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Total Synthesis of Bafilomycin A_1. 1. Syntheses of the C5~C11, C12~C17 and C18~C25 Segments.

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Abstract: The effective syntheses of the C5~C11 (**2**), C12~C17 (**3**) and C18~C25 (**4**) segments, which are promising synthetic intermediates toward the total synthesis of the macrolide antibiotic, bafilomycin A_1 (**1**), were described.

Bafilomycin A_1 (**1**) isolated in 1983 by Werner and Hagenmaier[1] is the first specific potent inhibitor of vacuolar H^+-ATPase.[2] The structure and absolute configuration of **1** were established by X-ray crystallographic analysis[3] and by NMR spectroscopy.[4] Bafilomycin A_1 (**1**) belongs to a family of structurally related polyketide macrolide antibiotics. The other macrolide antibiotics such as elaiophylin,[5] the concanamycins[6] and the hygrolidins[7] are closely related to the bafilomycins. The most unique and striking structural feature of these macrolide families is an unusual 16- or 18-membered tetraenic lactone ring with a β-hydroxy hemiacetal side chain. An efficient aldol method for the assembly of **1** was recently reported by Evans and Calter,[8] and elegant syntheses of the C13~C25 segments of **1** have been independently announced by Roush's[9] and Paterson's[10] groups. Herein we disclose the effective syntheses of the C5~C11 (**2**), C12~C17 (**3**) and C18~C25 (**4**) segments which are promising synthetic intermediates toward the total synthesis[11] of the biologically important natural product, bafilomycin A_1 (**1**) (Figure 1).

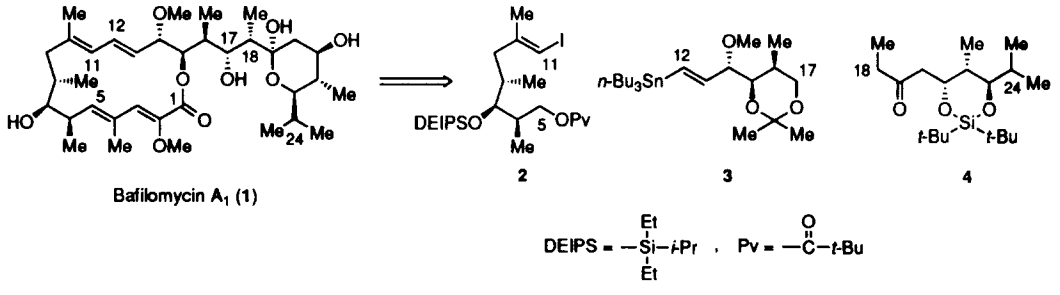
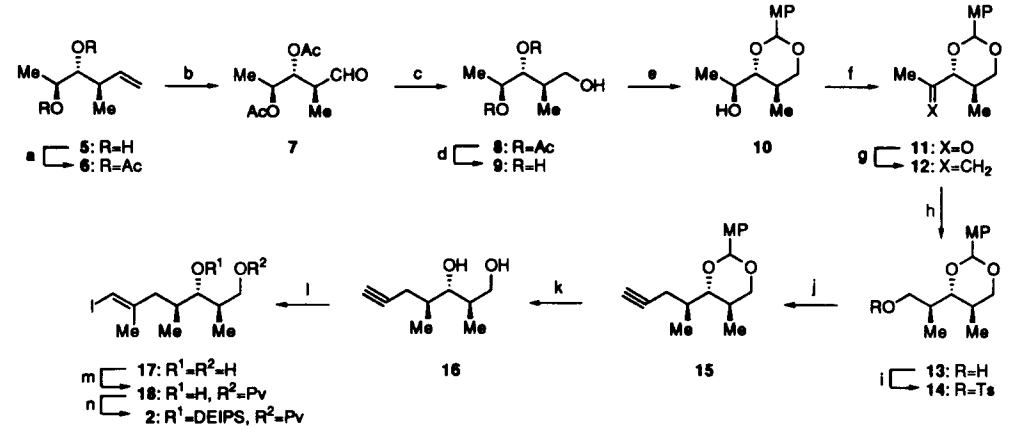


Figure 1

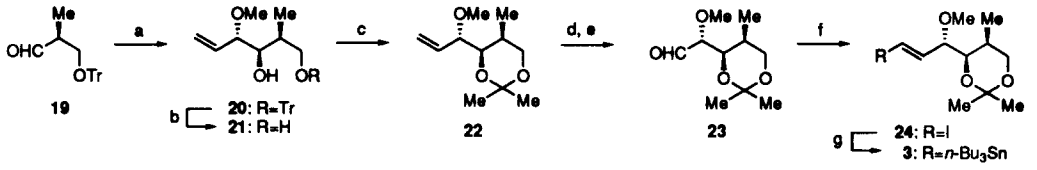
Synthesis of the C5~C11 segment 2. The synthesis of the vinyl iodide **2** corresponding to the C5~C11 segment of bafilomycin A_1 (**1**) is summarized in Scheme 1. The starting material **5**[12] was first converted into the triol **9** *via* oxidative cleavage of the double bond in **6** in four steps (1. Ac_2O, 4-DMAP, EtOAc, r. t., 1 h; 2. O_3, MeOH-CH_2Cl_2, -78 °C, 2 h then Me_2S; 3. $NaBH_4$, MeOH-CH_2Cl_2, r. t., 0.5 h; 4. NaOMe, MeOH, r. t., 3 h) in 94% overall yield. Selective *p*-methoxybenzylidenation of the 1,3-diol in **9** (*p*-methoxybenzaldehyde dimethyl acetal, CSA, DMF, r. t., 1.5 h), followed by oxidation (PCC, MS 3A, CH_2Cl_2, r. t., 1.5 h) and the Wittig reaction using $Ph_3P{=}CH_2$ in benzene afforded **12** in 89% overall yield. Hydroboration of **12** employing dicyclohexylborane in THF at room temperature for 1 h proceeded with complete stereoselectivity to give only the alcohol **13** in 88% yield after the subsequent oxidative workup. Tosylation of the alcohol **13** (TsCl, Py, r. t., 1.5 h) yielded the tosylate **14** which was subjected to the reaction with lithium acetylide (5 equiv.) in dimethyl sulfoxide to give the acetylene **15** in 66% overall yield. After deprotection of the *p*-methoxybenzylidene group in **15** under acidic conditions (80% AcOH-H_2O, 40 °C, 13 h), the resultant diol **16** was treated with Cp_2ZrCl_2, Me_3Al and I_2 in 1,2-dichloroethane[13] to afford only the tri-substituted *trans* vinyl iodide **17** in 63% overall yield from **15**. Selective pivaloylation (PvCl, Et_3N,CH_2Cl_2, r. t., 14 h) of the primary alcohol in **17**, followed by silylation (DEIPSOTf, 2,6-lutidine, CH_2Cl_2, r. t., 4 h) with the diethylisopropylsilyl (DEIPS) group[14] furnished the suitably protected vinyl iodide **2** in 97% overall yield.

Synthesis of the C12~C17 segment 3. Scheme 2 illustrates the synthesis of the vinyl butyltin **3** corresponding to the C12~C17 segment of bafilomycin A_1 (**1**). Treatment of the aldehyde **19**[15] with *in situ* generated γ-methoxyallylchromium reagent[9,16] ($CrCl_2$, $CH_2{=}CHCH(OMe)_2$, TMS-I, THF, -42 °C, 16 h) afforded the homoallylic alcohol **20** as a major diastereomer with 10 : 1.1 : 0.5 selectivity in 62% yield. The trityl goup in **20** was removed under acidic conditions (1% HCl-MeOH, r. t., 0.5 h) and the resultant diol **21** was then protected with an isopropylidene group (2,2-dimethoxypropane, CSA, CH_2Cl_2, r. t., 16 h) to provide the acetonide **22**. Dihydroxylation (OsO_4, NMO, acetone-H_2O, r. t., 16 h) of **22**, followed by sequential periodate-oxidation ($NaIO_4$, THF-H_2O, r. t., 0.5 h) and Takai's reaction[17] using $CrCl_2$ and CHI_3 in THF gave only the *trans* vinyl iodide **24** in 38% overall yield from **20**. Finally, treatment of **24** with *n*-Bu_3SnCl and *n*-BuLi in THF at -78 °C for 1 h afforded the vinyl butyltin **3** in 69% yield.

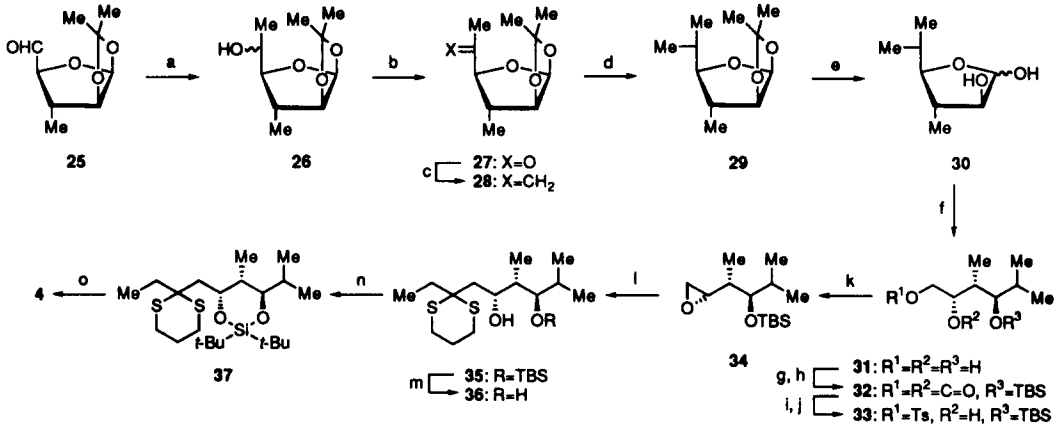
Synthesis of the C18~C25 segment 4. The synthesis of the ethyl ketone **4** corresponding to the C18~C25 segment of bafilomycin A_1 (**1**) is depicted in Scheme 3. This synthesis began with the conversion of the sugar derivative **25**[18] into **29** possessing an isopropyl group in standard manners in four steps (1. MeMgI, Et_2O, r. t., 0.5 h; 2. PCC, MS 3A, CH_2Cl_2, r. t., 0.5 h; 3. $Ph_3P{=}CH_2$, benzene, r. t., 0.5 h; 4. H_2, Raney-Ni(W4), dioxane, r. t., 24 h) and in 66% overall yield. Hydrolysis (50% AcOH-H_2O, 80 °C, 2 h) of the 1,2-isopropylidene group in **29**, followed by lithiumalminum hydride (LAH)-reduction afforded the triol **31** which was then subjected to the selective protection of the 1,2-diol with carbonate (*N,N'*-carbonyldiimidazole, CH_2Cl_2, r. t., 2.5 h) and silylation (TBS-Cl, imid., DMF, 40 °C, 16 h) of the resultant secondary alcohol to provide **32** in 52% overall yield from **29**. After removal of the carbonate group in **32** by hydrolysis (1*N* NaOH, MeOH, r. t., 16 h), selective tosylation (TsCl, Py, r. t., 16 h) of the resultant primary alcohol and sequential epoxidation (NaOMe, MeOH-$CHCl_3$, r. t., 16 h) gave the epoxide **34** in 46% overall yield. Reaction of **34** with 2-ethyl-2-lithio-1,3-dithiane (5 equiv.) in THF at -20 °C for 1 h afforded the dithioacetal **35** whose silyl group was removed (TBAF, THF, r. t., 2.5 h) to give the diol **36** in 97% overall yield. Finally, the diol **36** was protected (*t*-$Bu_2Si(OTf)_2$, DMF, r. t., 2 h) with a di-*t*-butylsilyl group and then the dithioacetal



Scheme 1. *Reagents and conditions*: a) Ac_2O, 4-DMAP, EtOAc, r. t., 1 h, 100%; b) O_3, MeOH-CH_2Cl_2, -78 °C, 2 h then Me_2S; c) $NaBH_4$, MeOH-CH_2Cl_2, r. t., 0.5 h; d) NaOMe, MeOH, r. t., 3 h, 94% from **6**; e) $(MeO)_2CHC_6H_4OMe$, CSA, DMF, r. t., 1.5 h, 94%; f) PCC, MS 3A, CH_2Cl_2, r. t., 1.5 h, 100%; g) $Ph_3P{=}CH_2$, C_6H_6, r. t., 1 h, 95%; h) $BH_3{\cdot}Me_2S$, C_6H_{10}, THF, r. t., 1 h then NaOH-H_2O, H_2O_2, 88%; i) TsCl, Py, r. t., 1.5 h, 100%; j) HC≡CLi, DMSO, r. t., 1.5 h, 66%; k) 80% AcOH-H_2O, 40 °C, 13 h, 77%; l) Cp_2ZrCl_2, Me_3Al, I_2, $(ClCH_2)_2$, r. t., 13 h, 82%; m) PvCl, Et_3N, CH_2Cl_2, r. t., 14 h, 97%; n) DEIPSOTf, 2,6-lutidine, CH_2Cl_2, r. t., 4 h, 100%.



Scheme 2. *Reagents and conditions*: a) $CrCl_2$, $CH_2{=}CHCH(OMe)_2$, TMS-I, THF, -42 °C, 16 h, 62%; b) 1% HCl-MeOH, r. t., 0.5 h, 100%; c) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, r. t., 16 h; d) OsO_4, NMO, acetone-H_2O, r. t., 16 h; e) $NaIO_4$, THF-H_2O, r. t., 0.5 h; f) $CrCl_2$, CHI_3, THF, r. t., 14 h, 38% from **21**; g) *n*-Bu_3SnCl, *n*-BuLi, THF, -78 °C, 1 h, 69%.



Scheme 3. *Reagents and conditions*: a) MeMgI, Et_2O, r. t., 0.5 h, 94%; b) PCC, MS 3A, CH_2Cl_2, r. t., 0.5 h, 94%; c) $Ph_3P{=}CH_2$, C_6H_6, r. t., 0.5 h, 81%; d) H_2, Raney-Ni(W4), dioxane, r. t., 24 h, 92%; e) 50% AcOH-H_2O, 80 °C, 2 h, 93%; f) LAH, THF, 60 °C, 16 h, 77%; g) *N,N*-carbonyldiimidazole, CH_2Cl_2, r. t., 2.5 h, 85%; h) TBS-Cl, imid., DMF, 40 °C, 16 h, 87%; i) 1*N* NaOH, MeOH, r. t., 16 h; j) TsCl, Py, r. t., 16 h; k) NaOMe, MeOH-$CHCl_3$, r. t., 16 h, 46% from **32**; l) 2-ethyl-1,3-dithiane, *n*-BuLi, THF, -20 °C, 1 h; m) TBAF, THF, r. t., 2.5 h, 97% from **34**; n) *t*-$Bu_2Si(OTf)_2$, DMF, r. t., 2 h, 95%; o) $CaCO_3$, MeI, MeCN-H_2O, r. t., 6 h, 69%.

group was cleaved ($CaCO_3$, MeI, MeCN-H_2O, r. t., 6 h) to furnish the ethyl ketone **4**[8] in 66% overall yield.[19]

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19. All new compounds were purified by silica-gel column chromatography and were fully characterized by spectoscopic means. Selected ^{1}H-NMR spectra [270MHz, $CDCl_3$, δ (TMS), *J* (Hz)] are the following. **2**: 0.64 (4H, q, *J* = 7.7), 0.86 (3H, d, *J* = 7.0), 0.95-1.03 (16H, m), 1.21 (9H, s), 1.80 (3H, s), 1.8-1.93 (1H, m), 1.95-2.07 (1H, m), 2.02 (1H, dd, *J* = 13.0 and 10.8), 2.42 (1H, br dd, *J* = 13.0 and 3.0), 3.51 (1H, dd, *J* = 4.5 and 4.5), 3.87 (1H, dd, *J* = 11.0 and 7.3), 4.25 (1H, dd, *J* = 11.0 and 4.9), 5.85 (1H, br s). **3**: 0.85-0.93 (15H, m), 1.10 (3H, d, *J* = 7.0), 1.24-1.38 (6H, m), 1.35 (3H, s), 1.37 (3H, s), 1.44-1.57 (6H, m), 1.77 (1H, m), 3.28 (3H, s), 3.40 (1H, ddd, *J* = 9.0, 6.3 and 1.2), 3.60 (1H, dd, *J* = 11.6 and 1.8), 3.82 (1H, dd, *J* = 9.0 and 2.2), 4.08 (1H, dd, *J* = 11.6 and 2.8), 5.79 (1H, dd, *J* = 19.0 and 6.3), 6.21 (1H, dd, *J* = 19.0 and 1.2). **4**: 0.73 (3H, d, *J* = 7.0), 0.86 (3H, d, *J* = 6.9), 0.97 (9H, s), 0.99 (9H, s), 1.01 (3H, d, *J* = 7.0), 1.07 (3H, d, *J* = 7.1), 1.73 (1H, d septet, *J* = 7.0 and 2.1), 2.23 (1H, m), 2.38 (1H, dd, *J* = 14.2 and 3.4), 2.53 (1H, dq, *J* = 10.8 and 7.0), 2.56 (1H, dq, *J* = 10.8 and 7.0), 2.71 (1H, dd, *J* = 14.2 and 10.1), 3.68 (1H, dd, *J* = 9.6 and 2.1), 4.62 (1H, ddd, *J* = 10.1, 5.9 and 3.4).

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