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# Total Synthesis of Bafilomycin $A_1$. 2. The Assemblage and Completion of the Synthesis.

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**Abstract:** The total synthesis of the macrolide antibiotic, bafilomycin $A_1$ (**1**), has been achieved by a convergent route involving aldol condensation between the 16-membered lactonic aldehyde **2** and the ethyl ketone **3**, followed by desilylation.

The remarkable biological properties of so-called unusual macrolides[1] have stimulated great interest in many organic chemists. The macrolide antibiotic, bafilomycin $A_1$ (**1**),[2] is a specific vacular-type $H^+$-ATPase inhibitor,[3] and also shows antibacterial, antifungal, and immunosuppressive activities.[4] Structurally, bafilomycin $A_1$ (**1**) is constructed from a 16-membered tetraenic lactone ring and a long side chain with an intramolecular hemiacetal. In a previous paper,[5] we described the effective syntheses of the enantiomerically pure C5~C11, C12~C17, and C18~C25 segments as promising synthetic intermediates toward the total synthesis of **1**. We report herein, the total synthesis of bafilomycin $A_1$ (**1**) by a convergent route, which makes use of these segments. This total synthesis involves an aldol condensation[6] between the 16-membered lactonic aldehyde **2** and the ethyl ketone **3**,[5,6] followed by desilylation (Figure 1).

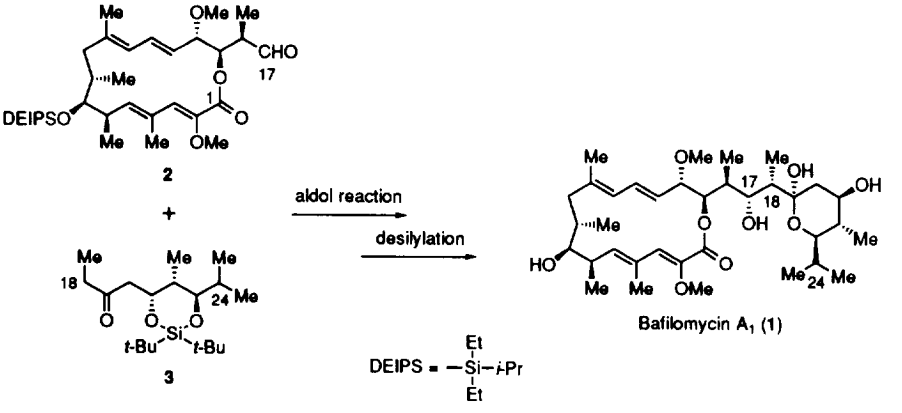


**Figure 1**

**Synthesis of the macrocyclic aldehyde 2.** The synthesis of bafilomycin $A_1$ (**1**) by a covergent route *via* the 16-membered lactonic aldehyde **2** is summarized in Scheme 1. The cross-coupling reaction between the vinyl iodide **4**[5] (1 equiv.) corresponding to the C5~C11 segment of **1** and the vinyl tributyltin **5**[5] (1 equiv.) corresponding to the C12~C18 segment of **1** by Stille method[7] using a catalytic amount of $PdCl_2(dppf)$[8] in DMF at 50 °C for 15 h afforded the desired *E,E*-diene **6** in 60% yield as the only isolated product. Deprotection of the pivaloyl group in **6** using methyl lithium ($Et_2O$, r. t., 0.5 h) followed by Swern oxidation gave the aldehyde **8**. The Wittig reaction of **8** with ethyl 2-(triphenylphosphoranylidene)propionate in toluene at 100 °C for 14 h proceeded smoothly to afford only the *trans* isomer **9** in 77% overall yield from **6**. Reduction of the ethyl ester in **9** using diisobutylaluminum hydride (DIBAL) (PhMe, -78 °C, 5 min) followed by oxidation using $MnO_2$ provided the α,β-unsaturated aldehyde **11** in 97% overall yield. The Horner-Wadsworth-Emmons reaction of **11** (1 equiv.) with the phosphonic ester **12**[9] (5 equiv.), which was prepared from methyl dimethoxy acetate in two steps (1. $PCl_5$, 50 °C, 0.5 h, 67%; 2. $P(OEt)_3$, NaI, 190 °C, 2 h, 55%), using sodium bis(trimethylsilyl)amide (NaHMDS) in THF at room temperature gave **13** in 89% yield as a mixture of the *cis*- and *trans*-isomers. Although these isomers could not be separated at this stage, each isomer was isolated in a pure form before the lactonization mentioned below. The isopropylidene group in **13** was removed under mild acidic conditions (pyridinium *p*-toluenesulfonate (PPTS), MeOH, r. t., 0.5 h) and then the resultant diol **14** was selectively protected (MTrCl, $Et_3N$, 4-DMAP, $CH_2Cl_2$, r. t., 3.5 h) with a monomethoxytrityl (MTr) group to afford the secondary alcohol **15** in 98% overall yield. Hydrolysis of the methyl ester of **15** under basic conditions (1*N* KOH, dioxane, 80 °C, 2 h) yielded the carboxylic acid **16** and the isomer, which resulted from the Horner-Wadsworth-Emmons reaction, in 64 and 32% yields, respectively. The cyclization of the seco-acid **16** to construct the 16-membered lactone ring was best effected by Yamaguchi method[10] under high dilution conditions to give the macrocyclic lactone **17** in 42% yield. Finally, treatment of **17** with PPTS in MeOH (r. t., 14 h) gave the alcohol **18** which was subjected to Swern oxidation to furnish the aldehyde **2** in 59% overall yield.

**Synthesis of 1.** With both the 16-membered lactonic aldehyde **2** and the ethyl ketone **3**[5] in hand, we next tried the stereoselective connection of these segments by several aldol reactions.[11] A similar type of aldol reaction was previously studied and performed in our total synthesis of elaiophylin[12] and in Seebach's elaiophylin aglycon synthesis.[13] The coupling of **2** and **3** by the method using *n*-$Bu_2BOTf$ and *i*-$Pr_2NEt$,[14] which were employed during the elaiophylin syntheses,[12,13] afforded the desired aldol product **19** (C16,C17-*anti*-C17,C18-*syn*) and its diastereomer (C16,C17-*syn*-C17,C18-*syn*)[11,15] in 44 and 13% yields, respectively. On the other hand, the aldol condensation between **2** (1 equiv.) and **3** (2 equiv.) was best achieved by Evans' recently disclosed procedure[6] using $PhBCl_2$[16] and *i*-$Pr_2NEt$ in $CH_2Cl_2$ at -78 °C for 2.5 h to produce **19** in 58% yield with >95 : 5 diastereoselectivity as a major aldol product. Finally, the desilylation of **19** using tetrabutylanmonium fluoride (TBAF) and acetic acid in THF at 60 °C for 12 h gave **1** in 45% yield. Thus, the obtained **1** was identical to an authentic sample of natural bafilomycin $A_1$ based on $^1$H-NMR, $[\alpha]_D$, mp, mmp, and TLC behaviors in several solvent systems.[17]

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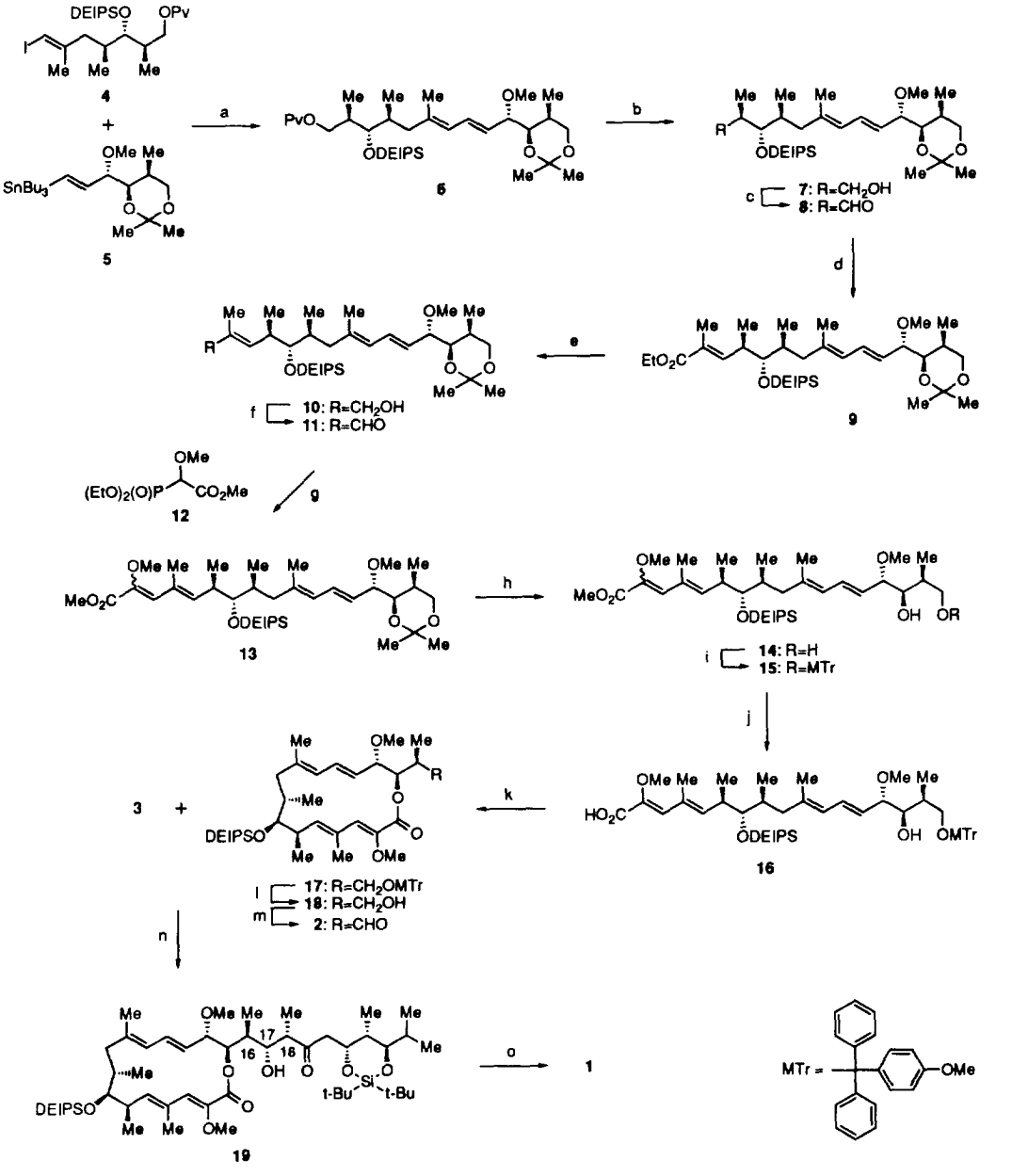

**Scheme 1.** *Reagents and conditions*: a) $PdCl_2(dppf)$, DMF, 50 °C, 15 h, 60%; b) MeLi, $Et_2O$, r. t., 0.5 h, 79%; c) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, -78 °C, 20 min; d) $Ph_3P{=}C(Me)CO_2Et$, PhMe, 100 °C, 14 h, 98% from **7**; e) DIBAL, PhMe, -78 °C, 5 min, 97%; f) $MnO_2$, $CH_2Cl_2$, r. t., 2 h, 100%; g) NaHMDS, THF, r. t., 0.5 h, 89%; h) PPTS, MeOH, r. t., 0.5 h, 98%; i) MTrCl, $Et_3N$, 4-DMAP, $CH_2Cl_2$, r. t., 3.5 h, 100%; j) 1*N* KOH, dioxane, 80 °C, 2 h, 64%; k) 2,4,6-trichlorobenzoyl chloride, $Et_3N$, THF, 4-DMAP, PhMe (0.002 M for **16**), 110 °C, 16 h, 42%; l) PPTS, MeOH, r. t., 14 h, 80%; m) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, -78 °C, 20 min, 74%; n) $PhBCl_2$, *i*-$Pr_2NEt$, $CH_2Cl_2$, -78 °C, 2.5 h, 58%; o) TBAF, AcOH, THF, 60 °C, 12 h, 45%.

$A_1$ and other bafilomycins. We are also indebted to Emeritus Prof. M. Kinoshita (Keio University ) and Prof. K. Tatsuta (Waseda University) for their stimulating and helpful discussions. Financial support by The Naito Foundation is gratefully acknowledged.

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17. 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**: 0.67-0.80 (4H, m), 0.98-1.13 (13H, m), 1.01 (3H, d, *J* = 7.0), 1.05 (3H, d, *J* = 7.0), 1.17 (3H, d, *J* = 7.0), 1.68 (3H, s), 1.7-1.8 (2H, m), 1.93 (3H, d, *J* = 1.3), 2.4-2.55 (2H, m), 2.78 (1H, ddq, *J* = 9.2, 7.0 and 1.9), 3.31 (3H, s), 3.62 (1H, dd, *J* = 2.4 and 1.9), 3.65 (3H, s), 3.87 (1H, dd, *J* = 6.0 and 5.6), 5.31 (1H, dd, *J* = 5.6 and 5.4), 5.36 (1H, dd, *J* = 15.2 and 6.0), 5.87 (1H, d, *J* = 9.2), 5.92 (1H, d, *J* = 11.0), 6.50 (1H, dd, *J* = 15.2 and 11.0), 6.62 (1H, s), 9.77 (1H, d, *J* = 1.8). **19**: 0.68-0.80 (4H, m), 0.73 (3H, d, *J* = 7.2), 0.85 (3H, d, *J* = 6.9), 0.91 (3H, d, *J* = 7.0), 0.95-1.12 (22H, m), 0.95 (9H, s), 0.97 (9H, s), 1.16 (3H, d, *J* = 7.2), 1.65-1.85 (3H, m), 1.66 (3H, s), 1.94 (3H, s), 1.98 (1H, m), 2.20 (1H, m), 2.4-2.55 (2H, m), 2.45 (1H, dd, *J* = 15.4 and 3.6), 2.80 (1H, dd, *J* = 15.4 and 10.0), 2.83 (1H, ddq, *J* = 9.2, 7.0 and 2.2), 3.28 (3H, s), 3.60-3.70 (2H, m), 3.66 (3H, s), 3.81 (1H, ddd, *J* = 9.8, 4.0 and 2.4), 3.96 (1H, dd, *J* = 6.0 and 4.0), 4.66 (1H, ddd, *J* = 10.0, 5.9 and 3.6), 5.29 (1H, dd, *J* = 4.0 and 2.6), 5.43 (1H, dd, *J* = 15.6 and 6.0), 5.90 (1H, d, *J* = 9.2), 5.93 (1H, d, *J* = 11.2), 6.47 (1H, dd, *J* = 15.6 and 11.2), 6.68 (1H, s).

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