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Synthetic Studies of 18-Membered Anti-Tumor Macrolide, Tedanolide. Computer-Aided Conformational Design of a Seco-Acid Derivative for Efficient Macrolactonization[1]

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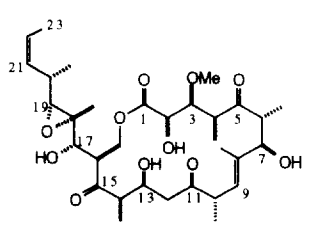
Abstract: *Computer-aided conformational analyses are successfully applied to the synthesis of a key intermediary 18-membered lactone of tedanolide (1). The design of a seco-acid derivative based on computation in order to achieve its efficient macro-lactonization is described.*

For the past decade, the search for biologically active marine natural products has been one of the most stimulating fields in natural product chemistry, and a large number of complex molecules has been found.

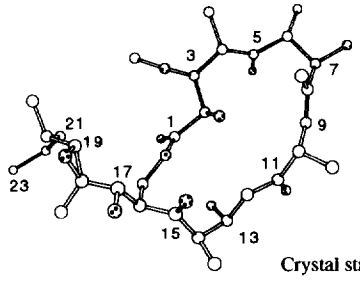
Tedanolide (**1**), an anti-tumor macrolide, was isolated from a Caribbean sponge *Tedania igunis* in 1984,[3] and its structure, which was revealed by X-ray analysis, is quite unusual: **1** has four labile aldol units, a side chain containing an α-epoxy alcohol, and an 18-membered lactone constructed with C1-carbonyl and C16-*primary (not the usual secondary)* hydroxy groups and for this reason, synthesis seemed to be difficult.

During the course of our synthetic studies of macrolides, we have accomplished a very efficient macrolactonization[4] and some stereoselective transformations on the macrolactone ring[5] on the basis of conformational analyses by MM calculation, and this methodology is now extended to our synthetic work on **1**.

In this paper, we report the design and computer-aided conformational analysis of a seco-acid derivative in order to achieve its efficient macrolactonization, the most crucial step in the total synthesis of **1**.



Tedanolide (**1**)

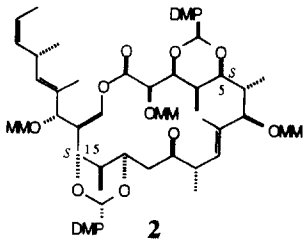


Crystal structure of **1**

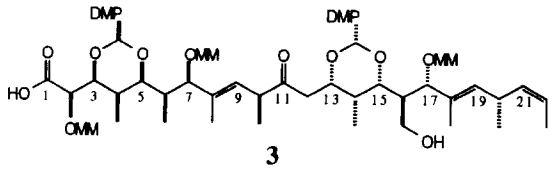
Figure 1

In macrolide synthesis, it is extremely important to design a seco-acid derivative suitable for macrolactonization, that is, the seco-acid should be designed so that its conformation is as close as possible to that of the corresponding macrolactone.[4, 6] The aldol structures of **1** are all arranged not antiperiplaner so as to avoid decomposition or dehydration, and two pairs of the carbonyl groups (C1-C11, C5-C15) are situated opposite to each other to maintain stability of the 18-membered lactone skeleton (Figure 1). However, in the course of the synthesis of **1**, such stable conformations cannot be expected in the flexible acyclic intermediates before

macrolactonization. Therefore, the aldol groups should be replaced by protected diol groups, which can be oxidized selectively to form the aldols after formation of the intermediary 18-membered lactone, whose conformation is also required to be very close to that of **1**.



DMP: 3,4-dimethoxyphenyl



MM: methoxymethyl

Figure 2

After careful consideration with the aid of molecular models, we designed **2** and **3** as the most promising intermediary lactone and the corresponding seco-acid, respectively, in which the C5 and C15 carbonyl groups are reduced to *S*-hydroxy groups[7] and protected as two acetals. First, we decided to leave the C11 carbonyl group facing the C1 ester group unchanged because conversion of the C11 carbon from trigonal to tetrahedral may cause a great conformational change in the 18-membered lactone. However, the C5 and C15 carbonyl groups cannot but be transformed into protected alcohols. The local conformation of the C3-C7 portion of **1** is shown as A in Figure 3. When the C5 carbonyl group is reduced to the *S*-alcohol,[7] two conformations, favorable B and unfavorable C, being controlled by minimization of 1,3-*syn*-pentane interaction,[8] are predictable. The B conformation can be fixed by the formation of the 6-membered acetal (D) involving the C3 and C5 hydroxy groups. Similarly, the C13-C17 portion (E) can be replaced by H. The C7-C10 portion should be naturally aligned so as to avoid allylic strains.[8] The least strained global conformation of **2** was, as a result, expected to be similar to that of **1**.

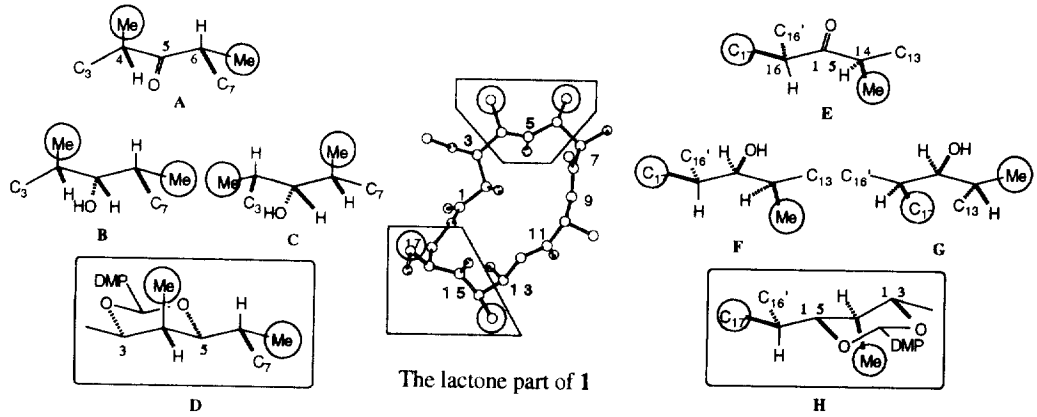
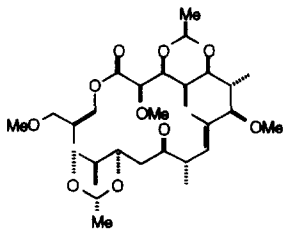


Figure 3

This prediction was supported by the MM2-CONFLEX3 calculation[9] of **4** (a model for the lactone portion of **2**), in which both acetals are directed toward the outside of the lactone ring, and the axial methyl groups at C4 and C14 restrict the conformational mobility of the C2-C6 and C12-C16 portions. The most dominant calculated



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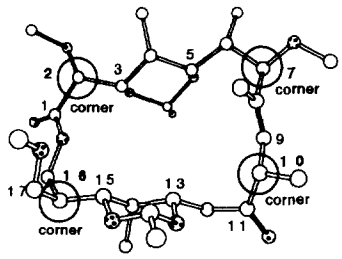
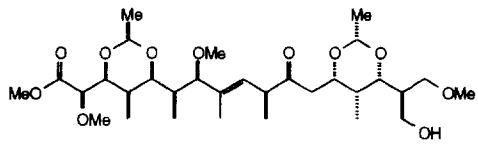


The most stable conformer of **4**

Figure 4

conformation of **4**[10] is in a nearly square shape with four corners at C2, C7, C10 and C16 positions, and there is virtually no difference from that of the lactone part in **1** (Figure 4).

The next and most important issue was to verify that the corresponding seco-acid (**3**) has a dominant global conformation clearly favorable to lactonization into **2**. Although it is generally very difficult to confirm correctly conformations of flexible acyclic complex molecules like **3**, the MM2-CONFLEX3 method[9] was again applied to the model seco-acid (**5**) in order to obtain reliable computation results within a reasonable time, and calculations were performed from two different starting geometries, **5a** and **5b**. The former **5a** is an arbitrary combinated structure of previously calculated conformers of partially overlapped two fragments **6** (C1-C12) and **7** (C8-C17), while the latter **5b** was generated only by severing the ester bond of **4**. As shown in Figure 5, the calculations starting independently from **5a** and **5b** gave the completely same result, in which the most stable conformation of **5** with a hydrogen bonding between C1-carbonyl and C16-hydroxy groups as well as with minimum 1,3-*syn*-pentane and allylic interactions[8] is very similar to that of **4** in excellent accord with our expectation only except for the angle of the C11-carbonyl group. In macrolactonization, this seco-acid is accordingly expected to cyclize smoothly via only easy rotation of the most flexible C11-C12 bond without forced conformational changes.



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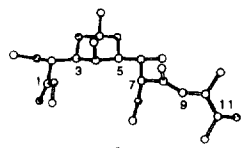

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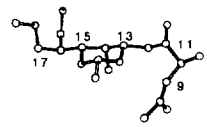

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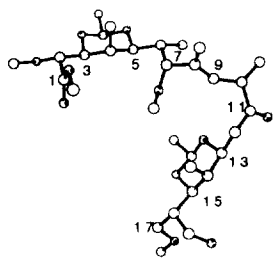
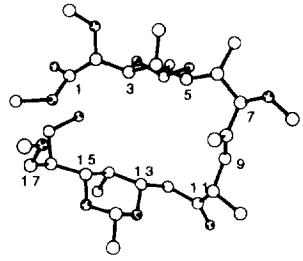
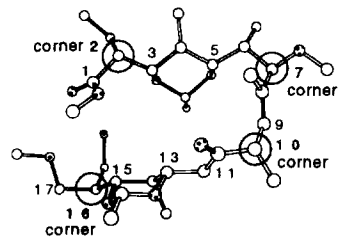


5a



5b



The most stable conformer of **5**

Figure 5

Actually, the seco-acid derivative (**3**) was synthesized starting from *R*- and *S*-3-hydroxy-2-methylpropionic acids and subjected to the macrolactonization.[11] It is noteworthy that **3** cyclized quite smoothly to the corresponding 18-membered lactone (**2**) without using the usual high dilution method, that is, when **3** was first derived to a mixed anhydride with the Yamaguchi reagent[12] and then treated with DMAP (4 equiv., 20 mM) in benzene at room temperature for 3 hr, the lactone (**2**) was isolated in 87% yield.

Table 1. Vicinal proton coupling constants (J ; Hz) of the seco-acid methyl ester

$J_{H\text{-}H}$	obs.(**3**-Me)	calcd.(**5**)
2-3	9.0	8.2
3-4	1.5	2.5
4-5	1.0	2.2
5-6	10.0	10.0
6-7	0	5.7
9-10	9.0	-
12-13	8.5;4.0	9.2;3.3
13-14	2.0	2.6
14-15	1.5	2.4
15-16	10.0	10.9
16-16'	4.5;2.0	4.2;2.3

Table 2. Vicinal proton coupling constants (J ; Hz) of the lactone derivative

$J_{H\text{-}H}$	obs.(**2**)	calcd.(**4**)
2-3	8.5	8.2
3-4	1.5	1.8
4-5	1.0	2.7
5-6	0	0
6-7	10.5	12.2
9-10	8.5	-
12-13	8.5;6.0	9.1;2.0
13-14	2.0	1.8
14-15	1.5	2.1
15-16	10.5	12.2
16-16'	1.5;0.5	2.8;0.5

Finally, as shown in the two tables, the observed vicinal proton coupling constants of both the seco-acid methyl ester (methyl ester of **3**)[13] and the lactone (**2**) were compared with the calculated data of **5** and **4**. There is no practical difference between the observed and calculated data except for the coupling constants at the rather flexible C6-C7 bonds of the seco-acid methyl esters. The reliability of the computation method was thus substantiated. Further synthetic approach to **1** from **2**, via deprotection of the two acetals and selective oxidation on the 18-membered ring, is now in progress.

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