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# Retro-Aldol Cleavage of Bafilomycin Derivatives

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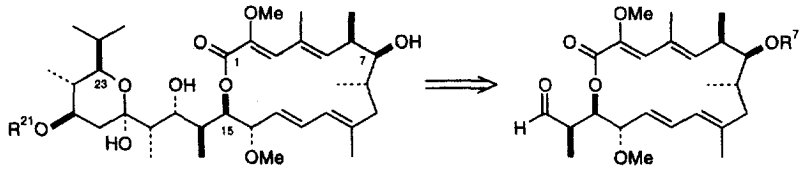
**Abstract:** The intermediates **3** and **4**, useful in the preparation of new biologically active bafilomycin derivatives, were obtained via a thermal retro-aldol reaction in diphenyl ether. The starting materials **5** and **7** for the retro-aldol reaction were synthesized in a few steps from bafilomycin $C_1$ (**2**) with or without a protective group at 7-OH. 

*Keywords:* Biologically active compounds; Cleavage reactions; Macrolides

Bafilomycin $A_1$ (**1**) and $C_1$ (**2**), 16-membered macrolides (Figure 1) produced by fermentation of *Streptomyces griseus* [1], are selective and very potent inhibitors of vacuolar $H^+$-ATPases. In the osteoclast [2], the large multinucleated cell responsible for bone resorption, these pumps produce the low pH necessary for efficient resorption of bone. Since inhibition of vacuolar $H^+$-ATPase has been shown to inhibit bone resorption both *in vitro* [3] and *in vivo* [4], such compounds are potentially useful for the treatment of osteoporosis, i.e. the loss of bone, which is especially pronounced in women after menopause. Unfortunately, the native bafilomycins, such as **1** and **2**, show an acute toxicity in animals [5] which has to be dealt with in order to develop a useful drug. In the search for intermediates useful for syntheses of novel bafilomycin analogues, we and others [6-9] have developed methods for the cleavage of the carbon-skeleton of bafilomycins.

**Figure 1**




**1**: (Bafilomycin $A_1$) $R^{21}$ = H

**2**: (Bafilomycin $C_1$) $R^{21}$ =

**3a**: $R^7$ = H

**3b**: $R^7$ = $Si(Me)_3$

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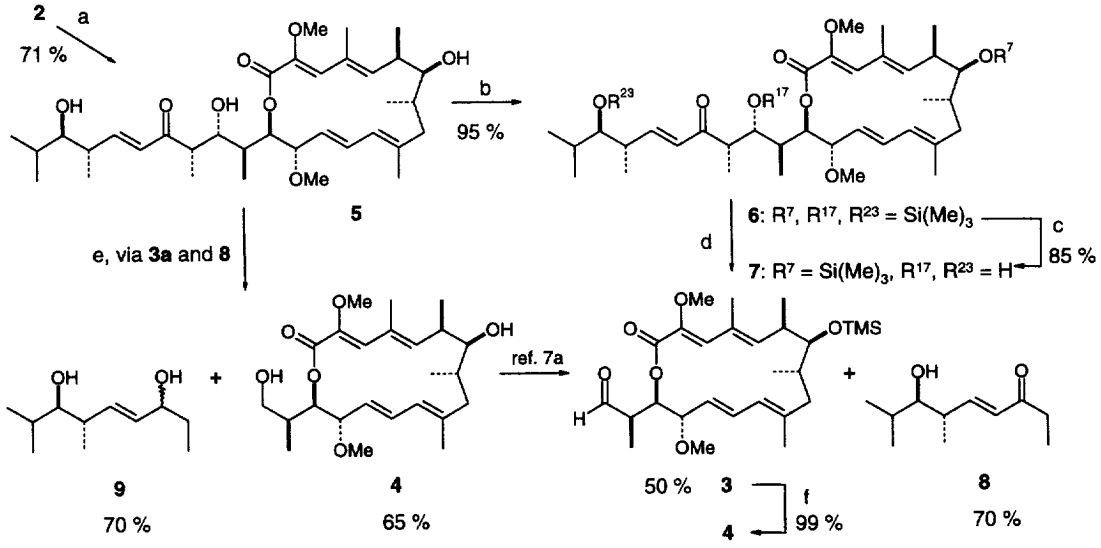
The first total synthesis of bafilomycin $A_1$ (**1**) was reported by Evans and Calter [10,11], Toshima and coworkers [12,13] have subsequently reported their synthesis. In both cases a key step involves the addition of a suitably protected ketone to aldehyde **3** as shown in Figure 1.

However, our interest was focused on the reverse process, that is methods for controlled degradation of bafilomycins **1** and **2** in a few steps. We now report on the facile thermal retro-aldol cleavage of β-hydroxy ketones such as **5** and **7** as shown in Scheme 1.[2]

Preparation of bafilomycin D (**5**) from bafilomycin $C_1$ (**2**) has been reported previously [14]. In our hands however, **5** was consistently obtained as a mixture containing bafilomycin $A_1$ (**1**) in a 2:1 ratio,[3] but could be separated on silica gel in 35 % isolated yield. In contrast, good yields were obtained when using a two phase system (toluene / DMF / $H_2O$, 2:1:1) and $Cs_2CO_3$ as base. The crude product showed predominantly **5** with only 10 % of **1**, after chromatography **5** was isolated in 71 % yield.

**Scheme 1**




Reagents and conditions: (a) Toluene/DMF/$H_2O$, 2:1:1, $Cs_2CO_3$ 8 eq, rt, 3 days; (b) TMSCl, $NEt_3$, $CH_2Cl_2$, rt; (c) Amberlyst-15, MeOH, rt; (d) $Ph_2O$, 230 °C, 20 min; (e) i. $Ph_2O$, 230 °C, 20 min; ii. *in situ* addition of MeOH, $NaBH_4$, 2 eq, 0 °C; (f) MeOH, $NaBH_4$, 1.2 eq, 0 °C.

To obtain the monosilylated product **7**, bafilomycin D (**5**) was first fully silylated with TMSCl / $NEt_3$ to give **6** followed by partial deprotection under acidic conditions with

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[2] **CAUTION:** Bafilomycins are very toxic. The lethal single iv. dose in rats, of bafilomycin $C_1$ is 0.1 μmol/kg. Extrapolated to a human of 70 kg, a lethal dose would be 5 mg! Crude bafilomycin fermentation extracts were purchased from ABP Lund, Sweden. After chromatography on silica gel followed by preparative reversed phase hplc, pure bafilomycins $A_1$ and $C_1$ were isolated.

[3] A major byproduct was isolated (by reversed phase hplc) and shown to be a double bond isomer of **5**. The stereochemistry of the C21-C22 double bond was established by steady state n.O.e to be *E*.

Amberlyst-15 in MeOH.[4] Notably there was no selectivity in the protection / deprotection steps between the 23- and 17-OH groups, the least reactive position is the 7-OH, due to the steric hindrance caused by the two flanking methyl groups as evidenced from the X-ray crystal structure [15,6] of bafilomycin $A_1$ (**1**).

Heating of **7** in diphenyl ether at or above 225 °C resulted in a facile retro-aldol process.[5] After cooling (ice bath) the crude product was purified by quick chromatography on silica gel to afford 50 % of **3b**.[6] We have not been able to detect any other isomers from the crude reaction mixture which shows that the reaction is mild enough to preserve the stereochemistry. The reaction was found to be reproducible on a 0.5 - 15 mmol scale. However, we have noted a marked decrease in isolated yield when leaving aldehyde **3** on silica gel for an extended period of time during chromatography. Furthermore, a marked sensitivity to base of **3** was demonstrated by addition of triethylamine to the mobile phase, resulting in complete degradation of the aldehyde at room temperature.[7] On the contrary, addition of acetic acid to the mobile phase was well tolerated.[8]

Application of the retro-aldol reaction to **5** provides the fastest and shortest route to the fragmented products **3a** and **8**.[9] The purification of **3a** by silica gel chromatography was plagued however by its instability and by the difficult removal of ketone **8** from the mixture. To avoid this problem, we reduced mixture **3a** and **8** to **4a** and **9** respectively by addition of MeOH and $NaBH_4$(s) to the cooled retro-aldol reaction. After flash chromatography **4a** and **9**

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[4] It is important that deprotection is carried out under non-basic conditions since treatment of **6** with $Bu_4NF$ in THF gave poor yields of **7**. We believe that this is a result of base induced retro-aldol degradation since fragment **8** was isolated from the reaction mixture.

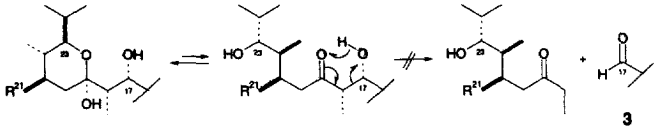
[5] For notable examples on the thermal retro-aldol reaction see references [16-19].

[6] Preparation of **3b**: A sample of **7** (1.10 g, 1.62 mmol) was dissolved in 15 mL of diphenyl ether. The reaction flask was evacuated and filled with argon five times and was then kept under a positive argon pressure. After being heated for 20 min. at 230 °C, the reaction flask was cooled on an ice bath for 5 min. Quick chromatography on silica gel with heptane (eluting diphenyl ether) followed by heptane / ethyl acetate (4:1) yielded 397 mg (50%) of **3b** as a yellow glass. $^1$H NMR was in accordance with data previously reported [10].

[7] The major, unstable, byproduct isolated was shown to be the C15-C16 eliminated compound according to $^1$H NMR and MS(ESI).

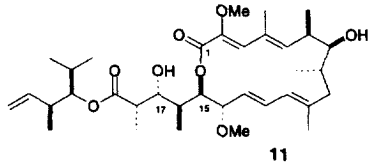
[8] The dimethyl acetal of **3a** was obtained in 89 % yield from **3b** after treatment with Amberlyst-15 (strongly acidic) in MeOH.

[9] We reasoned that since the pyran ring in bafilomycin $A_1$ (**1**) is a hemiketal it should in principle be possible to obtain **3** from the "intact bafilomycins" **10** by a retro-aldol reaction as shown below. It was however not possible to isolate the desired compound, instead complex mixtures was obtained. We also attempted the retro-aldol step on ester **11** [6]. This resulted in a complex mixture.



**10**: $R^{21}$ = OH, $OSiMe_3$, Me,

**3**



**11**

were isolated in 65 % and 70 % yield respectively. On a scale larger than 1 mmol, it is more convenient to selectively reduce the intermediate aldehyde **3a** in the presence of the ketone **8** by addition of MeOH followed by slow addition of 0.5 eq. of $NaBH_4$(s) to the crude retro-aldol reaction mixture at 0 °C. The alcohol **4a** was easily separated from **8** by normal flash chromatography and was isolated in 50 % yield.

The use of **3** and **4** in the synthesis of new bafilomycin analogues as well as biological results will be reported elsewere.

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