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AN UNPRECEDENTED RING EXPANSION IN THE MACROLIDE SERIES – SYNTHESIS OF *ISO*-BAFILOMYCIN A_1

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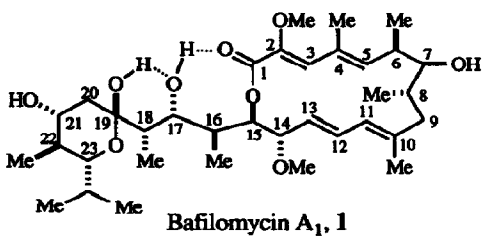
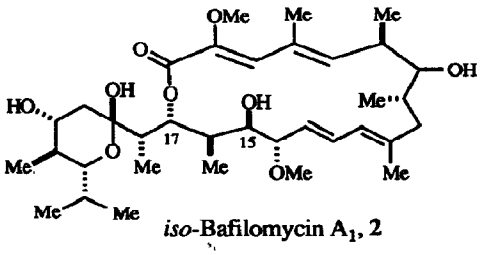
Abstract: When treated with a reagent prepared from equimolar quantities of methyllithium and copper iodide, 7,21-di-O-TMS bafilomycin A_2 **3** undergoes ring expansion to give the 18-membered lactone homolog **5** in nearly quantitative yield. Acid hydrolysis gives *iso*-bafilomycin A_1. Ring contraction to the original 16-membered lactone takes place in the presence of fluoride ion. A mechanistic rationale and X-ray crystallographic evidence are presented.

The hygrolide group of macrolide antibiotics comprises bafilomycin A_1 [1] and the hygrolidins[2,3] whose structures are characterized by an unusual 16-membered tetraenic lactone ring, containing a sugar-like appendage. The structure and absolute configuration of bafilomycin A_1 **1** was established by X-ray crystallographic analysis[4] and by NMR spectroscopy.[5]

Figure 1



Bafilomycin A_1, **1**



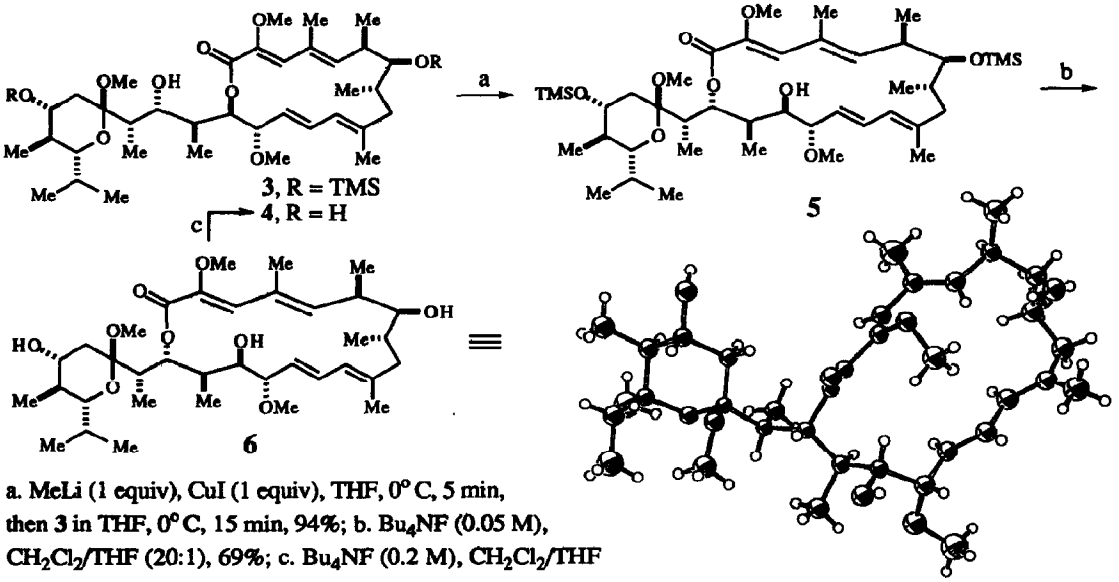
iso-Bafilomycin A_1, **2**

Bafilomycin A_1 and related analogs have been shown to inhibit the growth of Gram-positive bacteria[1,6] and fungi. More impressive is the selective enzyme inhibitory activity on membrane ATPases.[6,7] A unique H-bonding network involving the lactone carbonyl, the hemiacetal hydroxy group, and an intervening C_{17} hydroxy group in bafilomycin A_1 confers upon its structure a topological feature which may have important biological implications.

As part of a research program directed toward to the total synthesis[8,9] of bafilomycin A_1 and related macrolides, we investigated a number of chemical transformations on the natural product with the aim of probing the reactivity of various functional groups. We describe herein, an unexpected ring-expansion reaction during the treatment of a bafilomycin A_2 derivative with an organocopper reagent.

Addition of 7,21-di-O-trimethylsilyl bafilomycin A_2 **3**[10] to an organocopper reagent formed from equimolar quantities of methylithium and cuprous iodide in THF, led to a single product **5** in 94% isolated yield. Extensive ^1H and ^{13}C NMR (1D/2D) studies indicated the preservation of the general structure and functional features of the parent molecule with perceptible changes in the chemical shifts of methine protons associated with the C_{15}-C_{17} region. Desilylation under mild conditions using a dilute solution of Bu_4NF in CH_2Cl_2 (1 mL 1M THF solution of Bu_4NF in 20 mL CH_2Cl_2) led to a crystalline compound, mp 174-175°C (from CH_2Cl_2-hexane): $[\alpha]_D^{21}$ - 71° (c 0.24, CH_2Cl_2), whose structure was definitively confirmed as the 2-carbon ring expansion product from an X-ray analysis. We give the trivial name *iso*-bafilomycin A_2 **6** to this new 18-membered analog (Scheme 1).

Scheme 1



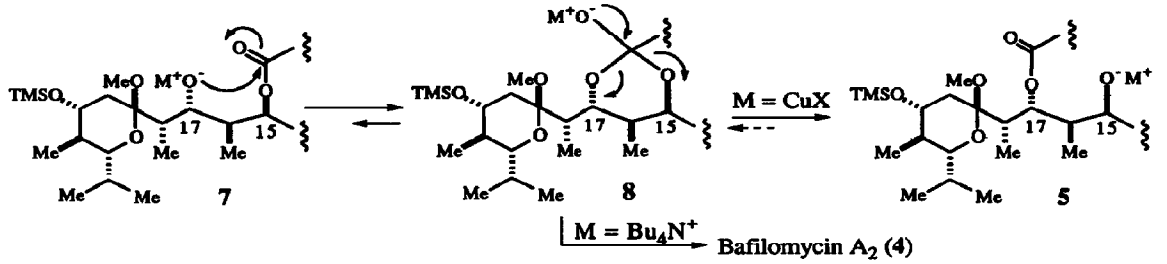
a. MeLi (1 equiv), CuI (1 equiv), THF, 0° C, 5 min, then **3** in THF, 0° C, 15 min, 94%; b. Bu_4NF (0.05 M), CH_2Cl_2/THF (20:1), 69%; c. Bu_4NF (0.2 M), CH_2Cl_2/THF

Treatment of **6** with 10% aq. citric acid -THF (1:1) at 25°C for 1hr gave *iso*-bafilomycin A_1, **2**, which was isolated as a chromatographically homogeneous syrup, $[\alpha]_D^{25}$ -50.5° (c 0.78, CH_2Cl_2)

A further surprising event occurred when the deprotection of the O-TMS groups in **5** was done in a solution of Bu_4NF in CH_2Cl_2 at a higher concentration (1-3 mL 1M THF solution of Bu_4NF in 5 mL CH_2Cl_2). In a slow but clean reaction (7 days, 50% conversion) *ring contraction* took place to give bafilomycin A_2 as confirmed by high field NMR, $[\alpha]_D$ and t.l.c. (Rf. 0.45 baf. A_2, 0.18 *iso* -baf. A_2 in hexane/EtOAc 1:1).

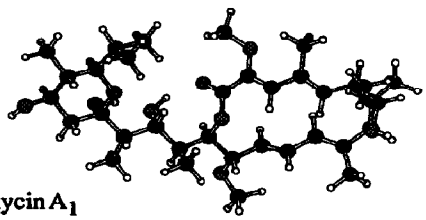
The ring expansion reaction can be rationalized on the basis of the initial formation of a C_{17} alkoxycopper species **7** which is suitably situated to undergo a potentially reversible rearrangement involving a copper I orthoacetate intermediate **8**. Evidently a kinetically controlled and presumably stereoelectronically allowed process leads to the ring expansion product **5** as the preponderant if not exclusive product. The behavior of **5** towards fluoride ion at different concentrations can be explained as follows: In dilute dichloromethane, the effective concentration of 15-alkoxy tetra-butylammonium salts is not high enough to allow reversion, hence the isolation of *iso*-bafilomycin A_2 **6**, as the major product. Presumably in a more concentrated solution of Bu_4NF, the ring-contraction takes place via the same orthoacetate with the tetrabutylammonium species as the cation (Scheme 2).

Scheme 2

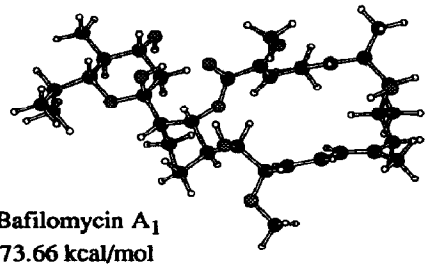


Intrigued by the above behavior toward the organocopper reagent, we investigated a variety of other organometallic reagents (e.g. MeMgBr) but without success. Thus, the basicity/nucleophilicity combination of the metallic copper species appears to be critical for the ring expansion. Undoubtedly, this phenomenon will also be encountered in related reactions under different circumstances depending on the reagent used.

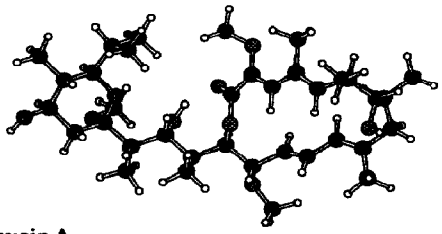
In an effort to assess the relative conformational energy differences between bafilomycins A_1, A_2 and the corresponding *iso*-derivatives, we performed energy minimization calculations using the x-ray crystallographic parameters available from bafilomycin A_1,[1] and those from *iso*-bafilomycin A_2, as a basis (Figure 2).



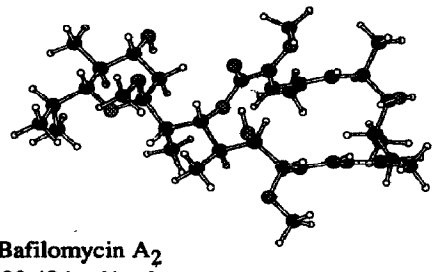
Bafilomycin A_1
E = 57.36 kcal/mol



iso–Bafilomycin A_1
E = 73.66 kcal/mol



Bafilomycin A_2
E =74.71 kcal/mol



iso–Bafilomycin A_2
E = 80.49 kcal/mol

Using the MM3* module of the MACROMODEL program,[11] the relative energies of the above-stated molecules were calculated and the results are shown in Figure 2. Both bafilomycin A_1 and A_2 are significantly more stable than their *iso*-analogs. Considerable distortion can be found in the C_1-C_4 region, as well as in the orientation of the pseudosugar part in the *iso*-series relative to the parent structures.[12]

In conclusion, we have demonstrated the existence of an unusual and unprecedented[13] ring-expansion reaction from a 16- to an 18-membered macrolide ring in the hygrolide group of macrocyclic lactone antibiotics.[14]

The reversibility of this reaction under specific reaction conditions has also been shown, and a plausible mechanism is presented. Further studies to probe the generality of the unusual reactivity of macrolides in this series, will be communicated in due course.[15]

Acknowledgments

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9. For the synthesis of the C_{13}-C_{25} segment of bafilomycin A_1, see Roush, W.R.; Bannister, T.T. *Tetrahedron Lett.*, **1992**, *33*, 3587; Roush, W.R.; Bannister, T.D.; Wendt, M.D. *Tetrahedron Lett.*, **1993**, *34*, 8387.
10. Prepared from bafilomycin A_1, using a. MeOH, PPTS, 1h, 75% (syrup); b. TMSCl, Et_3N, DMAP, CH_2Cl_2, 24h, 80% (syrup).
11. Energy calculations were done using the MM3* force field in the MacroModel program version 3.5 (W.C. Still, Columbia University).
12. The minimized structures of bafilomycin A_2 and *iso*-bafilomycin A_1 were created by replacement of the C-19 substituent of the corresponding X-ray structures 1 and 6 with methoxy and hydroxy respectively. The actual orientation of the pseudosugar ring, hence the energies involved may be somewhat different than those depicted in Figure 2. Monte Carlo calculations led to energy values similar to MM3*.
13. For an authoritative treatise on ring expansion reactions, see Hesse, M. in "Ring Enlargement in Organic Chemistry", VCH Publishers, Weinheim, Germany, 1991.
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15. New compounds were adequately characterized by spectroscopic and microanalytical methods.

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