Pergamon

Tetrahedron Letters, Vol. 37, No. 7, pp. 1073-1076, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02351-8

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).

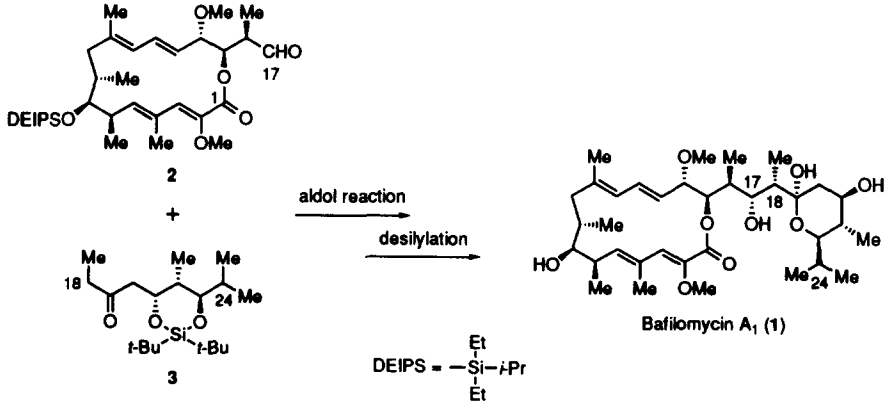
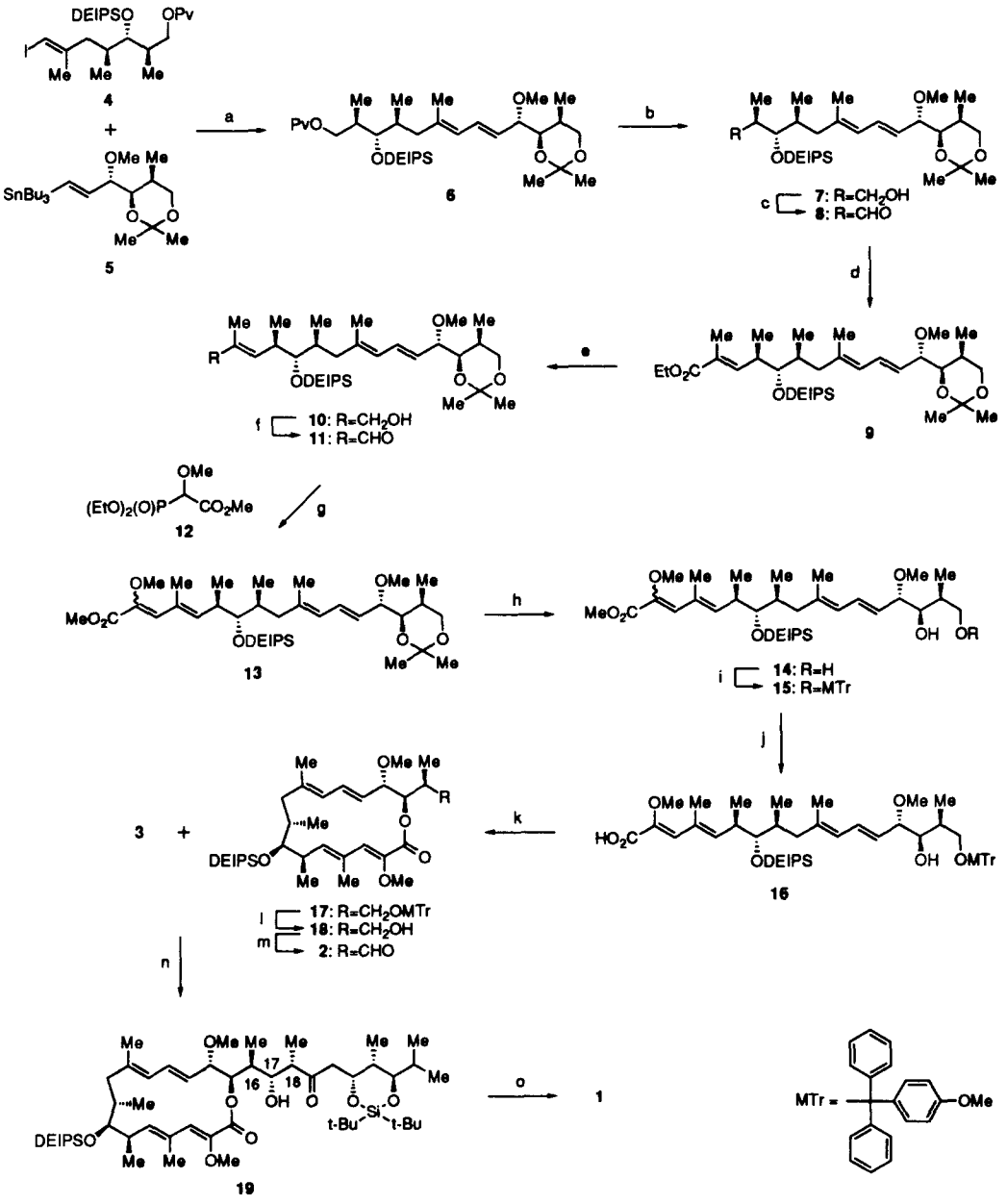


Figure 1

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 ^1H-NMR, $[\alpha]_D$, mp, mmp, and TLC behaviors in several solvent systems.[17]

Acknowledgment. We sincerely thank Prof. A. Zeeck (Georg-August-Universität Göttingen), Profs. H. Hagenmaier and H. Zähner (Universität Tübingen), Prof. H.-P. Fiedler (Eberhard-Karls-Unibersität Tübingen), Prof. W. Keller-Schierlein (Eidgenössischen Technischen Hochschule), Dr. R. J. J. Dorgan (SmithKline Beecham), and Dr. H. H. Peter (Ciba-Geigy Ltd.) for supplying authentic samples of bafilomycin



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%.

A1 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).

(*Received in Japan* 13 *November* 1995; *revised* 4 *December* 1995; *accepted* 7 *December* 1995)