trans*,*trans*-diene was now critical for successful evolution of the route. Importantly, if realizable it would offer an alternative to the traditional palladium-catalyzed cross-coupling approaches for the introduction of the C10–C13 diene subunit in all previous syntheses of bafilomycin A_1.[7–10]



Scheme 4. a) $Zn(OTf)_2$, (+)-NME, iPr_2NEt, toluene, RT, 91%, >95:5 d.r.; b) $(EtO)_3SiH$, $[Cp^*Ru(NCMe)_3]PF_6$, CH_2Cl_2, 0 °C to RT; c) TBAF, CuI, THF, 0 °C, 72% (over 2 steps); d) MeI, NaH, THF/DMF (1:1), 89%; e) HF·py, THF, 91%; f) AcO(O)CH, DMAP, CH_2Cl_2, 99%; g) CSA, MeOH; then K_2CO_3, MeOH, 68% (79% brsm); h) aq. LiOH (1 N), THF/MeOH/H_2O (5:1:1); i) 2,4,6-trichlorobenzoylchloride, iPr_2NEt, toluene, 60% (over 2 steps); j) TASF, H_2O, DMF, 90%; k) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 71%; l) TMSCl, NEt_3, LiHMDS, THF, −78 °C; m) **2**, $BF_3{\cdot}OEt_2$, M.S. (4 Å), CH_2Cl_2, −78 °C; n) TASF, H_2O, DMF, 35% (over 3 steps, 76% brsm). brsm = based on recovered starting material, Cp* = C_5Me_5, CSA = camphorsulfonic acid, (+)-NME = (+)-*N*-methyl ephedrine, TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate, TBAF = tetra-*n*-butylammonium fluoride, TEMPO = 2,2,6,6-tetramethylpiperidin-1-yloxyl.

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After a number of prospecting studies, the installation of the *trans* diene was carried out by a sequence consisting of metal-catalyzed hydrosilylation and subsequent protodesilylation by using the method developed by Trost et al.[15a,c,e] In the experiment, treatment of **3** with $(EtO)_3SiH$ and $[Cp^*Ru(NCMe)_3]PF_6$ afforded an intermediate silylated 1,3-diene. Protodesilylation proved to be a considerable challenge, as it needed to be executed in the presence of two silyl ethers (TESO at C7 and TBDPSO at C21) and the acid-sensitive acetonide. Indeed, the reaction conditions first reported proved excessively harsh. However, we noted that the use of 1 equivalent of TBAF at 0 °C for 10 minutes furnished the desired diene (72 %, over 2 steps). Importantly, the silyl ethers were untouched, thus highlighting the unique chemoselectivity of the process. Subsequent methylation provided the C14 methyl ether **19** (89 % yield), followed by removal of the TES group (91 % yield). We observed that hydrolysis of the acetonide group led to by-products that resulted from allylic displacement of the methoxy group at C14 by the hydroxy group at C7. This displacement could be circumvented when the hindered hydroxy group at C7 was temporarily protected as a formate ester. This reaction sequence allowed isolation of triol **20** in 68 % yield overall. Saponification of the methyl ester with aq. LiOH (1N) was followed by formation of the mixed anhydride derived from 2,4,6-trichlorobenzoylchloride.[24] After dilution and addition of DMAP, selective cyclization[10] was observed to give the macrolactone in 60 % yield (over 2 steps). Removal of the TBDPS ether with TASF[9,25] then provided triol **21** (90 %).

The C21–C25 portion of the target molecule was introduced with a Mukaiyama aldol reaction, based on related precedence by Roush and co-workers.[9] However, in our case, the formation of the requisite methyl ketone demanded selective oxidation of the hydroxy group at C19 in this triol compound. This transformation was achieved in an excellent 71 % yield by oxidation of the hydroxy group at C19 using $TEMPO/PhI(OAc)_2$.[26] To the best of our knowledge, this is the first report of efficient differentiation of three secondary hydroxy groups in an oxidation reaction.[27] Subsequent formation of the silylenol ether derived from ketone **22** and concomitant in situ protection of the two free hydroxy groups as the TMS ethers was followed by $BF_3{\cdot}OEt_2$-mediated Mukaiyama aldol addition to aldehyde **2**.[9] The unpurified reaction mixture was directly treated with TASF to provide synthetic bafilomycin A_1 (**1**) in 35 % yield over three steps, or 76 % yield based on recovered methyl ketone **22**.

In summary, we have developed a highly stereoselective, convergent synthesis of bafilomycin A_1. The salient features of the route include: 1) a nitrile oxide cycloaddition reaction that enabled facile access to an advanced aldehyde fragment **5** and efficiently sets the four stereogenic centers of the C15–C18 portion of the target molecule; 2) a highly stereoselective zinc-mediated coupling of enyne **4** and aldehyde **5**; 3) the successful implementation of *trans*-reduction of the enyne moiety by a sequence consisting of a ruthenium-catalyzed *trans*-hydrosilylation and subsequent protodesilylation; and 4) selective oxidation of a triol compound to the corresponding diolketone. The synthesis we have delineated highlights the potential of a strategy involving enyne coupling reactions with aldehydes partnered with hydrosilylation/protodesilylation methodology as an alternative to the classic palladium-catalyzed cross-coupling reactions for the formation of 1,3-diene systems. As showcased in the described synthesis, the approach enables efficient, convergent coupling of complex and densely functionalized fragments that may be applicable to other targets.

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