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MODELLING TRANSANNULAR CYCLIZATION OF 1(10)E,4E-GERMACRANOLIDE COSTUNOLIDE INTO EUDESMANE DERIVATIVES

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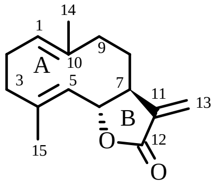
Semi-empirical quantum-chemical methods were used to model transannular cyclization of 1(10)E,4E-germacranolide costunolide into eudesmanolides. The conformational states favorable for the transformation and the energy barriers were calculated.

Key words: sesquiterpene lactones, germacranolides, eudesmanolides, guaianolides, transannular cyclization, quantum chemistry.

Germacranolides represent one of numerous sesquiterpene lactone structural types and are precursors of eudesmanolides and guaianolides according to the biogenetic theory of Ruzicka [1]. The *trans*-fused 1(10)E,4E-germacranolides are the most numerous and most susceptible to biomimetic transformations. Several chemical transformations were carried out for one of the representatives of this group, costunolide (**1**), in order to prepare cyclic derivatives [2-5]. Therefore, studies of the biomimetic transformation of costunolide are considered classical.



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Acid-catalyzed carbocyclization was used mainly with electron-deficient compounds such as mineral acids and Lewis acids acting as the catalysts. This suggested a cation-exchange mechanism for the reaction and certain involvement of the C1═C10 and C4═C5 double bonds. The reaction intermediates were considered to be carbonium ions. Cyclization occurred via rearrangement of the carbonium ion.

The direction and path of the transformation as a function of initial conformation of the lactone and the charge and energetics of the intermediate carbonium ions are interesting. We used semi-empirical methods of quantum-chemical MO LCAO calculations with PM3 parametrization (MOPAC version 7.0) for modeling [6].

Thus, we modelled transannular cyclization of costunolide by quantum-chemical MO LCAO methods with AM1 and PM3 parametrization (MOPAC version 7.0).

The 10-membered ring (A) in **1** is known to adopt four principal conformations that are classified according to the orientation of the methyls on C4 and C10 relative to the C4═C5 and C1═C10 double bonds: chair—chair ${}^{15}D_{5},{}_{1}D^{14}$ (**a**), chair—boat ${}_{15}D^{5},{}^{1}D_{14}$ (**b**), boat—boat ${}_{15}D^{5},{}_{1}D^{14}$ (*c*), and boat—boat ${}^{15}D_{5},{}^{1}D_{14}$ (**d**) [7]. Literature data [8] and our calculations of heats of formation ΔH^{o}_{f} (Table 1) confirm that four canonical conformations occur in **1**. Of these, the most stable is **a**, ΔH^{o}_{f}(**a**) = -55.82 kcal/mol.

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TABLE 1. Heats of Formation ΔH°_f of Costunolide (**1**) and Carbocations (**2**) and (**3**) in Four Conformational States (**a-d**) and Energy Barriers $\Delta(\Delta H^\circ_f)$ of **1**→**2** and **2**→**3** Transitions, kcal/mol

Conformer	ΔH°_f of (**1**)	$\Delta(\Delta H^\circ_f)$ **1**→**2**	ΔH°_f of **2**	$\Delta(\Delta H^\circ_f)$ **2**→**3**	ΔH°_f of **3**
a	-55.82	15.79	128.69	2.07	112.32
b	-51.20	5.45	131.35	2.77	120.39
c	-51.44	5.50	133.54	0.87	112.83
d	-53.08	6.44	131.79	8.21	113.11

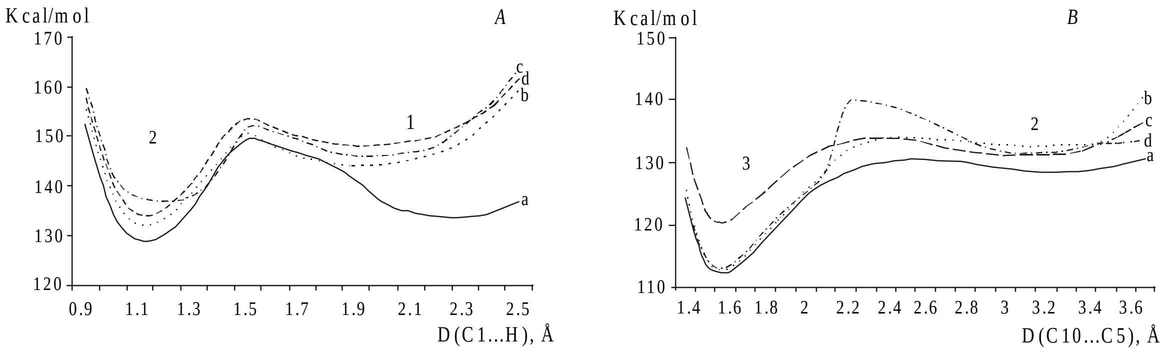
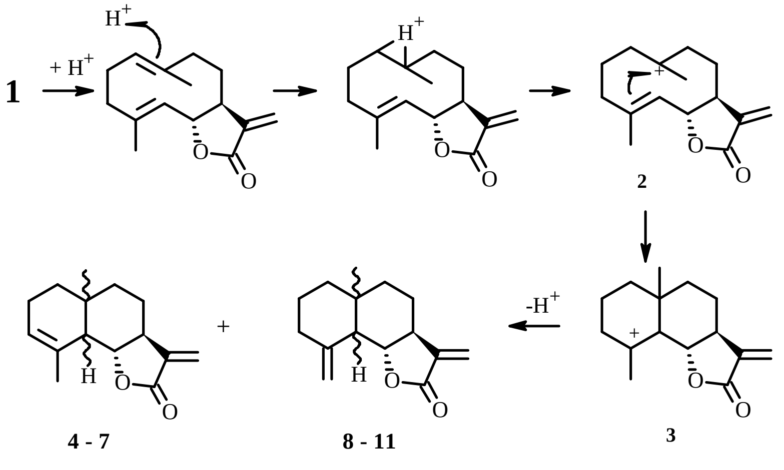


Fig. 1. The quantity ΔH°_f of the **1**→**2** transition as a function of C1...H$^+$ (*A*) distance; and of **2**→**3**, of C5...C10 (*B*) for the four conformational states **a-d**.

It was found that C1 becomes protonated to form a 1,10-hydride bridge [9]. Then the carbonium ion adopts structure **2**, which is more stable energetically.



4: 5α (H),10β; **5:** 5β (H), 10α; **6:** 5β(H),10β; **7:** 5α (H), 10α;
8: 5α(H), 10β; **9:** 5β(H), 10α; **10:** 5β(H), 10β; **11:** 5α(H), 10α

Protonation has an energy barrier, the height of which differs for the costunolide conformers. Figure 1*A* shows the energy of protonation of costunolide (**1**) as a function of interatomic distance d(Cl...H$^+$). The maximum corresponds to a transition state where the proton is practically equidistant from C1 and C10. Table 1 lists the energy barriers for the four principal conformers and the heats of formation of **2a-2d**.

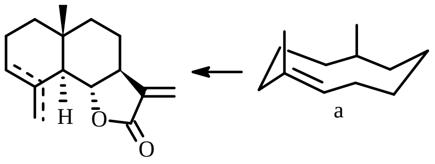
Interaction of the carbonium ion centered on C10 with the C4=C5 double bond results in cyclization to form the C5–C10 bond. The rearranged skeleton acquires the eudesmane structure **3**. Quantum-chemical investigations demonstrated that the height of the barrier to cyclization reaches 0.87-8.27 kcal/mol and that **3** has a smaller heat of formation than **2** for all conformational states. Transformation of **2** in all conformers (**a-d**) into carbonium ion **3** requires migration of the positive charge onto C4 (Fig. 1*B*).

TABLE 2. Heats of Formation ΔH^{o}_{f} of Costunolide Cyclization Products (**4-11**) and Heats of Cyclization $\Delta(\Delta H^{o}_{f})$, kcal/mol

Compound	ΔH°_{f}	$\Delta(\Delta H^{\circ}_{f})$
4	-68.93	-13.11
5	-59.65	-8.45
6	-67.86	-16.42
7	-67.65	-14.57
8	-66.11	-10.29
9	-56.96	-5.76
10	-63.38	-11.94
11	-63.87	-10.79

Elimination of a proton from C3 or C15 forms eudesmanolides **4-11**. Table 2 lists the heats of formation of cyclization products **4-11** and the heats of reaction.

We found during modeling of transannular cyclization of costunolide that geometric isomers of cyclized derivatives with *trans*- or *cis*-fusion of the six-membered carbocycles are formed depending on the conformational state of the starting lactone. This agrees with the literature [10]. Thus, cyclization of 1(10)E,4E-germacranolide costunolide, which occurs in conformational states **a** and **b**, forms *trans*-fused eudesmanolides (**4**, **5**, **8**, **9**). The *cis*-fused eudesmanolides (**6**, **7**, **10**, **11**) are formed via cyclization of costunolide in conformations **c** and **d**.



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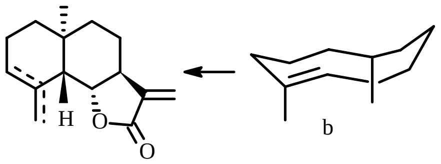

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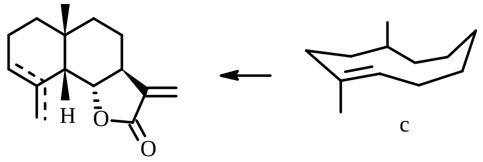

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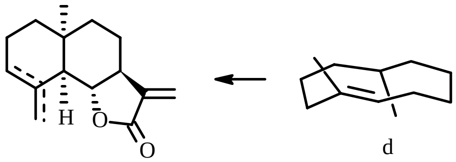
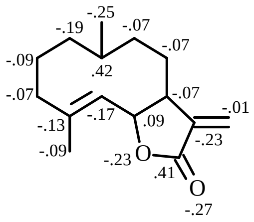
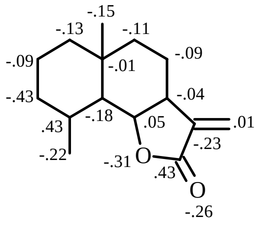


7, 11

Costunolide occurs in solution primarily in conformation **a**. Therefore intermediate **2** is formed through this state despite the fact that the height of the barrier arising during cyclization of conformer **1c** is slightly lower. Furthermore, ΔH^{o}_{f} is less (128.69 kcal/mol) for carbonium ion **2a** than for other conformers. The charge in **2a** is distributed such that the excess of positive charge is concentrated on C10 with further formation of eudesmane carbonium ion **3a**.



2a



3a

Therefore, it can be proposed that transannular cyclization of costunolide into eudesmane derivatives proceeds from conformational state **a**. The final cyclization products will be eudesmanolides with *trans*-fusion of the six-membered carbocycles with the C10 methyls (**4** and **8**) in the β-orientation. The results for the heats of formation of the reaction products (Tables 1 and 2) show that the transannular cyclization of costunolide is exothermic. A comparision of our data with that in the literature [2-5] showed that the results from the calculations agree well with those from experiments.

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