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A REMARKABLY FACILE AND STEREOCHEMICALLY CONTROLLED FRAGMENTATION REACTION IN THE HYGROLIDE GROUP OF MACROLIDE ANTIBIOTICS

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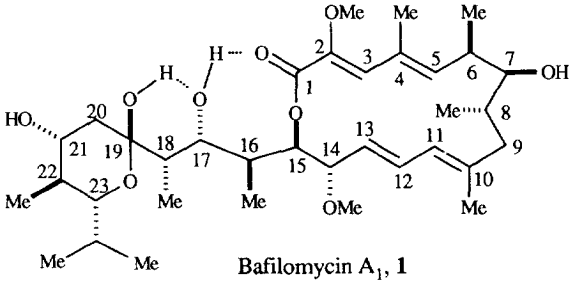
Abstract: Treatment of bafilomycin A_1 and isobafilomycin A_1 with triphenylphosphine and diethylazodicarboxylate under Mitsunobu conditions led to a fragmentation of the sugar-like ring to give the corresponding olefinic ester. The structure of the product from bafilomycin A_1 was confirmed by single crystal X-ray analysis and by ^1H NMR. Copyright © 1996 Elsevier Science Ltd

The bafilomycin group of 16-membered tetraenic macrolide antibiotics[1] represents a class of unusual macrocyclic structures in which strategically situated hydroxy groups are engaged in H-bonding as seen for bafilomycin A_1, **1** (Figure 1). This structural feature may play an important role in their fascinating and specific inhibitory activity on V-type ATPases.[2] Their interesting conformational features in the solid state and in solution have been highlighted by X-ray crystallographic[3] and detailed NMR[4] analyses on bafilomycin A_1. These studies have further revealed that the sugar-like subunit with its hydrophobic 2-propyl side-chain occupies a particular space vis-a-vis the macrolide ring.

Figure 1



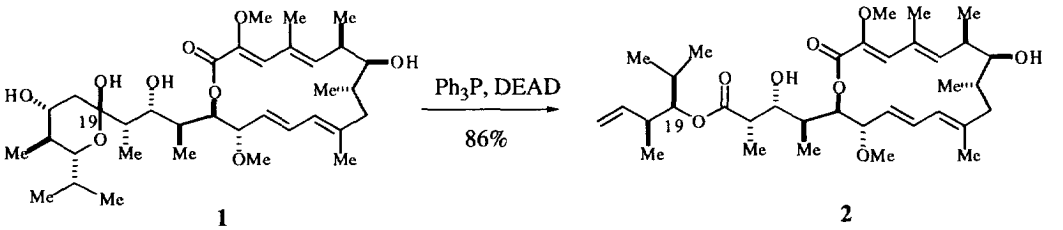
Bafilomycin A_1, **1**

The specificity of inhibition toward V-type ATPases, and recent reports[2a, 5] of an even greater inhibitory effect by concanamycin A, an 18-membered macrolide related to the same family, has instigated much interest in structure-activity relationships in this series. However, it has been reported that the isolation of bafilomycin A_1 is somewhat tedious, and that the purified antibiotic is rather unstable to mild acid.[6] The search and discovery of bafilomycin A_1-type structures via synthesis or degradation with improved stability in acidic media, while maintaining acceptable levels of biological activity is therefore a worthwhile research endeavor.

In a previous Letter,[7] we reported on the unprecedented ring-enlargement reaction of bafilomycin A_2 the methyl glycoside of A_1, to the 18-membered analog, isobafilomycin A_2. In this Letter we report on a remarkably facile and stereochemically controlled fragmentation of bafilomycin A_1, which was discovered while attempting various S_N2-type nucleophilic displacement reactions at the available hydroxyl group sites.

Thus, treatment of bafilomycin A_1 with triphenylphosphine and diethylazodicarboxylate in a mixture of ether and toluene, (25°C, 4 h) under the general conditions of the Mitsunobu reaction[8] led cleanly to a new product, which clearly lacked the intact pseudo-sugar ring as evidenced by ^1H and ^{13}C NMR. The crystalline product, mp 137-138°C; $[\alpha]_D^{25}$ -33.0° (c 1.28, $CHCl_3$) was subjected to X-ray structure analysis which revealed its identity as being the fragmentation product **2** (Scheme 1).

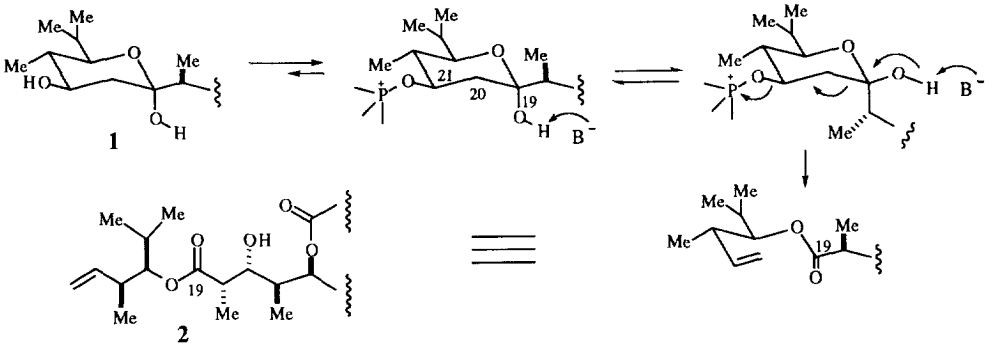
Scheme 1



1 **2**

This unusual fragmentation can be visualized as occurring via a base-catalyzed elimination of an alkoxy triphenylphosphonium group (as triphenylphosphine oxide) (Scheme 2). The antiperiplanar alignment of the C_{19}-C_{20} bond with the C_{21} oxygen bond is undoubtedly an inherent feature of this facile fragmentation. Whether there is prior partial anomerization to an equatorially disposed C_{19} hydroxy group, which may present a better alignment for bond breaking is not known.

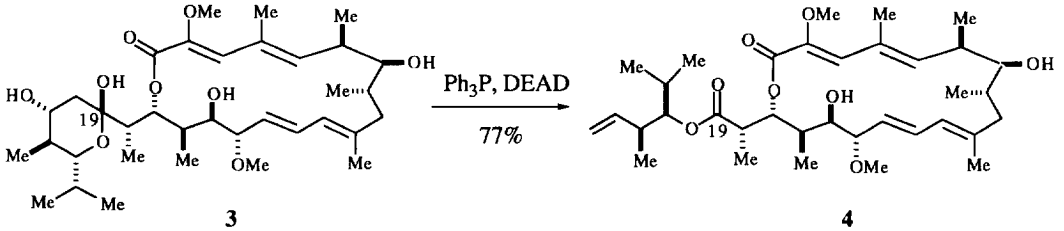
Scheme 2



1 **2**

An identical fragmentation occurred when isobafilomycin A_1, **3**, obtained by acidic treatment of isobafilomycin A_2,[7] was allowed to react with triphenylphosphine and diethyldiazocarboxylate as described above. (Scheme 3). The structure of the corresponding product **4**, $[\alpha]_D^{25}$ -49.5° (c 0.45, CH_2Cl_2) was confirmed by ^1H and ^{13}C NMR studies and by comparison with spectroscopic data obtained on **2**.

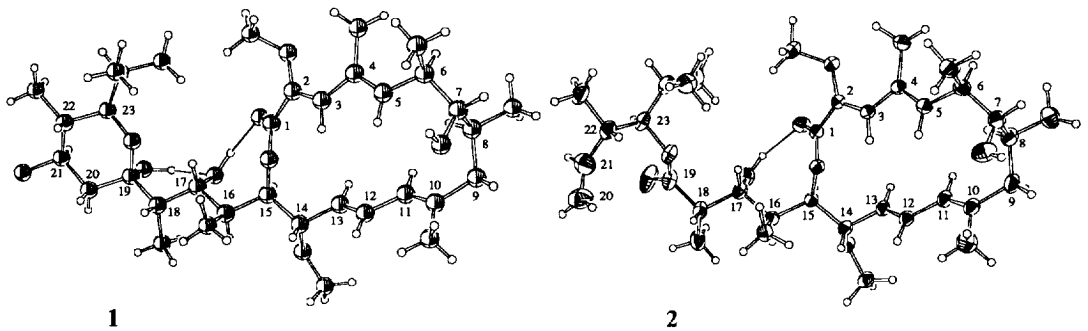
Scheme 3



3 **4**

Examination of the 3-dimensional X-ray structure of the fragmentation product **2** and comparison with that of bafilomycin A_1[3] reveals a remarkable degree of convergence of the carbon framework originally consisting of the sugar-like ring as shown in Figure 2. The s-*cis* conformation of the ester group and the presence of an intramolecular H-bond between C_1, carbonyl oxygen and the C_{17}-OH are noteworthy. The overall conformational resemblance between bafilomycin A_1 and **2** was also confirmed by ^1H NMR studies.

Figure 2



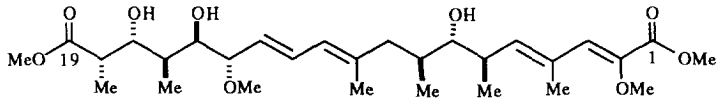
1 **2**

Thus, in addition to the expected convergence and quasi superposition of the macrolide carbon framework, in **1** and **2**, the acyclic portion C_{16}-C_{18} and the pendant ester segment comprising the 2-propyl and terminal vinyl groups adopt a conformation which approximates the position of atoms in the original pseudo-sugar (Figure 2). To be noted in particular is the coincidence of the 2-propyl groups in **1** and **2** respectively, where a hydrophobic interaction appears to be satisfied by proximity to the C_2 methoxy group.

Contrary to bafilomycin A_1, which is quite sensitive to acid and base, compound **2** was found to be unchanged in the presence of strong acids (1-3N HCl) and strong base (1N KOH) at room temperature! To what extent this stability is the consequence of a prevalent solution conformation in which the carbonyl group of the ester is shielded by two hydrophobic alkyl side-chains is not easy to assess.

With stronger aqueous base, it is the lactone ring that is hydrolyzed first to give the diester upon esterification. The use of methanolic KOH finally results in the formation of the diester corresponding to C_1-C_{19}.

Scheme 4



Although Grob-type fragmentations have many prevalent examples,[9] to the best of our knowledge, there are no precedents involving reactions that are triggered by a hemiacetal hydroxy group under Mitsunobu conditions.[10] It is possible that the observed fragmentation can also be induced in several other related types of pseudo-sugar rings where the prerequisite stereoelectronic and nucleofugal requirements are met. Examples are presently under investigation and will be reported in due course.[11]

Acknowledgments

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10. For related examples, see Hesse, M. "Ring Enlargement in Organic Chemistry", VCH Publishers, Weinheim 1991, Chapter 8.
11. All new compounds were adequately characterized by analytical and spectroscopic methods. Melting points are uncorrected.

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