CHEMICAL MODIFICATIONS OF BAFILOMYCIN-TYPE 16-MEMBERED DIENLACTONE MACROLIDES

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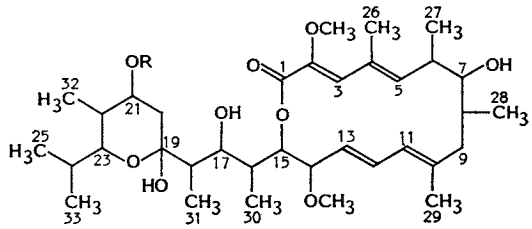
Derivatives of the 16-membered dienlactone bafilomycins were prepared in order to study the structure-activity relationship of these compounds. Some derivatives formed by hydrolysis, *O*-alkylation, *O*-acylation, trans-esterification and epoxidation were isolated and their structures determined by two-dimensional (2D) NMR studies and mass spectroscopy.

Recently several 16-membered dienlactones of the bafilomycin and hygrolidin type were isolated from different strains of streptomyces. Their insecticidal and antimicrobial activities were determined[1~6]. Chemical derivatives of this type of compound have not yet been described.

Bafilomycins A_1, B_1 and C_1 differ considerably in their biological activities, even though the structural differences (Fig. 1) are not pronounced[4]. Some derivatives of the bafilomycins, especially of bafilomycin A_1, were therefore prepared in order to study the structure-activity relationship of these compounds.

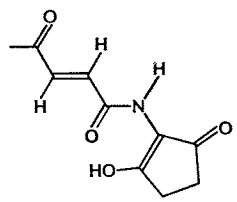
Under various reaction conditions the bafilomycins proved to be rather unstable compounds. Acid or alkaline conditions, in the presence of moderately nucleophilic reagents, led to a number of products which themselves were found to be unstable and which decomposed during the isolation procedure. Nevertheless some derivatives of the native bafilomycins were finally isolated and their structures determined. Thus information on the chemical behavior of the bafilomycins under various reaction conditions could be obtained. The biological activity of the derivatives was determined.

Fig. 1. Structures of native bafilomycins.

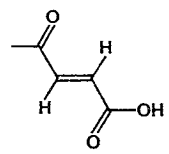


Bafilomycin A_1 R = H

Bafilomycin B_1 R =



Bafilomycin C_1 R =



Results and Discussion

The chemical reactivity of the natural bafilomycins (A_1, B_1 and C_1) and their general chemical behavior under different reaction conditions were studied by characterization of formed products and by-products. Major chemical reaction types which were found suitable for producing derivatives of the labile bafilomycins are; hydrolytic

reactions, *O*-alkylation and *O*-acylation.

In comparision with bafilomycin A_1 all derivatives described exhibit lower antibacterial, antifungal and insecticidal activities.

Hydrolytic Reactions

Bafilomycin D can be obtained by alkaline hydrolysis of a solution of bafilomycins B_1 and C_1 in dioxane - water (5 : 1)[3].

The alkaline hydrolysis of C(19)-*O*-methyl bafilomycin C_1 (Fig. 2) in MeOH with 1 N NaOH led to bafilomycin V_1 (**1**). The ester-bond at C(21) was cleaved and a trans-esterification at C(1) gave the open-chain methyl ester (**1**). In aqueous acidic methanolic solution, **1** yielded the hemiketals bafilomycin $V_{2'}$ (**2'**) and $V_{2''}$ (**2''**). The two diastereomers could be separated by chromatography. During the preparation of $V_{2'}$ and $V_{2''}$, the C(20)/C(21) dehydrated hemiketal bafilomycin V_3 (**3**) was formed also.

Fig. 2. Hydrolytic reaction of C(19)-*O*-methyl bafilomycin C_1.

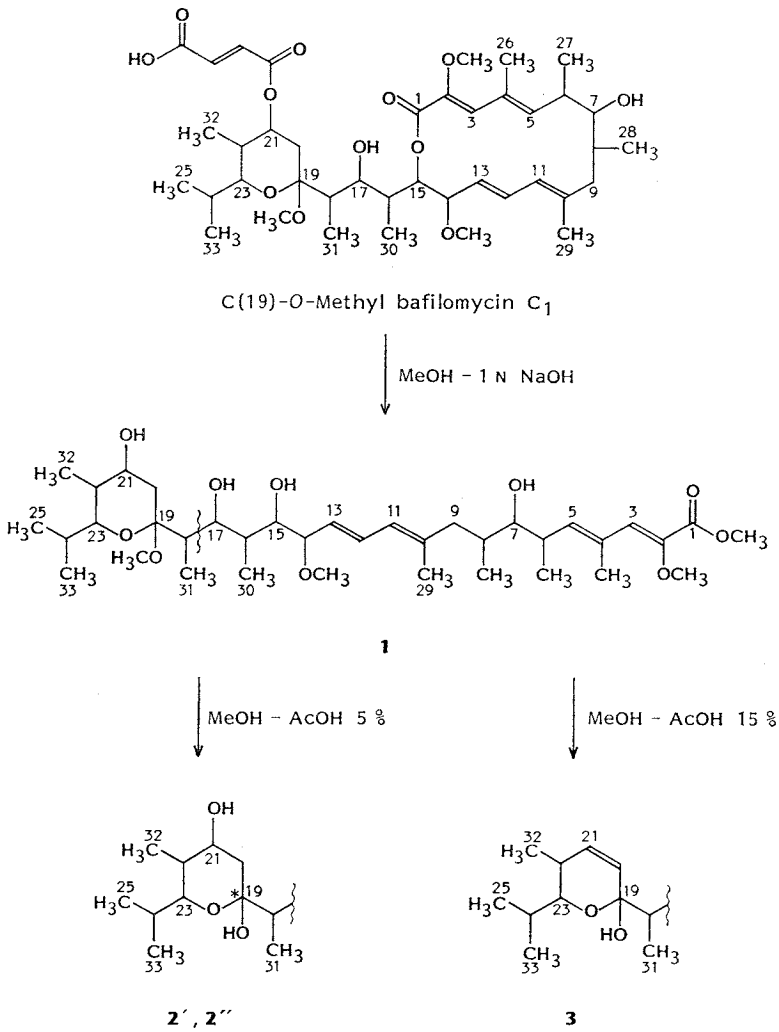
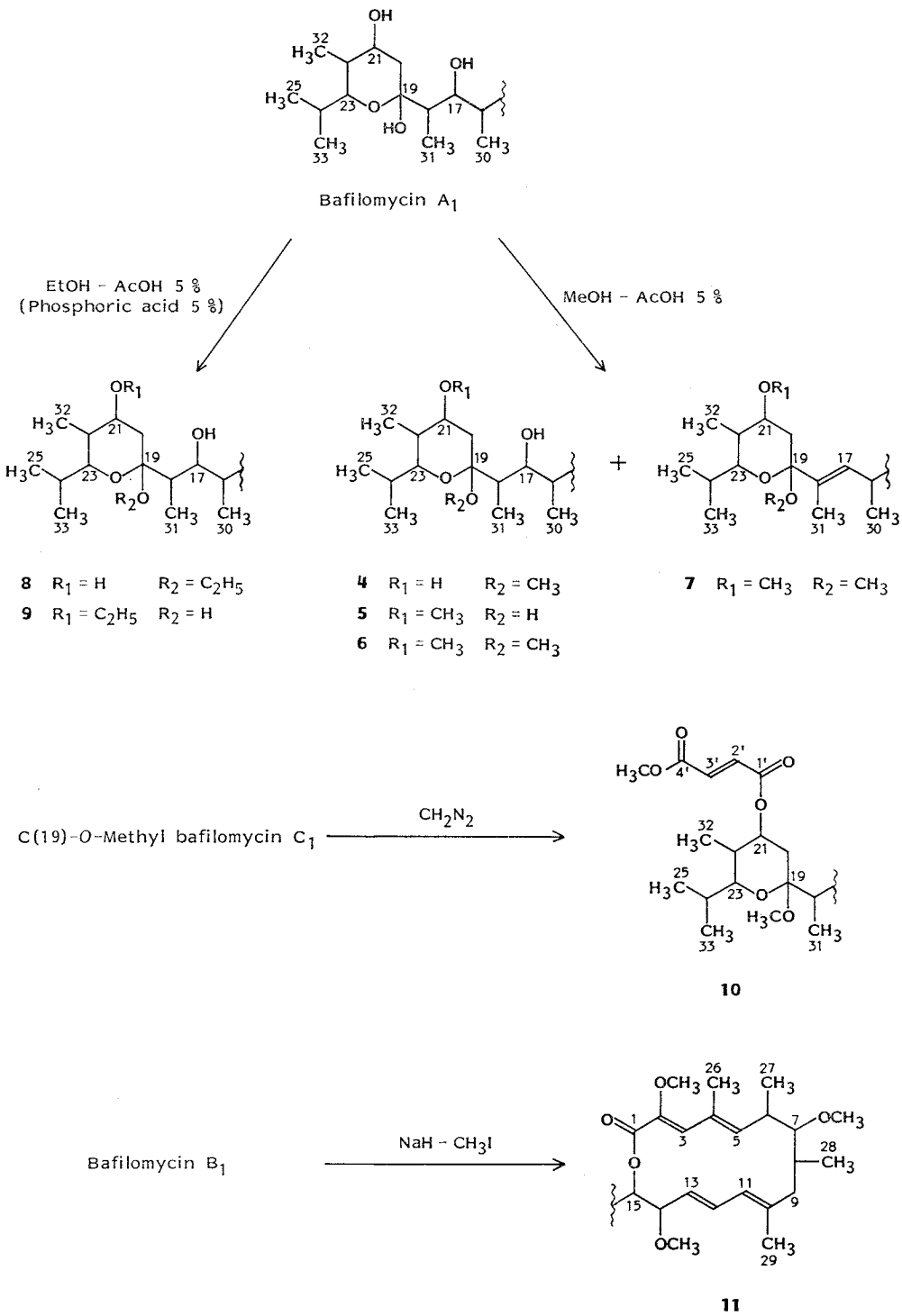


Fig. 3. *O*-Alkylation of bafilomycins A_1, B_1 and C_1.



O-Alkylation

Treatment of bafilomycin A_1 in methanol - acetic acid or ethanol - acetic acid (or phosphoric acid) led to the C(19)-*O*-alkyl bafilomycins (ketals) (**4**[1] and **8**) and the C(21)-*O*-alkyl bafilomycins (**5**, **6** and **9**) (Fig. 3). During the preparation of **6**, bafilomycin W (**7**) which is the C(17)/C(18) dehydrated form of **6** was formed too. C(21)-*O*-Methyl bafilomycin A_1 is most likely identical with L-681,110 B_1 isolated from *Streptomyces* sp. MA-5038 by HENSENS *et al.*[6]. Reaction of C(19)-*O*-methyl bafilomycin C_1 with diazomethane in methanolic solution led to the corresponding methyl ester (**10**).

Fig. 4. *O*-Acylation of bafilomycin A_1 and C(19)-*O*-methyl bafilomycin A_1.
a) Citraconic anhydride - DBU. b) *cis*-Cyclohexane-1,2-dicarbonic anhydride - DBU. c) Carbonylic acid chlorides - base. d) Maleic anhydride - DBU.

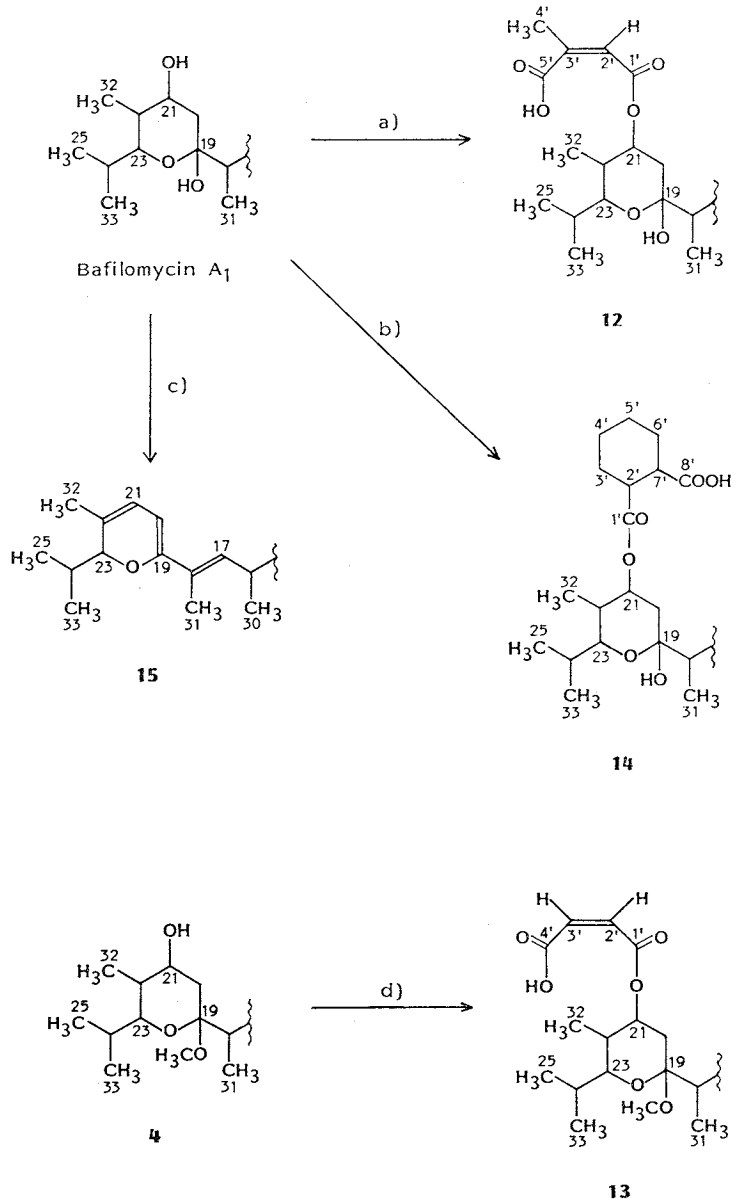
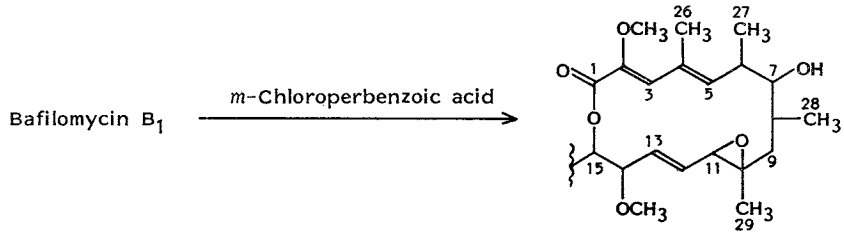


Fig. 5. Epoxidation of bafilomycin B_1.



16

With methyl iodide in the presence of sodium hydride bafilomycin B_1 is transformed into the C(7)-*O*-methyl derivative (**11**).

O-Acylation

For preparation of C(21)-*O*-acylated bafilomycins, bafilomycin A_1 and **4** were treated with a number of carboxylic acid chlorides and anhydrides. The reactions were carried out in various anhydrous solvents and in the presence of an excess of base (pyridine, 2,6-di-*tert*-butylpyridine, 1,8-diazabicyclo[5,4,0]undecen-7-en (DBU), *N*-methylmorpholine or dimethylaminopyridine) under mild conditions.

By reaction of bafilomycin A_1 or **4** with citraconic anhydride, maleic anhydride and cyclohexane-1,2-dicarbonic anhydride the C(21)-*O*-acyl bafilomycins (**12**, **13** and **14**) were obtained (Fig. 4).

Reaction of bafilomycin A_1 and **4** with different carboxylic acid chlorides (*e.g.* bromoacetyl chloride, *p*-toluenesulfonyl chloride, benzoyl chloride, isovaleryl chloride, methylmalonyl chloride, hexane-1,6-dicarbonyl chloride) under the above mentioned reaction conditions, led to a mixture of products. In all cases the major component formed was **15** which was isolated and shown to be the 3-fold dehydrated form of bafilomycin A_1 (Fig. 4). The other products formed were too unstable to be isolated.

Epoxidation

Bafilomycin B_1 was transformed by reaction with *m*-chloroperbenzoic acid (Fig. 5) into the C(10)/C(11) oxiran (**16**). The reaction conditions were found to be of low regio-selectivity since other oxirans of bafilomycin B_1 were detected by mass spectroscopy in the crude reaction product.

Experimental

The reactions were monitored by TLC and HPLC.

Analytical thin-layer chromatography was carried out on Silica gel plates ($60F_{254}$, Merck) developed with a mixture of CH_2Cl_2 - MeOH (9 : 1, solvent A) or CH_2Cl_2 - MeOH (97 : 3, solvent B) and the spots detected by UV light as 254 nm and by spraying with 18% methanolic HCl (pink color reaction).

Analytical HPLC was performed on reversed phase columns (Shandon ODS Hypersil 5 μm, 4.6×125 mm) using CH_3CN - MeOH - 0.017 M aq tetrabutylammonium phosphate (240 : 225 : 145) as a solvent system, (flow rate 1 ~ 3 ml/minute, UV detection at 254 nm).

Purification of Compounds

Preparative HPLC was carried out on reversed phase columns (Merck LiChrosorb RP 18 10 μm, 32×250 mm) (method I) and (Dynamax C18 7 μm, 21.4×250 mm) (method II) using various stepwise gradients of MeOH - H_2O from (70 : 30) to MeOH - H_2O (90 : 10) at pH 8.

Column chromatography on silica gel was carried out on Lobar columns (Merck, size A and B) (method III).

Preparative TLC was carried out on Silica gel plates ($60F_{254}$, $20\times20\times0.2$ cm, Merck) (method IV).

UV spectra were recorded on a Perkin-Elmer Lambda 5 and on a Kontron Uvicon 860. NMR spectra were measured with a Bruker AM 300 and a Bruker WM 400. Fast atom bombardment mass spectra (FAB-MS) were recorded with a Kratos MS 80 and negative chemical ionization mass spectra (NCI-MS) with a Finnigan MAT 8230.

The purity of the compounds described was tested by HPLC and TLC and was >95% in all cases.

Bafilomycin V_1 (1)

To a solution of C(19)-*O*-methyl bafilomycin C_1 (370 mg) in MeOH (40 ml) 2 ml 1 N NaOH were added dropwise. The reaction mixture was stirred for 15 minutes at 60°C, subsequently cooled in an ice bath to 5°C and neutralized with acetic acid. The solution was evaporated to dryness. The crude product was purified on reversed phase HPLC (method I) using MeOH - H_2O (80 : 20) as eluant. After lyophilization from a benzene solution **1** (180 mg, white powder) was obtained.

^{1}H NMR ($CDCl_3$) δ 3.88 (2H, H-15, H-17), 3.8 (C(1)-OCH_3), 3.61 (H-14), 2.03 (H-16); ^{13}C NMR ($CDCl_3$) δ 165.4 (C-1), 84.2 (C-14), 71.3 (C-15), 42.0 (C(1)-OCH_3); NCI-MS *m/z* 668 (M^-, $C_{37}H_{64}O_{10}$), 636 $(M-MeOH)^-$, 604 $(M-2MeOH)^-$, 586 $(M-2MeOH-H_2O)^-$; UV λ_{max}^{MeOH} nm (ε) 243 (28,200), 274 (19,600); TLC (solvent A) Rf 0.61.

Bafilomycin V_2 (2′+2″)

A solution of **1** (90 mg) in MeOH - AcOH - H_2O (90 : 5 : 5, 30 ml) was stirred 30 minutes at 50°C. The reaction mixture was neutralized with $NaHCO_3$, filtered and evaporated to dryness. The purification by reversed phase chromatography (method I) gave a mixture of **2′** and **2″** (62 mg). Chromatography on silica gel (method III) with $CHCl_3$ - MeOH (9 : 1) as eluant yielded after lyophilization from a benzene solution **2′** (36 mg, white powder) and **2″** (21 mg, white powder).

2′: ^{1}H NMR ($CDCl_3$) δ 5.20 (C(19)-OH), 4.70 (C(17)-OH), 3.98 (H-15), 3.79 (H-17), 3.77 (C(1)-OCH_3), 3.33 (H-21), 2.18 (H-20_{eq}), 1.72 (H-20_{ax}); ^{13}C NMR ($CDCl_3$) δ 101.9 (C-19), 72.2 (C-21), 72.0 (C-17), 71.8 (C-15), 41.5 (C-18), 35.7 (C-20); NCI-MS (M^-, $C_{36}H_{62}O_{10}$) *m/z* 636 $(M-H_2O)^-$, dominant signals 604, 490, 420, 390; UV λ_{max}^{MeOH} nm (ε) 243 (40,600), 273 (28,000); TLC (solvent A) Rf 0.91.

2″: ^{1}H NMR ($CDCl_3$) δ 3.78 (C(1)-OCH_3), 3.55 (H-17), 3.32 (H-21), 3.25 (H-15), 2.04 (H-20_{eq}), 1.3 (H-20_{ax}); ^{13}C NMR ($CDCl_3$) δ 101.2 (C-19), 69.5 (C-21), 75.3 (C-15), 73.6 (C-17), 41.3 (C-18), 32.4 (C-20); NCI-MS (M^-, $C_{36}H_{62}O_{10}$) *m/z* 636 $(M-H_2O)^-$, dominant signals 604, 420, 402; UV λ_{max}^{MeOH} nm (ε) 208 (22,300), 242 (35,100), 274 (23,750); TLC (solvent A) Rf 0.84.

Bafilomycin V_3 (3)

This compound was prepared by the procedure described for **2′** and **2″**, treating **1** (62 mg) with MeOH - AcOH - H_2O (80 : 15 : 5). After a reaction time of 6 hours **3** (28 mg, white powder) was obtained.

^{1}H NMR ($CDCl_3$) δ 5.80 (H-21), 5.70 (H-20), 3.78 (C(1)-OCH_3), 3.68 (H-17), 3.45 (H-15), 3.32 (H-23); ^{13}C NMR ($CDCl_3$) δ 136.7 (C-20), 123.0 (C-21), 97.8 (C-19), 52.0 (C(1)-OCH_3), 40.8 (C-22); NCI-MS *m/z* 636 $(M-C_{36}H_{60}O_9)^-$, dominant signals 568, 402, 390, 370, 330; UV λ_{max}^{MeOH} nm (ε) 206 (11,840), 242 (32,500), 275 (23,040); TLC (solvent A) Rf 0.83.

(C(19)-*O*-Methyl-, C(21)-*O*-Methyl- and C(19),C(21)-*O*-Methyl-)bafilomycin A_1 (4, 5 and 6) and Bafilomycin W (7)

A solution of bafilomycin A_1 (500 mg) in a mixture of MeOH - AcOH (95 : 5, 50 ml) was stirred 45 minutes at 60°C. The reaction mixture was cooled in an ice bath to 5°C, neutralized with $NaHCO_3$, filtered and evaporated to dryness. The purification (method II) with a stepwise gradient of MeOH - H_2O from (70 : 30) to (90 : 10) yielded, after lyophilization from a benzene solution **4** (45 mg, white powder), **5** (32 mg, white powder), **6** (92 mg, white powder) and **7** (28 mg, white powder).

4 was characterized by comparison of retention time (HPLC) with the reference compound[1].

5: ^{1}H NMR ($CDCl_3$) δ 5.48 (C(19)-OH), 3.32 (C(21)-OCH_3), 3.19 (H-21); ^{13}C NMR ($CDCl_3$)

δ 98.9 (C-19), 79.8 (C-21), 56.3 (C(21)-OCH_3), 41.2 (C-20); NCI-MS *m/z* 636 (M^-, $C_{36}H_{60}O_9$), dominant signals 618, 604, 586, 568, 420, 388; UV λ_{max}^{MeOH} nm (ε) 246 (36,000), 285 (16,000); TLC (solvent A) Rf 0.79.

6: ^1H NMR ($CDCl_3$) δ 3.81 (C(17)-OH), 3.45 (H-17), 3.08 (H-21), 3.00 (C(19)-OCH_3); ^{13}C NMR ($CDCl_3$) δ 103.2 (C-19), 56.3 (C(21)-OCH_3), 46.4 (C(19)-OCH_3); NCI-MS *m/z* 650 (M^-, $C_{37}H_{62}O_9$), dominant signals 618, 586, 568, 420, 388, 356; UV λ_{max}^{MeOH} nm (ε) 246 (33,100), 284 (14,250); TLC (solvent B) Rf 0.69.

7: ^1H NMR ($CDCl_3$) δ 5.68 (H-17), 3.32 (C(21)-OCH_3), 2.95 (C(19)-OCH_3), 1.65 (CH_3-31); ^{13}C NMR ($CDCl_3$) δ 131.6 (C-18), 125.1 (C-17), 56.2 (C(21)-OCH_3), 48.3 (C(19)-OCH_3); NCI-MS *m/z* 632 (M^-, $C_{37}H_{60}O_8$), dominant signals 600, 568, 420; UV λ_{max}^{MeOH} nm (ε) 245 (26,600), 278 (10,200); TLC (solvent B) Rf 0.73.

C(19)-*O*-Ethyl Bafilomycin A_1 (**8**)

A solution of bafilomycin A_1 (200 mg) in a mixture of EtOH - AcOH (5% in vol, 15 ml) was stirred 10 minutes at 60°C. The reaction mixture was cooled in an ice bath to 5°C, neutralized with $NaHCO_3$, filtered off, and evaporated to dryness. After chromatography on reversed phase HPLC (method II) using MeOH - H_2O (83 : 17) and lyophilization from a benzene solution **8** (46 mg, white powder) was obtained.

^1H NMR ($CDCl_3$) δ 3.76 (C(17)-OH), 3.63 (H-21), 3.32 (C(19)-OCH_2), 1.07 (C(19)-OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 103.0 (C-19), 53.6 (C(19)-OCH_2), 15.3 (C(19)-OCH_2CH_3); NCI-MS *m/z* 650 (M^-, $C_{37}H_{62}O_9$), dominant signals 618, 604, 572, 420, 388; UV λ_{max}^{MeOH} nm (ε) 246 (26,300), 284 (11,700); TLC (solvent A) Rf 0.71.

C(21)-*O*-Ethyl Bafilomycin A_1 (**9**)

A solution of bafilomycin A_1 (150 mg) in EtOH - phosphoric acid (5% in vol, 15 ml) was stirred 1 hour at room temperature. The purification was carried out as described for **8**. After lyophilization from a benzene solution **9** (62 mg white powder) was obtained.

^1H NMR ($CDCl_3$) δ 5.48 (C(19)-OH), 3.39 (H-21), 3.66 (C(21)-OCH_2), 1.18 (C(21)-OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 99.0 (C-19), 78.2 (C-21), 64.3 (C(21)-OCH_2), 15.7 (C(21)-OCH_2CH_3); NCI-MS *m/z* 650 (M^-, $C_{37}H_{62}O_9$), dominant signals 632, 618, 600, 568, 420, 388; UV λ_{max}^{MeOH} nm (ε) 247 (32,400), 287 (13,900); TLC (solvent A) Rf 0.81.

C(4')-*O*-Methyl Bafilomycin C_1 (**10**)

A solution of C(19)-*O*-methyl bafilomycin C_1 (511 mg) in MeOH was treated with diazomethane in diethyl ether. The reaction mixture was chromatographed (method III) on silica gel with trichloromethane as eluant. Yield of **10**: 80 mg (colorless amorphous powder).

^1H NMR ($CDCl_3$) δ 3.45 (C(19)-OCH_3), 3.70 (C(4')-OCH_3); ^{13}C NMR ($CDCl_3$) δ 168.0 (C-4'), 167.5 (C-1'), 134.6 (C-3'), 134.1 (C-2'), 98.2 (C-19), 51.7 (C(4')-OCH_3), 47.0 (C(19)-OCH_3); FAB-MS (M^+, $C_{41}H_{64}O_{12}$) *m/z* 689 $(M-C_2H_3O_2)^+$, 659 $(M-C_2H_3O_2-CH_2O)^+$, 618 $(M-C_5H_5O_4)^+$; UV λ_{max}^{MeOH} nm (ε) 210 (19,100), 247 (36,000), 282 (17,200); TLC (solvent A) Rf 0.67.

C(7)-*O*-Methyl Bafilomycin B_1 (**11**)

Sodium hydride (2 g) was stirred 2 hours in DMSO (16 ml) at 65°C. Bafilomycin B_1 (500 mg) in 3 ml DMSO was added and stirred 30 minutes at room temperature. After dropwise addition of 14 ml methyl iodide, the solution was stirred for 15 hours in the dark at room temperature. The reaction mixture was poured into 100 ml H_2O and extracted three times with 50 ml dichloromethane. The separated organic layer was washed with H_2O and $Na_2S_2O_3$ (3%), dried over Na_2SO_4 and evaporated to dryness. The material was chromatographed on silica gel (method III) with CH_2Cl_2 - MeOH (98 : 2) as eluant. Yield of **11**: 70 mg (yellow microcrystalline powder).

^1H NMR ($CDCl_3$) δ 3.95 (C(7)-OCH_3); ^{13}C NMR ($CDCl_3$) δ 80.7 (C-7), 55.8 (C(7)-OCH_3); FAB-MS (M^+, $C_{45}H_{67}NO_{13}$) *m/z* 852 $(M+Na)^+$, 868 $(M+K)^+$, 619 $(C_{36}H_{59}O_8)^+$, 600 $(C_{36}H_{56}O_7)^+$, 557 $(C_{33}H_{49}O_7)^+$; UV λ_{max}^{MeOH} nm (ε) 248 (36,800), 283 (14,000); TLC (solvent A) Rf 0.52.

C(21)-*O*-Citraconyl Bafilomycin A_1 (**12**)

To a solution of bafilomycin A_1 (310 mg, 0.5 mmol) in anhydrous dichloromethane (10 ml), DBU

(156 μl, 1 mmol) and a solution of citraconic anhydride (90 μl, 1 mmol) in dichloromethane (1 ml) was added dropwise and under stirring at −10°C. The mixture was stirred 30 minutes at −10°C, 2 hours at 0°C and 12 hours at room temperature. The solvent was evaporated *in vacuo* and the red oily residue purified by column chromatography on reversed phase HPLC (method II) using MeOH - H_2O (80 : 20). After lyophilization from a benzene solution **12** (57 mg, white powder) was obtained.

^1H NMR (CD_3OD) δ 6.03 (H-2′), 5.00 (H-21), 1.94 (CH_3-4′); ^{13}C NMR (CD_3OD) δ 174.4 (C-5′), 170.8 (C-1′), 136.2 (C-3′), 132.1 (C-2′), 75.9 (C-21); FAB-MS (M^+, $C_{40}H_{62}O_{12}$) *m/z* 779 $(M+2Na-H)^+$, 757 $(M+Na)^+$; UV λ_{max}^{MeOH} nm (ε) 245 (34,600), 285 (14,400); TLC (solvent A) Rf 0.24.

C(19)-*O*-Methyl-C(21)-*O*-maleinyl Bafilomycin A_1 (**13**)

To a solution of **4** (155 mg, 0.25 mmol) in anhydrous dichloromethane (10 ml), DBU (78 μl, 0.5 mmol) and a solution of maleic anhydride (49 mg, 0.5 mmol) in dichloromethane (3 ml) were added dropwise under stirring at −10°C. The mixture was stirred 30 minutes at −10°C and for 3 hours at room temperature. By the same procedure as described in the preparation of **12**, **13** (38 mg, white powder) was obtained.

^1H NMR (CD_3OD) δ 6.56 (H-2′), 5.72 (H-3′), 4.93 (H-21), 3.10 (C(19)-OCH_3); ^{13}C NMR (CD_3OD) δ 174.4 (C-4′), 167.0 (C-1′), 143.4 (C-2′), 118.9 (C-3′), 104.3 (C-19), 75.1 (C-21), 47.1 (C(19)-OCH_3); FAB-MS (M^+, $C_{40}H_{62}O_{12}$) *m/z* 773 $(M+K)^+$, 757 $(M+Na)^+$; UV λ_{max}^{MeOH} nm (ε) 245 (34,400), 283 (14,150); TLC (solvent A) Rf 0.16.

C(21)-*O*-*cis*-Cyclohexane-1,2-dicarbonic Acid Mono Ester of Bafilomycin A_1 (**14**)

To a solution of bafilomycin A_1 (350 mg, 0.5 mmol) in anhydrous pyridine (2 ml) *cis*-cyclohexane-1,2-dicarbonic anhydride (154 mg, 1 mmol) was added, followed by dropwise addition of a solution of DBU (0.156 ml) in pyridine (2 ml). After stirring 1 hour at −10°C, 1 hour at 4°C and 1 hour at room temperature, the solvent was evaporated *in vacuo*. The residue was dissolved in trichloromethane, washed 3 times with 0.5 N HCl and H_2O. The organic layer was dried over Na_2SO_4, concentrated *in vacuo*, and chromatographed on silica gel (method III) with a mixture of dichloromethane - hexane (7 : 3). Yield of **14**: 54 mg (colorless, microcrystalline).

^1H NMR (CD_3OD) δ 2.38 (H-2′), 2.44 (H-3′), 1.2～1.9 (8H, H-4′～H-7′); ^{13}C NMR (CD_3OD) δ 178.6 (C-8′), 172.9 (C-1′), 42.5 (C-3′), 42.0 (C-3′), 23.7～26.5 (4C, C-4′～C-7′); FAB-MS *m/z* 776 (M^+, $C_{43}H_{68}O_{12}$), 799 $(M+Na)^+$, 815 $(M+K)^+$; UV λ_{max}^{MeOH} nm (ε) 246 (36,500), 283 (16,000); TLC (solvent A) Rf 0.57.

Bafilomycin Z (**15**)

To a solution of bafilomycin A_1 (310 mg, 0.5 mmol) in anhydrous dichloromethane (20 ml), 2,6-di-*tert*-butylpyridine (204 mg, 1 mmol) was added, followed by dropwise addition of a solution of bromoacetylchloride (66 μl, 0.8 mmol) in THF (2 ml) at −20°C. The reaction mixture was stirred 2 hours at −10°C and 24 hours at room temperature. The solution was poured into ice water and extracted twice with 20 ml dichloromethane. The organic layer was washed twice with a saturated $NaHCO_3$ solution, twice with a saturated aqueous NaCl solution, dried over Na_2SO_4, and evaporated to dryness. Preparative TLC on five silica gel plates (method IV) with $CHCl_3$ - Me_2CO (98 : 2) as eluant yielded **14** (47 mg, white powder).

^1H NMR ($CDCl_3$) δ 6.02 (H-17), 5.75 (H-21), 5.28 (H-20), 1.79 (CH_3-31, CH_3-32); ^{13}C NMR ($CDCl_3$) δ 150.7 (C-19), 130.2 (C-18), 127.9 (C-22), 124.7 (C-17), 118.6 (C-21), 98.9 (C-20); NCI-MS *m/z* 568 (M^-, $C_{35}H_{50}O_6$); UV λ_{max}^{MeOH} nm (ε) 244 (16,800), 285 (9,800); TLC (solvent B) Rf 0.77.

Bafilomycin B_1-C(10)/C(11)-oxiran (**16**)

To a solution of bafilomycin B_1 (420 mg, 0.5 mmol) in trichloromethane (10 ml), 0.138 ml triethylamine was added. After dropwise addition of *m*-chloroperbenzoic acid (200 mg, 1 mmol) at −10°C, the mixture was stirred 1 hour at this temperature and an additional 2 hours at room temperature. After addition of sodium dithionite (200 mg), the mixture was stirred for 1 hour at room temperature, filtered and evaporated to dryness *in vacuo*. The residue was dissolved in trichloromethane (10 ml), washed three times with 1% aq $NaHCO_3$ solution (10 ml), dried over Na_2SO_4 and evaporated

to dryness. After purification on reversed phase HPLC (method I) with a gradient from H_2O - MeOH (9:1) to MeOH **16** (60 mg, yellow, microcrystalline) was obtained.

^1H NMR ($CDCl_3$) δ 1.35~1.45 (H-9), 3.15 (H-11), 6.02 (H-12); ^{13}C NMR ($CDCl_3$) δ 144.1 (C-12), 64.1 (C-10), 62.9 (C-11), 34.8 (C-9); FAB-MS *m/z* 831 (M^+, $C_{44}H_{65}NO_{14}$), 854 $(M+Na)^+$; UV λ_{max}^{MeOH} nm (ε) 247 (37,200), 284 (13,500); TLC (solvent A) Rf 0.44.

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