

# Conformational analysis of sesquiterpene lactones of the germacrane type

## 1. 1(10)*E*,4*E*-Germacranolides

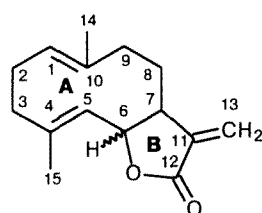
K. M. Turdybekov\* and T. T. Edil'baeva

Institute of Organic Synthesis and Coal Chemistry, Kazakhstan Academy of Sciences,  
1 ul. 40 Let Kazakhstana, 470061 Karaganda, Kazakhstan.  
Fax: 007 (321 2) 57 1330

The structure of 1(10)*E*,4*E*-germacranolides was studied by a molecular mechanics method. Possible conformers, the probabilities of their occurrence, and the barriers to conformational transitions were determined.

**Key words:** germacranolide, conformational analysis, molecular mechanics.

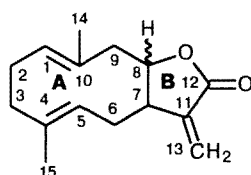
Germacranolides containing a 1,5-diene ten-membered carbocycle belong to the largest class of natural sesquiterpene  $\gamma$ -lactones.<sup>1</sup> They can be classified into four groups (*E,E*-, *E,Z*-, *Z,E*-, and *Z,Z*-isomers) in which *trans,trans*-germacranolides are the most abundant. In order to investigate the stereochemistry of the latter compounds, X-ray structural studies of several *E,E*-germacranolides (hanphyllin,<sup>2</sup> salonenolide,<sup>2</sup> and jurinelloide<sup>3</sup>) were carried out previously. In this work, we report the results of conformational analysis of model nonlinear (1 and 2) and linear (3 and 4) 1(10)*E*,4*E*-germacranolides.



1, 2

1: 6 $\beta$ ,7 $\alpha$ (H)

2: 6 $\alpha$ ,7 $\alpha$ (H)



3, 4

3: 7 $\alpha$ ,8 $\beta$ (H)

4: 7 $\alpha$ ,8 $\alpha$ (H)

Molecules 1–4 were chosen as model compounds because they represent the main framework of *E,E*-germacranolides.

### Calculation Procedure

Molecular-mechanics calculations of the conformations of molecules 1–4 were carried out on a PC/AT 386 using an MMX86 program and the standard parameters included in the version used. During the calculations, the geometries of the resulting conformers of molecules 1–4 were fully optimized. The barriers and pathways to conformational transitions were determined by consecutive rotation around one or two corre-

sponding  $sp^3-sp^3$  or  $sp^3-sp^2$  bonds with a step of  $5^\circ$  and with optimization of the molecular geometry after each step.

The initial conformers of molecules 1–4 were derived from the Dreiding molecular models.

### Results and Discussion

According to the accepted classification, the conformations of 1,5-diene 10-membered carbocycles in germacranolides are determined by the orientation of the Me groups at the C(4) and C(10) atoms with respect to the C(1)=C(10) and C(4)=C(5) double bonds.<sup>4</sup> In conformity with this classification, the 10-membered ring in molecules 1–4 can assume four main conformations: chair–chair of the  ${}^{15}D_{5,1}D_{14}^{14}$  type (a), chair–boat of the  ${}^{15}D^5, {}^{14}D_{14}$  type (b), boat–boat of the  ${}^{15}D^5, {}^{14}D^{14}$  type (c), and boat–boat of the  ${}^{15}D_5, {}^{14}D_{14}$  type (d).<sup>5</sup>

We calculated the conformational energies for all four canonical conformers of molecules 1–4 with conformations a–d of ring A. After optimization of the geometry by molecular mechanics, it was found that all four theoretically possible conformations can exist for molecules 1–4. The most stable conformer in the case of nonlinear A/B-*trans*-annulated germacranolide 1 is conformer 1a, in which ring A has the  ${}^{15}D_{5,1}D_{14}^{14}$  type of chair–chair conformation (the torsion angles in the 10-membered ring are presented in Table 1). This conformer is more favorable than the others by 4.1–5.2 kcal mol<sup>-1</sup>; with no allowance for the entropy factor, the probability of its existence is 0.965. For nonlinear *cis*-annulated germacranolide 2, conformer 2b is the most stable. It is 1.1–4.2 kcal mol<sup>-1</sup> energetically more favorable than the other conformers, and the probability of its existence is 0.866. The 10-membered ring in 2b assumes the  ${}^{15}D^5, {}^{14}D_{14}$  type of chair–boat conformation (Fig. 1).

An analysis of the published data dealing with the crystal structures of *trans,trans*-germacranolides showed

**Table 1.** Torsion angles ( $\varphi$ ) in the 10-membered ring, conformational energies ( $E$ ), and probabilities of the occurrence ( $P$ ) of conformers of molecules 1–4

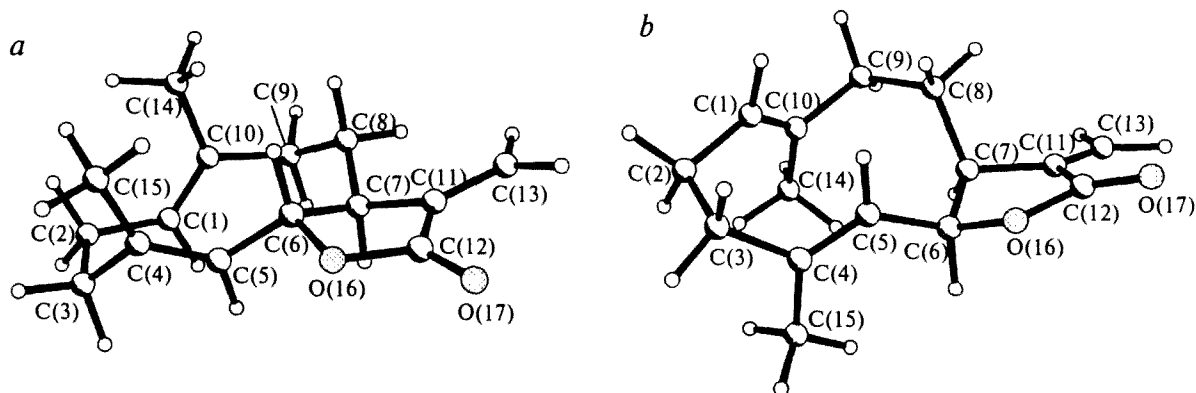
Con- for- mer	Angles around bonds ( $\varphi$ /deg)										$E$ /kcal mol <sup>-1</sup>	$P$
	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–10	10–1		
<b>1a</b>	-98	48	-83	156	-138	83	-79	69	-116	164	26.3	0.965
<b>1b</b>	109	-39	89	-166	68	69	-121	46	62	-171	31.5	0.001
<b>1c</b>	-78	-22	92	-166	71	75	-102	60	-98	178	30.4	0.001
<b>1d</b>	76	29	-92	163	-125	76	-102	58	63	-173	30.8	0.001
<b>1b'</b>	108	-44	86	-166	58	79	-58	-39	118	-164	28.3	0.031
<b>1c'</b>	-114	27	50	-166	62	81	-89	61	-105	169	29.9	0.002
<b>1c''</b>	-74	-31	89	-160	59	80	-37	-41	-22	166	32.9	0.001
<b>1d'</b>	122	-23	-49	165	-121	74	-109	50	65	-169	33.3	0.001
<b>2a</b>	-97	46	-85	175	-123	54	-74	83	-119	168	31.8	0.002
<b>2b</b>	96	-47	86	-172	109	26	-96	57	75	-172	28.3	0.866
<b>2c</b>	-76	-31	93	-163	101	41	-94	78	-101	171	29.4	0.131
<b>2d</b>	78	19	-93	172	-101	44	-94	71	61	-171	32.5	0.001
<b>2d'</b>	112	-27	-54	172	-91	37	-96	62	70	-166	32.3	0.001
<b>3a</b>	-99	46	-86	172	-129	74	-88	80	-112	169	25.6	0.270
<b>3b</b>	105	-42	90	-170	83	51	-117	55	63	-170	25.55	0.295
<b>3c</b>	-76	-29	90	-168	85	62	-109	70	-96	171	25.4	0.381
<b>3d</b>	77	26	-94	169	-117	65	-107	67	62	-171	26.7	0.041
<b>3c'</b>	-117	26	49	-170	75	71	-99	72	-102	167	27.7	0.007
<b>3d'</b>	120	-28	-47	170	-114	59	-111	59	66	-167	27.8	0.006
<b>4a</b>	-97	52	-84	169	-143	66	-54	56	-119	170	30.5	0.072
<b>4b</b>	102	-45	84	-172	66	64	-40	-50	126	-163	29.5	0.404
<b>4c</b>	-75	-32	88	-163	65	66	-22	-55	-16	164	30.9	0.036
<b>4d</b>	80	22	-88	165	-150	69	-12	-58	126	-168	32.1	0.005
<b>4a'</b>	-98	44	-84	164	-147	48	41	-70	-43	169	29.4	0.479
<b>4c'</b>	-114	25	47	-166	53	44	31	-69	-40	166	34.2	0.001
<b>4d'</b>	114	-18	-54	167	-146	76	-30	-48	125	-163	32.3	0.003

bered ring occurs in the 19 nonlinear *trans*-annulated *E,E*-germacranolides studied. Of the non-linear *cis*-annulated *E,E*-germacranolides, only three compounds were studied by X-ray diffraction analysis. In all of these compounds, the 10-membered ring occurs in the chair–boat conformation.<sup>5</sup>

These data confirm the fact that crystals are normally built of the energetically most stable conformers. In all probability, the fact that conformers **1a** and **2b** of molecules **1** and **2** are more favorable is due to the orientation of the O(6) atom of the lactone ring. In

conformer **1a** (see Fig. 1) of the *trans*-annulated germacranolide **1**, the O(6) atom of the lactone ring is oriented equatorially. A comparison of conformer **1a** with **1d**, in which the O(6) atom is also equatorial, showed that the former is energetically more favorable (by 4.5 kcal mol<sup>-1</sup>) than the latter, which is primarily due to the more favorable conformation at single bonds (the difference in the torsion constituent of the energy is 3.8 kcal mol<sup>-1</sup>).

In the case of *cis*-annulation along the C(6)–C(7) bond in the <sup>15</sup>D<sub>5,1D<sup>14</sup> type of chair–chair conformation</sub>

**Fig. 1.** The most favorable conformers of molecules **1** (a) and **2** (b).

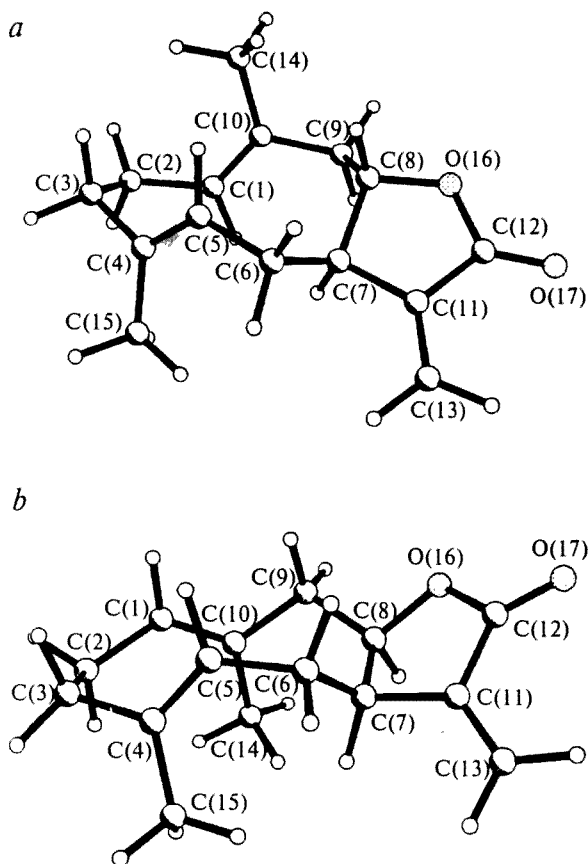


Fig. 2. The most favorable conformers of molecules 3 (a) and 4 (b).

(2a), the O(6) atom is axial; therefore, this conformer is energetically less favorable than the chair-boat conformer of the  $_{15}D^5,_{14}D^4$  type (2b) in which the  $\gamma$ -lactone ring is oriented equatorially with respect to ring A.

For linear molecules 3 and 4, the difference between conformations is much less pronounced (see Table 1). The main conformers 3c and 4b (Fig. 2) exist with probabilities of 0.381 and 0.404, respectively. In the case of linear *trans*-annulated *E,E*-germacranolides, all four canonical conformers have been detected by X-ray diffraction.<sup>5</sup>

The fact that the probabilities of the existence of conformers of molecules 3 and 4 are relatively close is most likely due to the orientation of the O(6) atom of the lactone ring. In fact, in the case of *trans*-annulation of the rings, the  $\alpha$ -oriented O(6) atoms in all four conformers are equatorial, whereas the  $\beta$ -oriented atoms in the case of *cis*-annulation of the rings occupy axial positions alone. Therefore, the energies of conformers of molecule 4 are 4.0–5.5 kcal mol<sup>-1</sup> higher than those of the corresponding conformers of 3. The forced axial orientation of the O(6) atom in the lactone ring could be one of the reasons why no linear *cis*-annulated *E,E*-germacranolides can be found in natural objects.

After determination of the main conformers, we modeled the conformational transitions in compounds 1–4 and estimated the energy barriers to them. In the first approximation, all mutual transitions in 10-membered germacran rings can be modeled by consecutive rotation of the fragments containing C(1)=C(10) and C(4)=C(5) endocyclic double bonds. Varying the C(8)–C(9)–C(10)–C(1) and C(2)–C(3)–C(4)–C(5) torsion angles does not always allow describing a particular conformational transition. Therefore, the 4b  $\leftrightarrow$  4c and 4d  $\leftrightarrow$  4a transitions were modeled by varying the C(3)–C(2)–C(1)–C(10) torsion angle. The rotation was carried out by turns, i.e., first one angle was varied and then the other. For example, the C(8)–C(9)–C(10)–C(1) angle was changed starting from conformer 1a until it was transformed into conformer 1d; the latter was converted

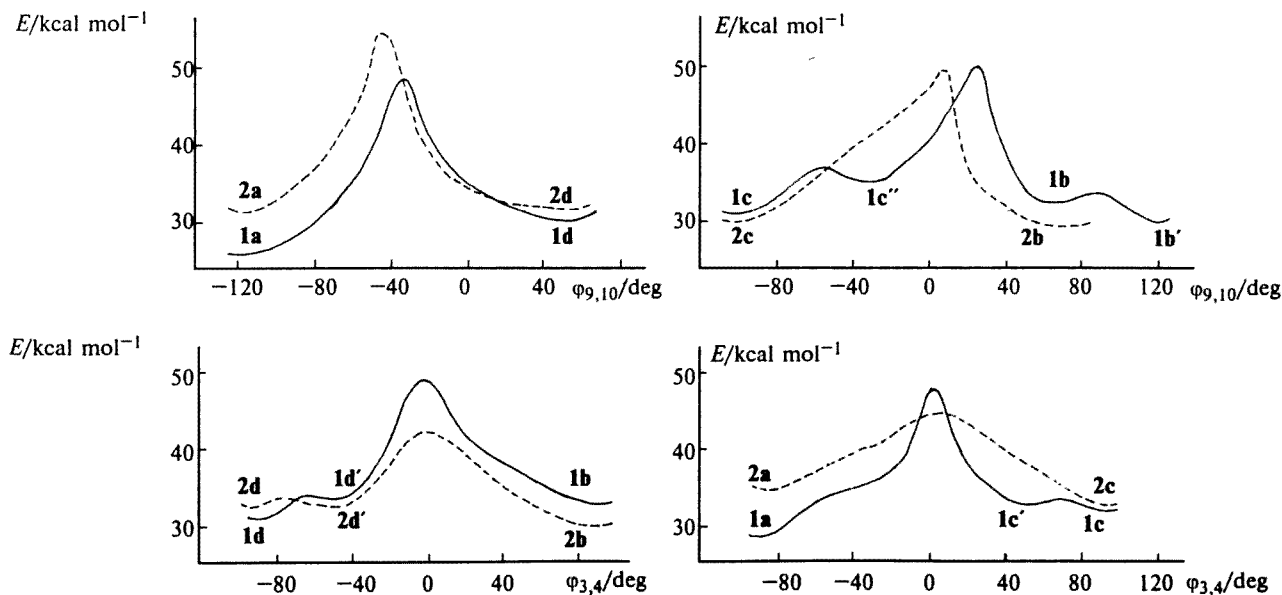


Fig. 3. Pathways of conformational transitions of molecules 1 and 2.

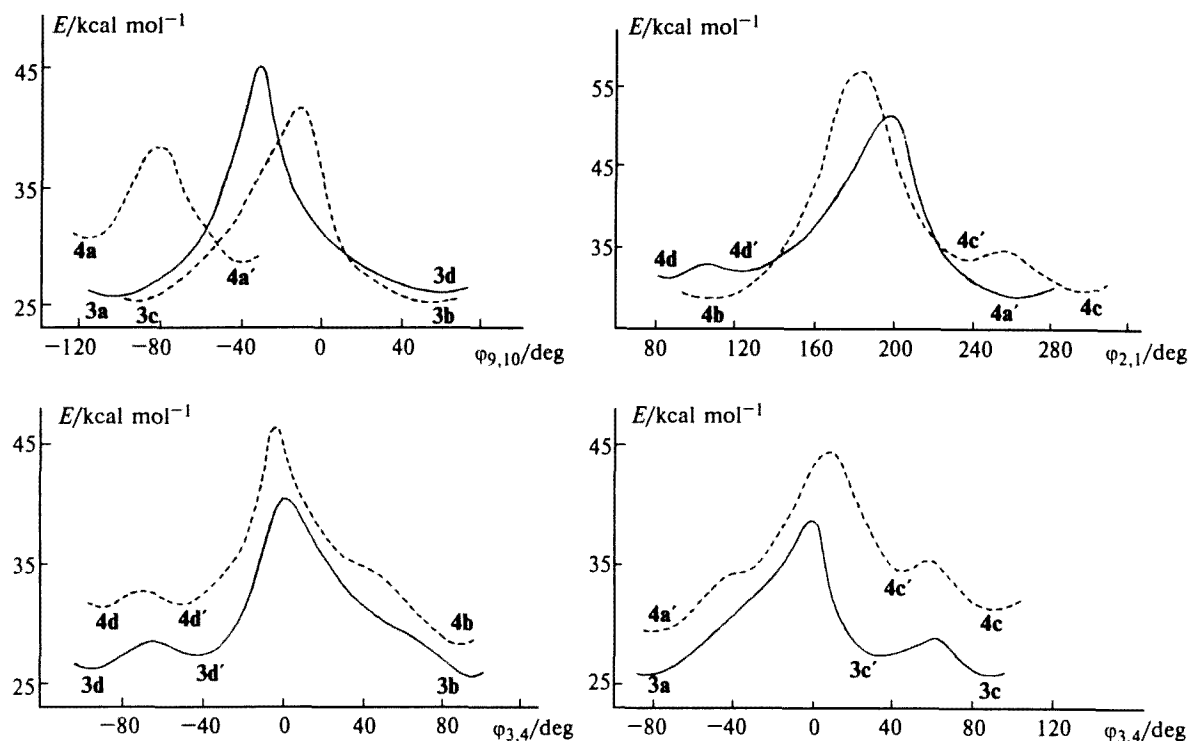


Fig. 4. Pathways of conformational transitions of molecules 3 and 4.

into conformer **1b** by varying the C(2)—C(3)—C(4)—C(5) torsion angle, etc. These transitions can be designated as **a—d—b—c—a**. When the transitions were modeled in the opposite order (**a—c—b—d—a**), some shifts of the maximum points of conformational transitions and some differences in the barrier heights were observed, although the curves near the maxima were virtually identical. This is due to the fact that as the system gradually leaves the energetic minimum following the variation of a particular torsion angle, the tension energy ( $E_{\text{tens}}$ ) smoothly increases, and after a maximum is passed, it sharply decreases. The same occurs during movement in the opposite direction. Consequently, we obtain different maximum points for these conformational transitions.

Figures 3 and 4 show the routes of conformational transitions averaged over two opposite directions, because our calculations provide only a qualitative description of the conformational transitions.

It can be seen from Figs. 3 and 4 that the barriers to the conformational transitions ( $\Delta E$ ) vary over a fairly wide range: from 15.5 kcal mol<sup>-1</sup> for the **1c—1a** transition to 23.0 kcal mol<sup>-1</sup> for the **1a—1d** transition for molecule **1**, from 10.2 kcal mol<sup>-1</sup> for the **2d—2b** transition to 25.2 kcal mol<sup>-1</sup> for the **2a—2d** transition for molecule **2**, from 13.6 kcal mol<sup>-1</sup> for the **3a—3c** transition to 19.9 kcal mol<sup>-1</sup> for the **3a—3d** transition for molecule **3**, and from 14.5 kcal mol<sup>-1</sup> for the **4a—4c** transition to 26.5 kcal mol<sup>-1</sup> for **4b—4c** transition for molecule **4**.

In addition, in some of the pathways of conformational transitions, local minima corresponding to

subconformers to the main states were detected. The probabilities of their existence are normally less than 0.01, except for subconformers **1b'** and **4a'**, which are more favorable than the corresponding main conformers **1b** and **4a** by 3.2 and 1.1 kcal mol<sup>-1</sup>, respectively, and are not included in the **a—d—b—c—a** cycle of transitions (see Figs. 3 and 4).

Thus, using model molecules **1—4** as examples, we estimated the probabilities of the occurrence of various conformers of nonlinear *E,E*-germacranolides and, in the first approximation, elucidated the pathways and energies of conformational transitions.

## References

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