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Intramolecular cycloaddition/cycloreversion of (*E*)-3β,17β-diacetoxy-5,10-secoandrost-1(10)-en-5-one

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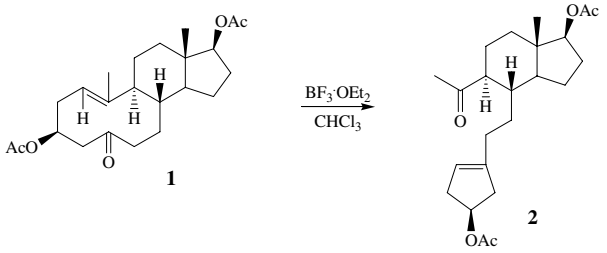
Abstract—Treatment of 3β,17β-diacetoxy-5,10-secoandrost-1(10)-en-5-one with $BF_3{\cdot}Et_2O$ was shown to proceed with cleavage of the macrocycle and formation of a new compound containing a cyclopentenone ring. Based on DFT calculations, an intramolecular Lewis acid promoted [2+2]cycloaddition, followed by a cycloreversion of the intermediate oxetane, is proposed as a possible reaction mechanism.

In connection with our work on seco steroids, further synthetic modifications of compounds derived from radical oxidation of 5α-alcohols[1] have been investigated. Surprisingly, attempts to carry out transformation of (*E*)-enone **1** in the presence of Lewis acid (e.g., to protect the keto group as dithioketal) led to fragmentation product **2** in reasonable to good yields.[2]



It is evident that intramolecular rearrangement has taken place under the conditions used. While trying to understand this unusual reaction, we came to the conclusion that the stereochemistry of the starting macrocyclic compound **1** determinates the transformation, as no similar reaction took place with the corresponding (*Z*)-isomer. It is known that 5,10-seco steroidal cyclodecanones are prone to photochemical,[3] acid-catalyzed and thermal cyclization[4] with formation of derivatives such as **3**–**6**. The isolation of **2** showed that this list is not exhaustive, and that the process of intramolecular cyclization of these macrocycles is not yet fully understood.

The presence of a flexible macrocycle in **1** implies the existence of a set of conformers. At least two conformers were detected by NMR for similar 5,10-seco steroids.[5,6] However, the accuracy of such estimations is not satisfactory. They only allow proof of the presence or absence of a fixed conformer with a certain level of probability. More reliable data can be obtained from modern computation methods.[7,8]

To explain the experimental results obtained we have performed a conformational analysis of **1** based on DFT calculations. In the present work, the nonempirical generalized gradient approximation for the exchange functional of Perdew et al.[9] was employed. Its well-documented performance,[10] together with a sound physical basis, makes it competitive with, if not superior to, other popular approximations of this type. Contracted Gaussian basis sets of TZ2P quality were used to represent the Kon–Sham orbitals in conjunction with the corresponding density-fitting basis sets.[11] The correspondence for

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all structures to their local minima on the potential energy surface was confirmed by calculations of the Hessian eigen values. Unscaled ZPE corrections were included in the relative energy values. For comparison, similar calculations were performed also by the semi empirical AM1[12] method as implemented in the MOPAC package[13] and the obtained results were correlated with the DFT method. In all calculations, the geometry parameters were optimized with gradient norm 0.00001 hartree/Bohr. The geometries of the most important conformers are shown in Table 1.

At the level of the isolated molecule, a brief description of the potential energy surface (PES) of **1** was obtained. A conformational PES is a multidimensional object whose dimensions depend on the degrees of freedom associated with all internal geometrical parameters. All possible conformers of **1**, including those caused by rotation of the acetoxy groups, were investigated. It was found that only eight structures with similar locations of the acetoxy groups corresponded to 'pure' conformers of **1** and structure **1a** proved to be the most stable one. Four more rota-

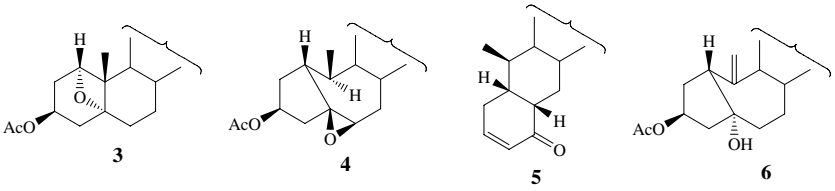
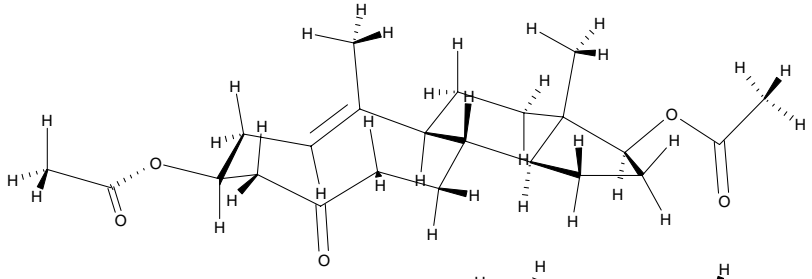
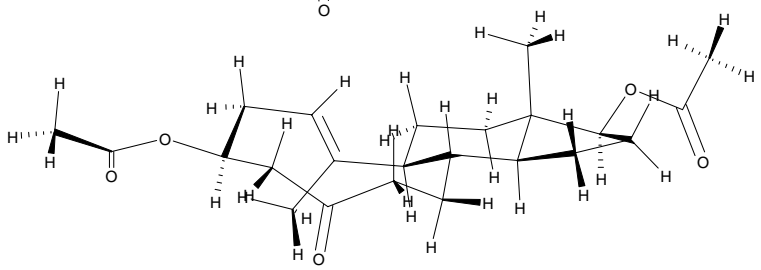
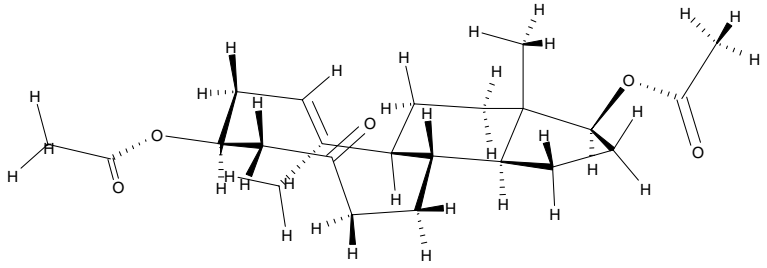
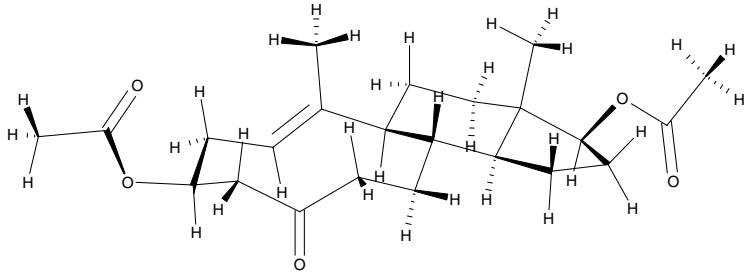


Table 1. Calculated structures of important conformers of **1**

Entry	Conformation	Relative energies (ΔE_0, kcal/mol)[a]	Relative content in gas phase at 298 K (n, %)
1a		0.0	75.2
1b		1.25	9.3
1c		1.33	8.1
1d		1.66	5.0

[a] According to DFT calculations.

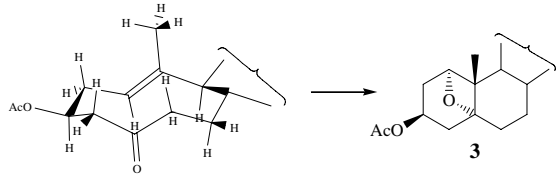
mers were also studied based on preliminary calculations.

The data on relative thermodynamic stabilities were obtained using Boltzmann's formula

$$n_1/N = \left\{1 + \sum_{i=2}^{12} \exp[(E_1 - E_i)/RT]\right\}^{-1}$$

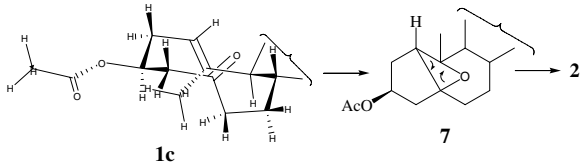
($N = n_1 + n_2 + \cdots + n_{12}$) for each isomeric structure, and their partial contents in the equilibrium mixture in the ideal gas approximation at 298 K are given in Table 1 for the most important conformers. The calculations clearly show that substituents at C-3 prefer to adopt (pseudo)equatorial orientation. The maximum amount of axial conformers does not exceed 3%. The major conformation is the 'crown-type' form **1a** which is in accordance with the data obtained from NMR studies.[6] Its contribution is about 75% according to the calculations. It is necessary to pay attention also to the rather high value of the dipole moment evaluated for this structure. For this reason, it is possible to assume that the amount of **1a** will increase with the polarity of the solvent.

In view of the results obtained, the mechanisms of some synthetic transformations of (*E*)-5,10-seco-1(10)-en-5-ones can be explained in the following way. The macrocycles are inclined to form oxetanes **3** via an intramolecular Paterno–Büchi reaction under UV-irradiation. The oxetanes **3** have a slightly distorted 'crown-type' conformation,[14] suggesting that they originate from conformation **1a** of the (*E*)-5,10-secoandrost-1(10)-en-5-ones. Oxetanes **3** are interesting intermediates for the preparation of other steroids (e.g., 1α-hydroxy steroids[15]).



1a **3**

Also, a possibility of regioisomeric formation was hypothesized for the photochemical transformation of (*E*)-5,10-seco-1(10)-en-5-ones,[16] however, such oxetanes have never been isolated. Inspection of the molecular model of conformer **1c** showed that the steric arrangement of the carbonyl group and the double bond facilitates the Lewis acid promoted [2+2]cycloaddition[17] as observed here to oxetane **7**. Under the reaction conditions, the intermediate oxetane **7** then undergoes a cycloreversion to give the fragmentation product **2**. In this way, the observed fragmentation can be explained as a cycloaddition/cycloreversion sequence.



1c **7**

The results obtained in this study have provided additional experimental evidence for the high conformational flexibility of 5,10-seco steroids. The same compound can adopt a number of very different conformations which are close together in energy. Sometimes analysis of minor conformations is important in understanding the formation of many reaction products of such macrocycles.

Supplementary data

Detailed calculation data for all the conformers and NMR spectral data for compound **1**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.096.

References and notes

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2. Illustrative experimental procedure. A solution of **1** (20 mg, 0.05 mmol) and $BF_3{\cdot}OEt_2$ (0.02 mL) in $CHCl_3$ (0.5 mL) was kept at room temperature for 2 h. The reaction mixture was diluted with water and the organic layer separated, dried and evaporated. The residue was chromatographed on SiO_2 to give **2** (12 mg, 60%) as white amorphous crystals. ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.85 (s, 3H, H-18), 1.20 (m, 1H, H-14α), 1.21 (m, 1H, H-12α), 1.36 (m, 1H, H-7α), 1.41 (m, 1H, H-7β), 1.42 (m, 1H, H-15β), 1.51 (m, 1H, H-16β), 1.53 (m, 1H, H-11β), 1.70 (m, 1H, H-15α), 1.73 (m, 1H, H-11α), 1.76 (m, 1H, H-12β), 1.89 (m, 1H, H-8β), 1.97 (m, 2H, H-6α and H-6β), 2.02 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.17 (s, 3H, H-10), 2.18 (m, 1H, H-16α), 2.23 (d, 1H, $J = 18$ Hz, H-4α), 2.30 (m, 1H, H-9α), 2.33 (m, 1H, H-2α), 2.63 (dd, 1H, $J_1 = 15$ Hz, $J_2 = 7.5$ Hz, H-4β), 2.71 (ddd, 1H, $J_1 = 21$ Hz, $J_2 = 7.5$ Hz, $J_3 = 3$ Hz, H-2α), 4.62 (dd, 1H, $J_1 = 10$ Hz, $J_2 = 9$ Hz, H-17α), 5.25 (br s, 1H, H-1), 5.31 (m, 1H, H-3α). ^{13}C NMR (150 MHz, $CDCl_3$): δ 12.3 (C-18), 24.5 (C-15), 26.1 (C-11), 27.5 (C-16), 29.9 (C-19), 30.1 (C-7), 21.5 (OAc), 27.5 (C-6), 21.7 (OAc), 36.8 (C-12), 43.3 (C-13), 48.0 (C-14), 36.7 (C-8), 42.5 (C-4), 39.9 (C-2), 56.8 (C-9), 82.7 (C-17), 74.9 (C-3), 120.9 (C-1), 142.5 (C-5), 171.4 (OAc), 171.5 (OAc), 213.0 (C-10).
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