Selective Oxidation of Hydroxy Groups of Bafilomycin A_1

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Received April 19, 1996

Bafilomycin A_1 (**1**), a 16-membered antibiotic macrolide isolated from the fermentation of *Streptomyces griseus*,[1] belongs to the class of so-called "unusual macrolides".[2] This class also comprises the 18-membered concanamycin A and the C_2-symmetric 16-membered elaiophylin[3] and is characterized by the presence of a tetrahydropyran ring within a long side chain. These macrolides are endowed with several biological activities, including antitumor,[4] antiviral,[5] and immunosuppressant[6] properties. In particular, **1** is a specific inhibitor of vacuolar H^+-ATPase[7] and has also been found to inhibit, *in vitro*, the release of β-amyloid[8] and the mitogen-induced DNA synthesis.[9]

Total synthesis of **1** has been recently achieved;[10] however, owing to its highly functionalized nature, selective derivatization of bafilomycin A_1 still represents a challenging target. Little information is available in the literature about modification of the hydroxy groups of bafilomycin, and this is limited to alkylation and acylation.[11] Whereas the OH at 19 easily forms a ketal by reaction with alcohols in the presence of catalytic amounts of acid, the 21-OH is the most reactive group toward alkylation and acylation, since the 7-OH is sterically hindered and the 17-OH is involved in a strong hydrogen bonding system with the 19-OH and the lactone carbonyl.[12]

In the framework of a research program aimed at studying the pharmacological activity of bafilomycin derivatives, we became interested in the selective oxidation of the hydroxy groups at positions 7 and 21 of **1**. Although the biological activity of 21-oxobafilomycin (**2**) has been previously reported,[13] its synthesis was not disclosed.[14] Apart from degradative ozonolysis,[15] nothing is reported in the literature about the oxidation of this macrolide, and we thought it worthwhile to investigate this reaction with the aim of achieving selective oxidation of the different hydroxy groups of **1**.

First, a preliminary survey of the behavior of bafilomycin A_1 in the presence of several oxidizing agents was performed: while manganese dioxide or tetrapropylammonium perrhutenate (TPAP)[16] were ineffective, chromium compounds or Dess−Martin's periodinane[17] were able to afford several oxidized products. It was observed that long reaction times, high temperatures, or acidic conditions resulted in extensive decomposition of the macrolide. Therefore, all the subsequent reactions were performed using a large excess of the oxidizing agent, at low temperatures and in the presence of a buffering agent when using acidic oxidants. Thus, treatment of **1** with a 6-fold molar excess of PCC buffered with sodium acetate in CH_2Cl_2 afforded a mixture of 7-oxo (**6**) and 7,21-dioxo (**10**) derivatives, while oxidation with excess PDC afforded a mixture of **6** and of the 19,20-dehydrated 7,21-dioxo compound **9** (Scheme 1). When the 21-OH of **1** was protected by acylation (**3**−**5**), the corresponding 7-oxo derivatives **7** and **8** were smoothly obtained by treatment with PCC and, as expected, the 19-methoxy group in compound **4** was easily hydrolyzed during aqueous workup.

Dess−Martin reagent appeared to be a more eclectic oxidant, affording different oxidized compounds depending on the molar excess used. Thus, while in the presence of stoichiometric amounts no reaction was observed, a 3-fold molar excess of periodinane afforded a quantitative yield of the dioxo derivative **10** and a 7.5-fold excess afforded the 19,20-dehydrated trioxo compound **11** in 80% yield.

Rather surprisingly, we were never able to isolate the monooxidized 21-oxo derivative in any experimental conditions, using either chromium oxidants or periodinane.

Therefore, to obtain the desired 21-ketone **2**, we exploited the greater reactivity of the 21-hydroxy group toward electrophilic reagents, as in the case of acylation or alkylation. Consequently, the Swern reaction,[18] entailing an intermediate electrophilic sulfonium ion, proved successful: treatment of **1** with oxalyl chloride/DMSO at a temperature between −70 and −40 °C afforded **2** in good yield (48%).

When pure compound **2** was treated with a large excess of PCC, a very rapid and quantitative oxidation of the 7-hydroxy group, to give a mixture of **9** and **10** without any evidence of degradation, was observed, suggesting that oxidation of the more sterically hindered 7-hydroxy group is faster than oxidation at 21.

Unambiguous identification of the oxidized compounds was done by comparing ^{1}H-NMR and COSY-90 spectra

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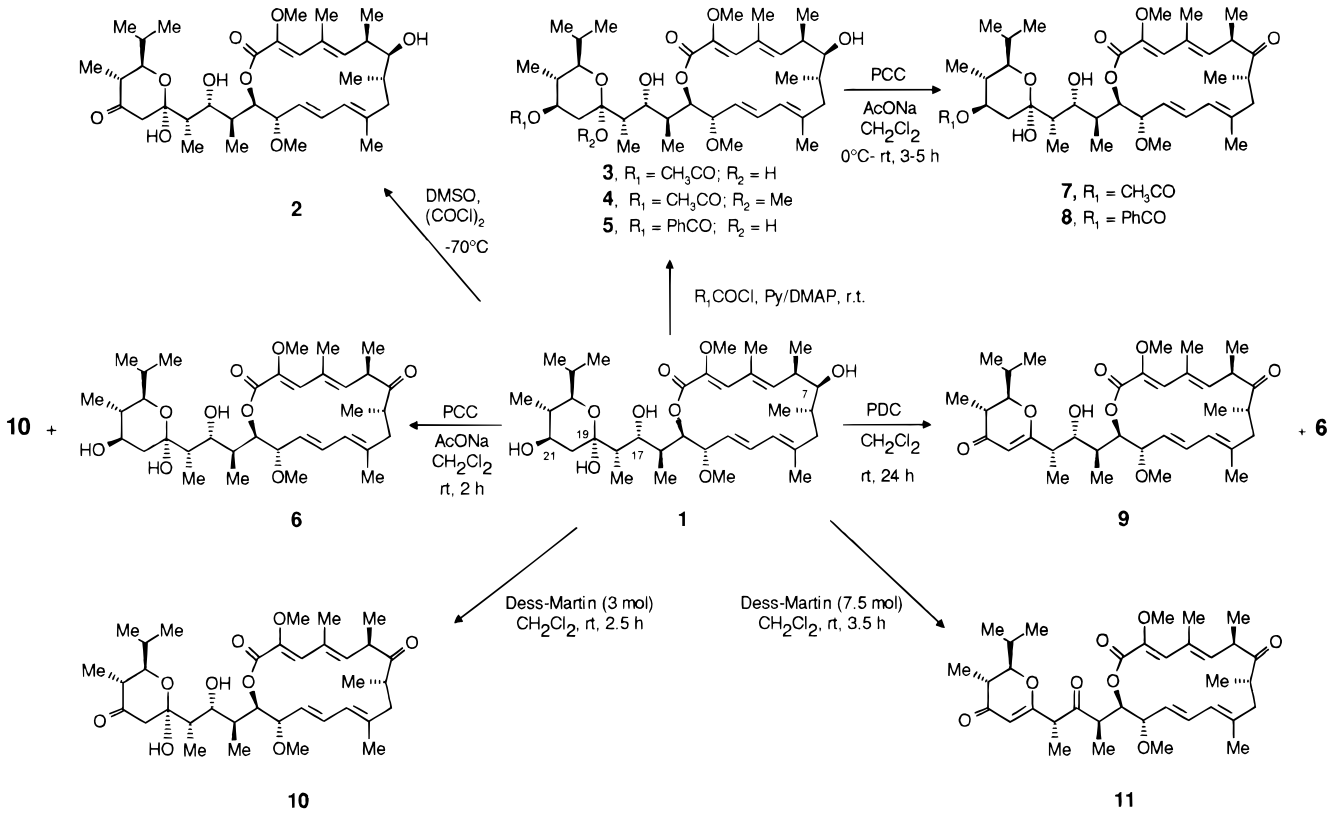
S0022-3263(96)00722-0 CCC: $12.00

Scheme 1



with the corresponding data for **1**.[19] Essentially, the disappearance of signals of the hydroxymethine group and the appearance of downfield protons α to C=O together with ^{13}C-NMR data were used to determine the number and position of the formed carbonyl groups. In compounds **9** and **11** the formation of the α,β-unsaturated carbonyl group was demonstrated by the presence of a singlet for an olefinic proton at C-20 at δ 5.42 or 5.45, respectively, and by the downfield shift of the allylic hydrogen at position 18 (δ 2.60 or 3.87, respectively).

In compounds **2**, **6**−**8**, and **10**, the diagnostic hydrogen bonding system involving 17-OH, 19-OH, and the lactone carbonyl system is maintained while in compounds **9** and **11** this is, of course, no longer possible owing to the removal of the 19-hydroxy group.

In conclusion, the behavior of **1** in the presence of oxidizing agents has been investigated and selective oxidation of the different hydroxy groups has been achieved for the first time. The present work also offers a convenient and easy entry for further modifications of bafilomycin A_1 useful for the study of the structure activity relationships of this biologically interesting macrolide.

Experimental Section

General Procedures. Melting points were determined in open capillaries and are uncorrected. Optical rotations were determined in a polarimeter with a 100 mm optical cell, operating at 589 nm (sodium D line) at 20 °C in the solvent indicated. UV spectra were obtained using a spectrophotometer in the solvent indicated. NMR were recorded on a 300 MHz spectrometer in $CDCl_3$ (7.26 ppm and 77.7 ppm) at 303 K. *J* values are given in Hz. Two-dimensional COSY-90 experiments were carried out using standard software. FAB mass spectra were recorded with a triple quadrupole mass spectrometer; experimental conditions were Xe gas, 8 kV, source temperature 50 °C, using diethanolamine matrix in negative-ion mode or thioglycerol in positive-ion mode. Bafilomycin A_1 was isolated from the mycelium of *Streptomyces griseus* according to the reported procedure.[19] Reagents and solvent were purchased from common commercial suppliers and were used as received or distilled from the appropriate drying agent. Column chromatography (CC) was performed with silica gel 0.063−0.200 mm. TLC was performed on Merck silica gel 60 F_{254} precoated plates eluting with solvent A (hexane/AcOEt 3:2) or B (hexane/AcOEt 4:1) and detected by 5% vanillin/H_2SO_4. Analytical HPLC method: C-18 column (Vydac RP18), 250 × 4.6 mm i.d., flow rate 1 mL/min, λ = 254 nm; mobile phase A, 0.05 M NH_4OAc pH 6.5, B, MeOH, linear gradient indicated. Preparative HPLC was performed using the same conditions on a Vydac RP18 250 × 22 mm i.d. and a flow rate of 24 mL/min.

21-Deoxy-21-oxobafilomycin A_1 (2) from 1. To a solution of oxalyl chloride (0.26 mL, 2.97 mmol) in CH_2Cl_2 (20 mL), at −70 °C under nitrogen was added DMSO (0.45 mL, 6.34 mmol) dropwise. The solution was stirred for 1 h at −70 °C, and **1** (600 mg, 0.9 mmol) was added. The solution was stirred at −70 °C for 0.5 h. After this time, 1.8 mL of triethylamine was added, and the mixture was stirred for 5 min at −70 °C, warmed to −40 °C, and poured into 10% aqueous sodium hydrogensulfate (60 mL). The layers were separated, and the aqueous phase was extracted with 3 × 30 mL of dichloromethane. The organic layer was washed with 90 mL of brine, dried over $MgSO_4$, filtered, concentrated, and chromatographed (hexane/AcOEt 8:2) to yield 290 mg (52%) of compound **2** as a white powder. Mp: 149−152 °C. $[\alpha]^{20}_D = -12$ (c = 0.33, $CHCl_3$). TLC: (A) R_f 0.70. HPLC: gradient 70−75% of B in 40 min, t_R 33 min. FAB-MS (negative): m/z 619 $[M - H]^-$. ^{1}H-NMR: 6.68 (s, 1H, 3-H); 6.51 (dd, J = 15, 11, 1H, 12-H); 5.81 (dd, J = 11, 1, 1H, 11-H); 5.77 (dd, J = 9, 1, 1H, 5-H); 5.67 (d, J = 3, 1H, 19-OH); 5.16 (dd, J = 15, 9, 1H, 13-H); 4.95 (dd, J = 9, 1, 1H, 15-H); 4.72 (d, J = 4, 1H, 17-OH); 4.16 (ddd, J = 9, 4, 2, 1H, 17-H); 3.89 (dd, J = 9, 9, 1H, 14-H); 3.81 (dd, J = 11, 3, 1H, 23-H); 3.65 (s, 3H, 2-OMe); 3.29 (ddd, J = 1, 7, 7, 1H, 7-H); 3.25 (s, 3H, 14-OMe); 2.74 (d, J = 13, 1H, 20-H_{eq}); 2.54 (ddq, J = 9, 1, 7, 1H, 6-H); 2.34 (dq, J = 11,7, 1H, 22-H); 2.27 (dd, J = 13, 3, 1H, 20-H_{ax}); 2.14 (m, 1H, 9-H_{eq}); 2.14 (ddq, J = 9, 1, 7, 1H, 16-H); 2.00 (m, 1H, 9-H_{ax}); 2.00 (d, J

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= 1, 3H, 4-Me); 1.94 (d, J = 1, 3H, 10-Me); 1.90 (m, 1H, 8-H); 1.90 (dq, J = 2, 7, 1H, 18-H); 1.89 (dqq, J = 3, 7, 7, 1H, 24-H); 1.53 (d, J = 7, 1H, 7-OH); 1.07 (d, J = 7, 3H, 6-Me); 1.05 (d, J = 7, 3H, 18-Me); 0.97 (d, J = 7, 3H, 24-Me); 0.97(d, J = 7, 3H, 22-Me); 0.94 (d, J = 7, 3H, 8-Me); 0.87 (d, J = 7, 3H, 24-Me); 0.85 (d, J = 7, 3H, 16-Me). ^{13}C-NMR: 209.3, 167.9, 143.6, 143.4, 141.7, 134.1, 133.5, 133.4, 127.6, 125.7, 101.6, 82.7, 81.6, 77.6, 77.3, 71.2, 60.4, 56.0, 51.3, 47.8, 42.3, 41.7, 40.5, 37.6, 37.2, 29.2, 22.1, 21.4, 20.6, 17.7, 14.6, 14.4, 10.2, 9.3, 7.3; UV($CHCl_3$) λ_{max}: 249 nm (ϵ 43 800), 287 (22 300)

21-*O*-Acetylbafilomycin A$_1$ (3) from 1. To a solution of **1** (1 g, 1.6 mmol) and DMAP (103 mg, 0.8 mmol) in dry pyridine (15 mL) was added acetyl chloride (0.3 mL) dropwise. The mixture was stirred under nitrogen at room temperature for 2.5 h, diluted with AcOEt (150 mL), and washed with 5% citric acid, a saturated solution of $NaHCO_3$, and brine. After being dried over $MgSO_4$, evaporation of the solvent afforded the crude product that was purified by CC, eluting with hexane/AcOEt 4:1, obtaining 513 mg (48%) of **3** as a white powder. Mp: 68−69 °C. $[\alpha]^{20}_D$ = −23 (c = 0.31; MeOH). TLC (B): R_f = 0.32. HPLC: gradient 75−90% of B in 40 min, t_R 24.8 min. FAB-MS (negative): m/z 663 $[M - H]^-$. ^{1}H-NMR: 6.67 (s, 1H, 3-H); 6.50 (dd, J = 15, 11, 1H, 12-H); 5.81 (dd, J = 11, 1, 1H, 11-H); 5.76 (dd, J = 9, 1, 1H, 5-H); 5.46 (d, J = 2, 1H, 19-OH); 5.16 (dd, J = 15, 9, 1H, 13-H); 4.96 (ddd, J = 11, 11, 5, 1H, 21-H); 4.95 (dd, J = 9, 1, 1H, 15-H); 4.60 (d, J = 3, 1H, 17-OH); 4.12 (ddd, J = 10, 3, 2, 1H, 17-H); 3.87 (dd, J = 9, 9, 1H, 14-H); 3.64 (s, 3H, 2-OMe); 3.60 (dd, J = 11, 2, 1H, 23-H); 3.30 (s br, 1H, 7-H); 3.24 (s, 3H, 14-OMe); 2.54 (ddq, J = 9, 1, 7, 1H, 6-H); 2.34 (dd, J = 11, 5, 1H, 20-H$_{eq}$); 2.15 (m, 1H, 9-H$_{eq}$); 2.12 (ddq, J = 10, 1, 7, 1H, 16-H); 2.02 (s, 3H, 21-OAc); 2.00 (d, J = 1, 3H, 4-Me); 1.95 (m, 1H, 9-H$_{ax}$); 1.92 (m, 1H, 8-H); 1.92 (d, J = 1, 3H, 10-Me); 1.90 (dqq, J = 2, 7, 7, 1H, 24-H); 1.75 (dq, J = 2, 7, 1H, 18-H); 1.53 (ddq, J = 11, 11, 7, 1H, 22-H); 1.17 (ddd, J = 11, 11, 2, 1H, 20-H$_{ax}$); 1.07 (d, J = 7, 3H, 6-Me); 1.03 (d, J = 7, 3H, 18-Me); 0.94 (d, J = 7, 3H, 8-Me); 0.91 (d, J = 7, 3H, 24-Me); 0.83 (d, J = 7, 3H, 16-Me); 0.82 (d, J = 7, 3H, 22-Me); 0.77 (d, J = 7, 3H, 24-Me). ^{13}C-NMR: 171.1, 168.0, 143.7, 143.4, 142.1, 134.1, 133.7, 133.7, 128.0, 126.0, 99.5, 83.0, 82.0, 77.6, 76.3, 74.7, 71.3, 60.6, 56.2, 42.8, 42.0, 40.9, 40.7, 38.9, 37.9, 37.4, 28.7, 22.4, 21.9, 21.7, 20.8, 18.0, 15.0, 14.7, 13.0, 10.5, 7.7. UV(MeOH) λ_{max}: 247 nm (ϵ 28 900), 285 (12 200).

21-*O*-Acetyl-19-*O*-methylbafilomycin A$_1$ (4) from 3. A solution of compound **3** (489 mg, 0.7 mmol) in MeOH (50 mL) was treated with acetic acid (0.1 mL) and heated at 60 °C for 8 h. After cooling, an excess of solid $NaHCO_3$ was added. The mixture was concentrated under vacuum, diluted with AcOEt, and washed with water. The organic layer was dried over $MgSO_4$ and evaporated to give 412 mg of **4** (87%) as an amorphous white solid. TLC (B): R_f = 0.34. HPLC: gradient 75−90% of B in 40 min, t_R 29.9 min. FAB-MS (positive): m/z 717 $[MK]^+$. ^{1}H-NMR: 6.63 (s, 1H, 3-H); 6.49 (dd, J = 14, 10, 1H, 12-H); 5.81 (d br, J = 10, 1H, 11-H); 5.74 (d br, J = 9, 1H, 5-H); 5.20 (dd, J = 14, 9, 1H, 13-H); 5.09 (dd, J = 9, 1, 1H, 15-H); 4.93 (ddd, J = 11, 11, 5, 1H, 21-H); 3.88 (dd, J = 9, 9, 1H, 14-H); 3.82 (d br, J = 2, 1H, 17-OH); 3.71 (s, 3H, 2-OMe); 3.47 (d br, J = 9, 1H, 17-H); 3.30 (d br, J = 6, 1H, 7-H); 3.24 (s, 3H, 14-OMe); 3.16 (dd, J = 10, 2, 1H, 23-H); 3.05 (s, 3H, 19-OMe); 2.53 (ddq, J = 9, 2, 7, 1H, 6-H); 2.22 (dd, J = 13, 5, 1H, 20-H$_{eq}$); 2.10 (dd, J = 13, 13, 1H, 9-H$_{eq}$); 2.05 (s, 3H, 21-OAc); 2.00 (m, 1H, 9-H$_{ax}$); 2.00 (m, 1H, 16-H); 2.00 (m, 1H, 18-H); 1.98 (d, J = 1, 3H, 4-Me); 1.95 (m, 1H, 8-H); 1.95 (dqq, J = 2, 7, 7, 1H, 24-H); 1.93 (d, J = 1, 3H, 10-Me); 1.60 (dd, J = 13, 11, 1H, 20-H$_{ax}$); 1.54 (ddq, J = 11, 10, 7, 1H, 22-H); 1.07 (d, J = 7, 3H, 6-Me); 1.03 (d, J = 7, 3H, 8-Me); 0.99 (d, J = 7, 3H, 18-Me); 0.94 (d, J = 7, 3H, 24-Me); 0.91 (d, J = 7, 3H, 16-Me); 0.89 (d, J = 7, 3H, 24-Me); 0.80 (d, J = 7, 3H, 22-Me).

21-*O*-Benzoylbafilomycin A$_1$ (5) from 1. To a solution of **1** (400 mg, 0.64 mmol) and DMAP (44 mg, 0.36 mmol) in dry pyridine (4 mL) was added benzoyl chloride (0.2 mL) dropwise. The mixture was stirred under nitrogen at room temperature for 3 h and then poured into 5% citric acid (50 mL) and extracted with CH_2Cl_2. The organic layer was then washed with a saturated solution of Na_2CO_3 and brine. After the organic layer was dried over $MgSO_4$, the solvent was removed and the crude product was purified by CC, eluting with hexane/AcOEt 9:1, to obtain 165 mg of **5** (35%) as a white powder. Mp: 98−101 °C. $[\alpha]^{20}_D$ = −30 (c = 0.27; MeOH). TLC (A): R_f = 0.70. HPLC: gradient 75−90% of B in 40 min, t_R 38 min. FAB-MS (positive): m/z 765 $[MK]^+$. ^{1}H-NMR: 8.05 (d, J = 7, 2H, *o*-PhH); 7.56 (dd, J = 7, 7, 1H, *p*-PhH); 7.44 (dd, J = 7, 7, 2H, *m*-PhH); 6.69 (s, 1H, 3-H); 6.50 (dd, J = 13, 11, 1H, 12-H); 5.84 (d br, J = 11, 1H, 11-H); 5.79 (dd, J = 9, 1, 1H, 5-H); 5.51 (d, J = 2, 1H, 19-OH); 5.23 (ddd, J = 11, 11, 5,1H, 21-H); 5.18 (dd, J = 13, 9, 1H, 13-H); 4.98 (dd, J = 9, 1, 1H, 15-H); 4.63 (d, J = 4, 1H, 17-OH); 4.15 (ddd, J = 10, 4, 2, 1H, 17H); 3.90 (dd, J = 9, 9, 1H, 14-H); 3.69 (dd, J = 9, 2, 1H, 23-H); 3.67 (s, 3H, 2-OMe); 3.30 (dd, J = 6, 1, 1H, 7-H); 3.27 (s, 3H, 14-OMe); 2.55 (ddq, J = 9, 6, 7, 1H, 6-H); 2.48 (dd, J = 11, 5, 1H, 20-H$_{eq}$); 2.15 (dq br, J = 10, 7, 1H, 16-H); 2.10 (dd, J = 12, 12, 1H, 9-H$_{eq}$); 2.00 (d, J = 1, 3H, 4-Me); 1.95 (m, 1H, 9-H$_{ax}$); 1.95 (dqq, J = 2, 7, 7, 1H, 24-H); 1.94 (d, J = 1, 3H, 10-Me); 1.92 (m, 1H, 8-H); 1.80 (dq, J = 2, 7, 1H, 18-H); 1.73 (ddq, J = 11, 9, 7, 1H, 22-H); 1.34 (ddd, J = 11, 11, 2, 1H, 20-H$_{ax}$); 1.08 (d, J = 7, 3H, 6-Me); 1.04 (d, J = 7, 3H, 18-Me); 0.95 (d, J = 7, 3H, 8-Me); 0.95 (d, J = 7, 3H, 24-Me); 0.89 (d, J = 7, 3H, 22-Me); 0.84 (d, J = 7, 3H, 16-Me); 0.83 (d, J = 7, 3H, 24-Me). ^{13}C-NMR: 168.0, 166.7, 143.7, 143.4, 142.1, 134.1, 133.7, 133.4, 130.9, 130.3, 130.3, 129.2, 129.0, 129.0, 128.0, 126.0, 99.7, 83.0, 81.9, 77.6, 76.4, 75.4, 71.4, 60.7, 56.2, 42.9, 42.0, 40.9, 40.7, 39.1, 37.9, 37.5, 28.7, 22.4, 21.8, 20.8, 18.0, 15.1, 14.7, 13.1, 10.6, 7.8. UV(MeOH) λ_{max}: 237 nm (ϵ 51 800), 199 (38 300), 282 (21 000).

7-Deoxy-7-oxobafilomycin A$_1$ (6) from 1. To a solution of **1** (600 mg, 0.96 mmol) in CH_2Cl_2 (120 mL), at 0 °C under nitrogen, were added AcONa (468 mg, 5.7 mmol) and PCC (1.3 g, 6 mmol). The mixture was stirred at 0 °C for 2 h, diluted with Et_2O (60 mL), and filtered on Florisil. The crude product was purified by CC eluting with hexane/AcOEt 8:2 obtaining 118 mg of **6** (20%) as a white powder. Mp: 126−132 °C. $[\alpha]^{20}_D$ = −88 (c = 0.29; MeOH). TLC (A): R_f = 0.55. HPLC (gradient 70−75% of B in 40 min, t_R 36 min). FAB-MS (negative): m/z 619 $[M - H]^-$. ^{1}H-NMR: 6.51 (s, 1H, 3-H); 6.49 (dd, J = 16, 11, 1H, 12-H); 5.84 (dd, J = 11, 1, 1H, 11-H); 5.47 (d, J = 2, 1H, 19-OH); 5.25 (d br,J = 10, 1H, 5-H); 5.22 (dd, J = 16, 10, 1H, 13-H); 4.95 (dd, J = 10, 1, 1H, 15-H); 4.57 (dd, J = 3, 1, 1H, 17-OH); 4.14 (ddd, J = 11, 3, 2, 1H, 17-H); 3.87 (dd, J = 10, 10, 1H, 14-H); 3.70 (ddd, J = 12, 10, 6, 1H, 21-H); 3.67 (s, 3H, 2-OMe); 3.50 (dd, J = 10, 3, 1H, 23-H); 3.43 (dq, J = 10, 7, 1H, 6-H); 3.25 (s, 3H, 14-OMe); 2.81 (ddq, J = 4, 1, 7, 1H, 8-H); 2.31 (dd, J = 13, 1, 1H, 9-H$_{eq}$); 2.28 (dd, J = 12, 6, 1H, 20-H$_{eq}$); 2.24 (ddq, J = 11, 1, 7, 1H, 16-H); 2.15 (dd br, J = 13,4, 1H, 9-H$_{ax}$); 2.09 (d, J = 1, 3H, 4-Me); 1.89 (dqq, J = 3, 7, 7, 1H, 24-H); 1.78 (ddq, J = 2, 1, 7, 1H, 18-H); 1.74 (d, J = 1, 3H, 10-Me); 1.34 (ddq, J = 10, 10, 6, 1H, 22-H); 1.16 (ddd, J = 12, 12, 2, 1H, 20-H$_{ax}$); 1.09 (d, J = 7, 3H, 6-Me); 1.05 (d, J = 7, 3H, 18-Me); 1.03 (d, J = 7, 3H, 8-Me); 0.95 (d, J = 6, 3H, 22-Me); 0.91 (d, J = 7, 3H, 24-Me); 0.84 (d, J = 7, 3H, 16-Me); 0.78 (d, J = 7, 3H, 24-Me). ^{13}C-NMR: 214.9, 167.2, 143.1, 141.0, 138.2, 135.3, 133.7, 132.0, 129.3,127.0, 99.4, 82.2, 77.0, 76.3, 71.4, 71.0, 60.2, 56.3, 47.0, 46.0, 44.0, 43.5, 42.7, 41.5, 36.7, 28.4, 21.7, 19.8, 19.7, 14.8, 14.4, 14.0, 12.6, 10.0, 7.5; UV(MeOH) λ_{max}: 245 (37 000), 280 nm (ϵ 12 700).

21-*O*-Acetyl-7-deoxy-7-oxobafilomycin A$_1$ (7) from 4. To a solution of **4** (382 mg, 0.56 mmol) in CH_2Cl_2 (100 mL), at 0 °C and under nitrogen, were added AcONa (650 mg, 8 mmol) and PCC (1.4 g, 6.6 mmol). The reaction mixture was stirred at 0 °C for 3 h and at room temperature for 4 h, diluted with Et_2O (150 mL), and filtered on Florisil. After evaporation of the solvent, the crude product was purified by CC, eluting with CH_2Cl_2/MeOH 98:2, to obtain 190 mg (51%) of **7** as an amorphous white solid. $[\alpha]^{20}_D$ = −131 (c = 0.07; MeOH). HPLC: gradient 75−90% of B in 40 min, t_R 28.6 min. FAB-MS (negative): m/z 661 $[M - H]^-$. ^{1}H-NMR: 6.50 (s, 1H, 3-H); 6.49 (dd, J = 15, 11, 1H, 12-H); 5.84 (dd, J = 11, 1, 1H, 11-H); 5.45 (d, J = 2, 1H, 19-OH); 5.24 (dd, J = 11, 1, 5-H); 5.22 (dd, J = 15, 9, 1H, 13-H); 4.97 (ddd, J = 11, 11, 4, 1H, 21-H); 4.94 (dd, J = 9, 1, 1H, 15-H); 4.55 (d, J = 3, 1H, 17-OH); 4.12 (ddd, J = 9, 3, 2, 1H, 17-H); 3.85 (dd, J = 9, 9, 1H, 14-H); 3.66 (s, 3H, 2-OMe); 3.60 (dd, J = 10, 3, 1H, 23-H); 3.41 (dq, J = 11, 7, 1H, 6-H); 3.25 (s, 3H, 14-OMe); 2.80 (ddq, J = 6, 2, 7, 1H, 8-H); 2.35 (dd, J = 11, 4, 1H, 20-H$_{eq}$); 2.27 (dd, J = 6, 6, 1H, 9-H$_{eq}$); 2.17 (ddq, J = 9, 1, 7, 1H, 16-H); 2.15 (dd, J = 6, 2, 1H, 9-H$_{ax}$); 2.08 (d, J = 1, 3H, 4-Me); 2.05 (s, 3H, 21-OAc); 1.90 (dqq, J = 3, 7, 7, 1H, 24-H); 1.73 (dq, J = 2, 7, 1H, 18-H); 1.73 (d, J = 1, 3H, 10-Me); 1.55 (ddq, J = 11, 10, 7, 1H, 22-H); 1.20 (ddd, J = 11, 11, 2, 1H, 20-H$_{ax}$); 1.08 (d, J = 7, 3H, 6-Me); 1.03 (d, J = 7, 3H, 8-Me); 1.03 (d, J = 7,

3H, 18-Me); 0.91 (d, $J = 7$, 3H, 24-Me); 0.83 (d, $J = 7$, 3H, 16-Me); 0.82 (d, $J = 7$, 3H, 22-Me); 0.78 (d, $J = 7$, 3H, 24-Me). ^{13}C-NMR: 215.2, 171.5, 167.5, 143.3, 141.3, 138.5, 135.6, 133.9, 132.3, 129.6, 127.3, 99.7, 82.5, 77.3, 76.4, 74.7, 71.2, 60.4, 56.6, 47.3, 46.3, 43.8, 43.0, 40.9, 38.9, 37.0, 28.7, 21.9, 21.8, 20.1, 20.0, 15.0, 14.7, 14.3, 13.0, 10.3, 7.7. UV(MeOH) λ_{max}: 244 nm (ϵ 40 000), 278 (16 000).

21-*O*-Benzoyl-7-deoxy-7-oxobafilomycin A_1 (8) from 5. To a solution of **5** (750 mg, 1 mmol) in CH_2Cl_2 (150 mL), at room temperature and under nitrogen, were added AcONa (1.3 g, 16 mmol) and PCC (2.8 g, 13 mmol). The reaction mixture was stirred for 5 h, diluted with Et_2O (300 mL), and filtered on Florisil. After evaporation of the solvent, the crude product was purified by CC, eluting with CH_2Cl_2/MeOH 98:2, and then crystallized from MeOH to give 174.3 mg (24%) of **8**. Mp: 186−187 °C. $[\alpha]^{20}_D = -140$ ($c = 0.28$; $CHCl_3$). HPLC: gradient 75−90% of B in 40 min, t_R 41.5 min. FAB-MS (negative): m/z 723 $[M - H]^-$. ^{1}H-NMR: 8.04 (d, $J = 8$, 2H, *o*-PhH); 7.55 (dd, $J = 8, 8$, 1H, *p*-PhH); 7.42 (dd, $J = 8, 8$, 2H, *m*-PhH); 6.50 (s, 1H, 3-H); 6.49 (dd, $J = 15, 11$, 1H, 12-H); 5.85 (d br, $J = 11$, 1H, 11-H); 5.49 (d, $J = 3$, 1H, 9-OH); 5.24 (d br, $J = 11$, 1H, 5-H); 5.22 (dd, $J = 15, 9$, 1H, 13-H); 5.22 (ddd, $J = 11, 11, 5$, 1H, 21-H); 4.95 (dd, $J = 9, 2$, 1H, 15-H); 4.57 (d, $J = 4$, 1H, 17-OH); 4.15 (ddd, $J = 11, 4, 2$, 1H, 17-H); 3.86 (dd, $J = 9, 9$, 1H, 14-H); 3.68 (dd, $J = 11, 3$, 1H, 23-H); 3.66 (s, 3H, 2-OMe); 3.42 (dq, $J = 11, 7$, 1H, 6-H); 3.25 (s, 3H, 14-OMe); 2.80 (ddq, $J = 12, 4, 7$, 1H, 8-H); 2.48 (dd, $J = 11, 5$, 1H, 20-H_{eq}); 2.29 (dd, $J = 12, 12$, 1H, 9-H_{eq}); 2.25 (ddq, $J = 7, 2, 11$, 1H, 16-H); 2.15 (dd, $J = 12, 4$, 1H, 9-H_{ax}); 2.10 (d, $J = 1$, 3H, 4-Me); 1.93 (dqq, $J = 3, 7, 7$, 1H, 24-H); 1.80 (dq, $J = 2, 7$, 1H, 18-H); 1.74 (d, $J = 1$, 3H, 10-Me); 1.70 (ddq, $J = 11, 11, 7$, 1H, 22-H); 1.33 (ddd, $J = 11, 11, 3$, 1H, 20-H_{ax}); 1.08 (d, $J = 7$, 3H, 6-Me); 1.03 (d, $J = 7$, 3H, 18-Me); 1.02 (d, $J = 7$, 3H, 8-Me); 0.94 (d, $J = 7$, 3H, 24-Me); 0.89 (d, $J = 7$, 3H, 22-Me); 0.83 (d, $J = 7$, 3H, 16-Me); 0.82 (d, $J = 7$, 3H, 24-Me). ^{13}C-NMR: 215.2, 167.4, 166.6, 143.4, 141.2, 138.5, 135.6, 133.9, 133.4, 132.2, 131.6, 130.3, 130.3, 129.6, 129.0, 129.0, 127.3, 99.7, 82.5, 77.3, 76.4, 75.4, 71.3, 60.5, 56.6, 47.3, 46.2, 43.8, 43.0, 41.0, 39.1, 37.0, 28.7, 21.9, 20.1, 20.0, 15.1, 14.7, 14.3, 13.1, 10.3, 7.7. UV($CHCl_3$) λ_{max}: 249 nm (ϵ 38 000), 282 (14 400).

19,20-Didehydro-7,19,21-trideoxy-7,21-dioxobafilomycin A_1 (9) from 1. To a solution of **1** (200 mg, 0.32 mmol) in CH_2Cl_2 (20 mL), at 0 °C and under nitrogen, were added PDC (120 mg, 0.32 mmol) and molecular sieves (4 Å, 500 mg). The mixture was stirred at 0 °C for 3 h and then at room temperature overnight. After this time an additional mole of PDC was added. After 6 h, the reaction mixture was diluted with Et_2O (50 mL) and filtered on Florisil. The crude product was obtained by evaporation of the solvent. Purification by CC eluting with hexane/AcOEt 4:1 afforded 13 mg (7%) of **9** ($R_f = 0.65$) as a white foam and 22 mg (11%) of **6** as a more polar fraction ($R_f = 0.32$ TLC (B)). FAB-MS (positive): m/z 639 $[MK]^+$. ^{1}H-NMR: 6.47 (s, 1H, 3-H); 6.46 (dd, $J = 15, 11$, 1H, 12-H); 5.82 (dd, $J = 11, 1$, 1H, 11-H); 5.42 (s, 1H, 20-H); 5.22 (dd, $J = 11, 1$, 1H, 5-H); 5.21 (dd, $J = 15, 9$, 1H, 13-H); 5.02 (dd, $J = 9, 1$, 1H, 15-H); 3.84 (dd, $J = 13, 3$, 1H, 23-H); 3.80 (dd, $J = 9, 9$, 1H, 14-H); 3.67 (s, 3H, 2-OMe); 3.59 (ddd, $J = 10, 6, 4$, 1H, 17-H); 3.48 (d, $J = 6$, 1H, 17-OH); 3.41 (dq, $J = 11, 7$, 1H, 6-H); 3.22 (s, 3H, 14-OMe); 2.80 (ddq, $J = 12, 3, 7$, 1H, 8-H); 2.60 (dq, $J = 4, 7$, 1H, 18-H); 2.42 (dq, $J = 13, 7$, 1H, 22-H); 2.29 (dd, $J = 12, 12$, 1H, 9-H_{eq}); 2.20 (ddq, $J = 10, 1, 7$, 1H, 16-H); 2.17 (dd, $J = 12, 3$, 1H, 9-H_{ax}); 2.07 (d, $J = 1$, 3H, 4-Me); 2.00 (dqq, $J = 3, 7, 7$, 1H, 24-H); 1.73 (d, $J = 1$, 3H, 10-Me); 1.17 (d, $J = 7$, 3H, 18-Me); 1.08 (d, $J = 7$, 3H, 6-Me); 1.07 (d, $J = 7$, 3H, 22-Me); 1.06 (d, $J = 7$, 3H, 24-Me); 1.02 (d, $J = 7$, 3H, 8-Me); 0.96 (d, $J = 7$, 3H, 24-Me); 0.95 (d, $J = 7$, 3H, 16-Me). ^{13}C-NMR: 214.9, 196.3, 179.2, 166.6, 143.2, 140.9, 138.0, 135.2, 133.6, 131.6, 129.3, 127.0, 103.9, 88.2, 82.8, 76.8, 73.4, 60.2, 56.3, 47.0, 46.0, 43.6, 41.8, 41.5, 37.8, 29.1, 20.2, 19.8, 19.7, 15.1, 14.4, 14.0, 10.9, 10.8, 10.3.

7,21-Dideoxy-7,21-dioxobafilomycin A_1 (10) from 1. To a solution of Dess−Martin reagent (1.23 g, 2.9 mmol) in CH_2Cl_2 (60 mL), at room temperature, was added **1** (600 mg, 0.96 mmol). The solution was stirred at room temperature for 2.5 h, diluted with Et_2O (250 mL), and poured into a solution of 3 g of sodium thiosulfate in a saturated solution of $NaHCO_3$ (120 mL). The mixture was stirred for 15 min, and the organic layer was separated, washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated to yield 600 mg (100%) of **10** as a white foam. $[\alpha]^{20}_D = -119$ ($c = 0.32$; MeOH). HPLC: gradient 70−75% of B in 40 min, t_R 40.5 min. FAB-MS (negative): m/z 617 $[M - H]^-$. ^{1}H-NMR: 6.54 (s, 1H, 3-H); 6.50 (dd, $J = 15, 11$, 1H, 12-H); 5.85 (dd, $J = 11, 1$, 1H, 11-H); 5.66 (d, $J = 3$, 1H, 19-OH); 5.25 (dd, $J = 11, 1$, 1H, 5-H) 5.22 (dd, $J = 15, 9$, 1H, 13-H); 4.94 (dd, $J = 9, 2$, 1H, 15-H); 4.69 (d br, $J = 4$, 1H, 17-OH); 4.16 (ddd, $J = 11, 4, 2$, 1H, 17-H); 3.88 (dd, $J = 9, 9$, 1H, 14-H); 3.82 (dd, $J = 10, 3$, 1H, 23-H); 3.68 (s, 3H, 2-OMe); 3.44 (dq, $J = 11, 7$, 1H, 6-H); 3.26 (s, 3H, 14-OMe); 2.90 (dqq, $J = 3, 7, 7$, 1H, 24-H); 2.82 (ddq, $J = 6, 3, 7$, 1H, 8-H); 2.74 (d, $J = 13$, 1H, 20-H_{eq}); 2.35 (dq, $J = 10, 7$, 1H, 22-H); 2.31 (dd, $J = 13, 6$, 1H, 9-H_{eq}); 2.28 (dd, $J = 13, 3$, 1H, 20-H_{ax}); 2.25 (ddq, $J = 11, 2, 7$, 1H, 16-H); 2.15 (dd, $J = 13, 3$, 1H, 9-H_{ax}); 2.10 (d, $J = 1$, 3H, 4-Me); 1.96 (dq br, $J = 2, 7$, 1H, 18-H); 1.74 (d, $J = 1$, 3H, 18-Me); 1.09 (d, $J = 7$, 3H, 6-Me); 1.03 (d, $J = 7$, 3H, 8-Me); 1.03 (d, $J = 7$, 3H, 18-Me); 0.98 (d, $J = 7$, 3H, 22-Me); 0.97 (d, $J = 7$, 3H, 24-Me); 0.88 (d, $J = 7$, 3H, 24-Me); 0.87 (d, $J = 7$, 3H, 16-Me). ^{13}C-NMR: 214.9, 209.2, 167.3, 143.0, 141.1, 138.4, 135.2, 133.8, 132.3, 129.2, 127.0, 101.6, 82.2, 77.6, 77.0, 71.1, 60.3, 56.3, 51.3, 47.8, 47.0, 46.0, 43.5, 42.4, 36.7, 29.2, 21.5, 19.9, 19.7, 14.6, 14.4, 14.1, 10.0, 9.3, 7.3. UV (MeOH) λ_{max}: 245 nm (ϵ 39 500), 280 (13 400).

19,20-Didehydro-7,17,19,21-tetradeoxy-7,17,21-trioxobafilomycin A_1 (11) from 1. To a solution of Dess−Martin reagent (509 mg, 1.2 mmol) in CH_2Cl_2 (20 mL), at room temperature, was added **1** (100 mg, 0.16 mmol). The solution was stirred at room temperature for 3.5 h, diluted with Et_2O (80 mL), and poured into a solution of 1 g of sodium thiosulfate in a saturated solution of $NaHCO_3$ (40 mL). The mixture was stirred for 15 min. The organic layer was separated, washed with a saturated solution of $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by CC, eluting with CH_2Cl_2/MeOH 99:1, to obtain 76.4 mg (79%) of **11**. Mp: 63−65 °C. $[\alpha]^{20}_D = -30$ ($c = 0.27$; MeOH). HPLC: gradient 70−75% of B in 40 min, t_R 32.7 min. FAB-MS (negative): m/z 597 $[M - H]^-$. ^{1}H-NMR: 6.49 (dd, $J = 15, 11$, 1H, 12-H); 6.32 (s, 1H, 3-H); 5.86 (dd, $J = 11, 1$, 1H, 11-H); 5.45 (s, 1H, 20-H); 5.20 (dd, $J = 9, 1$, 1H, 5-H); 5.20 (dd, $J = 15, 9$, 1H, 13-H); 5.07 (dd, $J = 9, 4$, 1H, 15-H); 3.88 (dd, $J = 13, 3$, 1H, 23-H); 3.87 (q, $J = 7$, 1H, 18-H); 3.79 (dd, $J = 9, 9$, 1H, 14-H); 3.62 (s, 3H, 2-OMe); 3.40 (dq, $J = 4, 7$, 1H, 16-H); 3.38 (dq, $J = 9, 7$, 1H, 6-H); 3.22 (s, 3H, 14-OMe); 2.80 (ddq, $J = 11, 4, 7$, 1H, 8-H); 2.46 (dq, $J = 13, 7$, 1H, 22-H); 2.31 (dd, $J = 11, 11$, 1H, 9-H_{eq}); 2.14 (dd, $J = 11, 4$, 1H, 9-H_{ax}); 2.05 (d, $J = 1$, 3H, 4-Me); 2.00 (dqq, $J = 3, 7, 7$, 1H, 24-H); 1.74 (d, $J = 1$, 3H, 10-Me); 1.33 (d, $J = 7$, 3H, 18-Me); 1.11 (d, $J = 7$, 3H, 24-Me); 1.09 (d, $J = 7$, 3H, 16-Me); 1.09 (d, $J = 7$, 3H, 22-Me); 1.08 (d, $J = 7$, 3H, 6-Me); 1.02 (d, $J = 7$, 3H, 8-Me); 0.96 (d, $J = 7$, 3H, 24-Me). ^{13}C-NMR: 215.1, 206.6, 195.9, 174.3, 164.4, 143.3, 141.4, 137.1, 135.3, 134.1, 130.2, 128.4, 126.8, 104.8, 88.8, 83.3, 75.4, 59.9, 56.3, 51.3, 47.0, 46.3, 45.8, 43.9, 41.4, 29.2, 20.0, 19.8, 19.7, 15.1, 14.4, 14.1, 14.1, 10.3, 10.3. UV (MeOH) λ_{max}: 249 nm (ϵ 17 600).

Acknowledgment. The authors gratefully acknowledge R. Imrie and M. Verrall for the supply of bafilomycin A_1, Professor B. Danieli (University of Milan) for valuable discussions and assistance in elucidating NMR and MS data, and Professor C. Fuganti (Polytechnic of Milan) and V. Vecchietti for helpful advice.

Supporting Information Available: ^{1}H (300 MHz), ^{13}C (75 MHz), and ^{1}H,^{1}H COSY spectra of compounds **2**, **3**, **5**−**11** and ^{1}H (300 MHz) and ^{1}H,^{1}H COSY spectra of **4** (29 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9607222