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Novel Fragmentation Reactions of Bafilomycin A_1

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Abstract: Two novel fragmentations of the skeletal back bone of bafilomycin A_1 are reported. These reactions occur under mild conditions and afford new bafilomycin analogues lacking 4 and 8 carbon atoms of the tetrahydropyran ring, respectively. © 1997 Elsevier Science Ltd.

Bafilomycin A_1,[1] an *unusual* plecomacrolide[2] endowed with a potent and specific inhibitory activity of vacuolar H^+-ATPase, constitutes a particularly attractive and challenging target either for the synthetic chemist and for the medicinal chemist who is intrigued by its potential therapeutic or biochemical applications. The chemistry of bafilomycin A_1 is still poorly understood. Some recent papers showed that bafilomycin A_1 possesses an unique pattern of chemical reactivity which allows facile stereo and regioselective manipulations. These reactions included regioselective oxidations of the hydroxy groups,[3] replacement of the hydroxy group at position 21 by an alkoxy group with retention of configuration[4] and a fragmentation of the side chain occurring when bafilomycin A_1 was subjected to the classical conditions of the Mitsunobu reaction.[5]

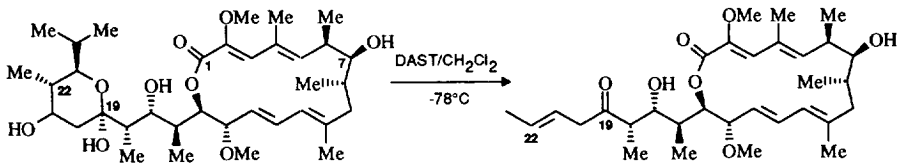
During a research programme aimed at finding the structural requirements for the biological activity, we were interested in replacing the 21-hydroxy group of bafilomycin by a fluorine atom or an amino group. Interestingly, instead of substituted bafilomycin derivatives we obtained products deriving from the stereocontrolled fragmentation of the tetrahydropyran ring, as described in the present communication.

In order to obtain the 21-fluoro analogue, bafilomycin was treated with diethylaminosulfur trifluoride (DAST) in CH_2Cl_2 (Scheme 1) at -78°C for 2 hours. Surprisingly, no fluorinated products could be obtained from this reaction; on the contrary, the novel non-conjugated ketone **2** was isolated in high yield (60%).

The ESI-MS spectrum[6] (*m/z* 555 MNa^+) indicates a loss of isobutyrraldehyde and water and no insertion of fluorine atoms. The structure of **2**, was assigned on the basis of ^1H, COSY 90 and $^{13}C\{^1H\}$ NMR experiments.[7] From ^1H and COSY spectra it was evident that no modifications occurred in the macrolactone

ring of the molecule because either the chemical shift and the multiplicity of the protons were very similar to those of the parent compound.

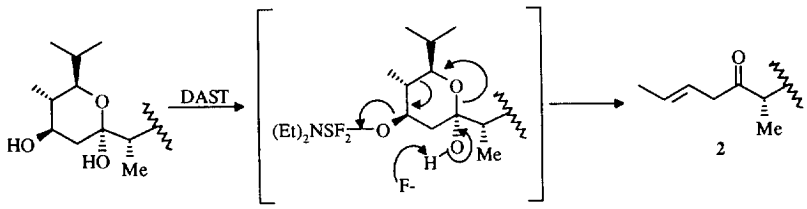
Scheme 1



1, bafilomycin A_1 2

The presence of a β,γ-pentenone moiety instead of the tetrahydropyran ring was demostrated by the doublet at δ = 1.70 ppm (22-Me) and by the chemical shift of olefinic protons at C-21 and C-22. The *trans* stereochemistry of the double bond was determined by the coupling constant (J = 15 Hz, solvent Py-d_5) of H-21 after irradiation of 22-Me. The downfield shift of H-18 (δ = 2.73 ppm) and H-20 (δ = 3.30-3.19 ppm), together with a signal at 205 ppm in ^{13}C spectrum, demonstrated the presence of a carbonyl at position 19 that was further supported by the lack of the 19-OH signal. This evidence, in addition to the upfield shift of 17-OH and H-17 (Δδ = -0.9 and -0.4 ppm), also suggested that the characteristic network of the hydrogen bonds[8] was missing. Although the mechanism of this fragmentation reaction has not been fully elucidated, a plausible rationalisation indicates that the hydroxy group at position 21 plays a central role since no reaction was observed when the 21-*O*-methyl analogue was reacted with DAST in the same conditions. Possibly, the first step involves the attack of DAST on 21-OH and the presence of an extremely efficient leaving group produces a stereoelectronically assisted fragmentation (Scheme 2) entailing the breakdown of the antiperiplanar C22-C23 bond and elimination of isobutyraldehyde.

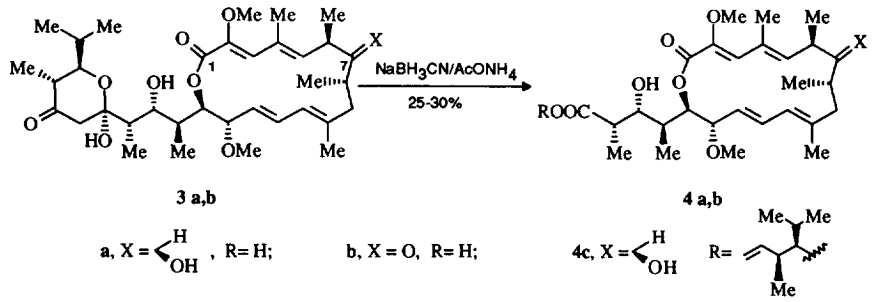
Scheme 2



To synthesize the 21-amino analogue, the 21-oxo derivatives **3a,b**[3] were subjected to reductive amination with an excess of sodium cyanoborohydride and ammonium acetate in methanol (Scheme 3). A slow reaction occurred and, after 4 days, the only compounds isolable in moderate yield by preparative HPLC,[9] were the free carboxylic acids **4a,b**. While the 7-oxo group was clearly not involved in the reaction, the presence of a keto group at position 21 was essential: using bafilomycin A_1 as the starting material, a complex mixture was obtained in which compound **4a** was not present. Replacing ammonium acetate with

benzylamine, the same compound **4a** was obtained. Conversely, sodium cyanoborohydride in the absence of bases provided a complex mixture in which the carboxylic acid **4a** was not detected.

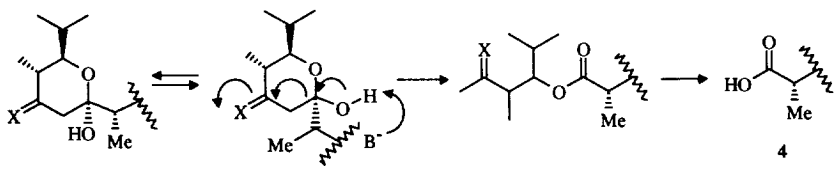
Scheme 3



The structures of **4a,b** were assigned on the basis of FAB-MS[10] (*m/z* 493 and 491, respectively, $(M-H)^-$) and NMR[11] spectra. Again, the ^1H and the COSY spectra of **4a,b** showed no modifications in the macrocyclic moiety in comparison with the starting compounds. On the contrary, no signals due to the tetrahydropyran ring were present. The downfield shift ($\Delta\delta$ = 1 ppm) of H-18 was in agreement with the presence of a carboxylic residue. Moreover, for compound **4b**, the presence of the unreacted carbonyl group at position **7** was proven by the downfield shift of H-6 and H-8 ($\Delta\delta$ = 0.9 ppm) and by the presence of a signal at δ= 214.9 ppm in ^{13}C spectrum.

A possible mechanistic rationale for this reaction is closely related to that recently proposed by Hanessian *et al.*, [5] who described a similar fragmentation of bafilomycin A_1 was described affording the ester **4c** from which the free acid **4a** could not be obtained by hydrolysis either in acidic or in basic conditions. In our hands, after anomerisation of C19 hydroxy group, an internal retro-Claisen reaction of the ketone (or of the intermediate imine) might be postulated (Scheme 4) with the formation of the corresponding β-keto (or imino) ester. This intermediate, differently from **4c**, can be hydrolized more easily, perharps via a retro-Michael elimination, to afford the free carboxylic acid **4a,b**.

Scheme 4



In conclusion, we have reported two novel fragmentations of the tetrahydropyran ring of bafilomycin A_1 with removal of 4 or 8 carbon atoms, respectively. These novel reactions contribute to increase the knowledge on this fascinating macrolide and, more importantly, permit to obtain new fragments useful for the preparation of biologically active bafilomycin analogues.

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References and Notes

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3. Gatti, P.A.; Gagliardi, S.; Cerri, A.; Visconti, M.; Farina, C.; *J. Org. Chem.* **1996**, *61*, 7185-7188.
4. Gagliardi, S.; Gatti, P.A.; Cerri, A.; Farina, C.; *Tetrahedron Lett.* **1997**, *38*, 479-482.
5. Hanessian, S.; Tehim A.; Meng Q.; Granberg K.; *Tetrahedron Lett.* **1996**, *37*, 9001-9004.
6. MS conditions: ESI POS; TSQ 700; solvent: methanol/spray 4.5 kV/skimmer: 60 V/capillary 220° C
7. Spectroscopic data for compound **2**: (300-MHz)^{1}H-N.M.R. ($CDCl_3$): 6.65 (s, 1H, H-3); 6.5 (dd, J= 14, 11 Hz, 1H, H-12); 5.82 (dd, J= 11, 1 Hz, 1H, H-11); 5.77 (dd, J= 8, 1 Hz, 1H, H-5); 5.63-5.45 (m, 2H, H-21 and H-22); 5.18 (dd, J= 14, 8 Hz, 1H, H-13); 5.04 (dd, J= 8, 2 Hz, 1H, H-15); 3.84 (dd, J= 8, 8 Hz, 1H, H-14); 3.74 (ddd, J= 9, 3, 1 Hz, 1H, H-17); 3.72 (d, J= 1 Hz, 1H, 17-OH); 3.69 (s, 3H, 2-OMe); 3.32 (m, 1H, H-7); 3.30-3.19 (m, 2H, H-20); 3.24 (s, 3H, 14-OMe); 2.73 (dq, J= 3, 7 Hz, 1H, H-18); 2.55 (ddq, J= 8, 2, 7 Hz, 1H, H-6); 2.14 (dd, J= 14, 1 Hz, 1H, H-9ax); 2.05 (dd, J= 14, 8, 1H, H-9eq); 2.00-1.86 (m, 2H, H-8 and H-16); 1.99 (d, J= 1 Hz, 3H, 10-Me); 1.92 (d, J= 1 Hz, 3H, 4-Me); 1.70 (d, J= 4 Hz, 3H, 22-Me); 1.18 (d, J= 7 Hz, 3H, 18-Me); 1.08 (d, J= 7 Hz, 3H, 6-Me); 0.95 (d, J= 7 Hz, 3H, 8-Me); 0.91 (d, J= 7 Hz, 3H, 16-Me).
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9. Preparative HPLC conditions: C-18 column Vydac RP-18 250 x22 mm; λ = 254 nm; mobile phase: A= 0.05 M NH_4OAc pH = 6.5, B= MeOH; linear gradient: 70-75% of B in 40 min.; flow rate 24 mL/min.
10. MS conditions: FAB NEG; matrix diethanolamine; FAB gas Xe; 8 kV; source 50° C
11. Spectroscopic data for compound **4a**: (300-MHz)^{1}H-N.M.R. ($CDCl_3$): 6.66 (s, 1H, H-3); 6.51 (dd, J= 15, 11 Hz, 1H, H-12); 5.81 (dd, J= 11, 1 Hz, 1H, H-11); 5.78 (dd, J= 9, 1 Hz, 1H, H-5); 5.15 (dd, J= 15, 9 Hz, 1H, H-13); 5.02 (d, J= 9 Hz, 1H, H-15); 3.87 (dd, J= 9, 9 Hz, 1H, H-14); 3.80-3.65 (m, 2H, H-17, 17-OH); 3.67 (s, 3H, 2-OMe); 3.30 (m, 1H, H-7); 3.25 (s, 3H, 14-OMe); 2.73-2.62 (m, 1H, H-18); 2.60-2.50 (m, 1H, H-6); 2.11 (dd, J= 13, 13 Hz, 1H, H-9_{ax}); 2.15-2.08 (m, 1H, H-16); 2.04 (d br, J= 13, 1H, H-9_{eq}); 1.98 (d, J=1 Hz, 3H, 4-Me); 1.94-1.90 (m, 1H, H-8); 1.93 (d, J= 1 Hz, 3H, 10-Me); 1.21 (d, J= 7 Hz, 3H, 18-Me); 1.07 (d, J= 7 Hz, 3H, 6-Me); 0.93 (d, J= 7 Hz, 3H, 8-Me); 0.88 (d, J= 7 Hz, 3H, 16-Me)

    Spectroscopic data for compound **4b**: (300-MHz)^{1}H-N.M.R. ($CDCl_3$): 6.47 (dd, J= 15, 11 Hz, 1H, H-12); 6.44 (s, 1H, H-3); 5.83 (dd, J= 11, 1 Hz, 1H, H-11); 5.23 (dd, J= 15, 9 Hz, 1H, H-13); 5.22 (dd, J= 10, 1 Hz, 1H, H-5); 5.04 (d, J= 9 Hz, 1H, H-15); 3.84 (dd, J= 9, 9 Hz, 1H, H-14); 3.80-3.55 (m, 2H, H-17, 17-OH); 3.69 (s, 3H, 2-OMe); 3.41 (dq, J= 10, 7 Hz, 1H, H-6); 3.24 (s, 3H, 14-OMe); 2.85-2,73 (m, 1H, H-8); 2.73-2.62 (m, 1H, H-18); 2.30 (dd, J= 12, 12 Hz,1H, H-9ax); 2.20-2.08 (m, 1H, H-16); 2.13 (dd, J= 12, 3, 1H, H-9eq); 2.08 (d, J= 1 Hz, 3H, 4-Me); 1.73 (d, J= 1 Hz, 3H, 10-Me); 1.21 (d, J= 7 Hz, 3H, 18-Me); 1.09 (d, J= 7 Hz, 3H, 6-Me); 1.02 (d, J= 7 Hz, 3H, 8-Me); 0.88 (d, J= 7 Hz, 3H, 16-Me).

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