Conformational analysis of sesquiterpene lactones of germacrane type
2. 1(10)*Z*,4*Z*-Germacranolides

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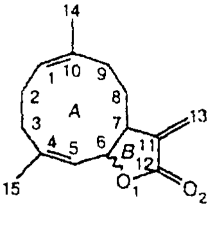
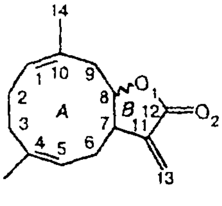
The structure of 1(10)*Z*,4*Z*-germacranolides was studied by the method of molecular mechanics. Possible conformers, the probability of their existence, and barriers to conformational transitions were determined.

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

Earlier we performed the conformational analysis for *trans,trans*-isomers of natural sesquiterpene lactones of the germacrane type.[1] In a continuation of the structural studies of germacranolides, we present in this paper the results of conformational analysis for *cis,cis*-isomers. *Z,Z*-Isomers belong to the smallest subgroup of germacranolides; therefore, their structural studies are the least documented.[2] The molecules of non-linear (**1** and **2**) and linear (**3** and **4**) 1(10)*Z*,4*Z*-germacranolides representing the main skeleton in this class of compounds were chosen as the model molecules for the conformational analysis:



1: 6β,7α(H)
2: 6α,7α(H)



3: 7α,8β(H)
4: 7α,8α(H)

Computational Procedure

The conformational calculations of the molecules **1**—**4** were performed on a PC/AT-386 computer by the method of molecular mechanics, using the program MMX86 with the standard parameters implemented in the given version of the program. The geometries of conformers obtained for the molecules **1**—**4** were fully optimized. The barriers to, and pathways of, conformational transitions were simulated by a consecutive rotation of one or two respective sp^3—sp^3- or sp^3—sp^2-bonds with a 5° step and geometry optimization after each step. The initial conformers for the molecules **1**—**4** were chosen with the use of Dreiding molecular models.

Results and Discussions

The following conformations of ten-membered ring are possible for 1(10)*Z*,4*Z*-germacranolides: $_{15}D_5$, $^1D^{14}$ (**a**), $_{15}D_5$, $_1D_{14}$ (**b**), $^{15}D^5$, $_1D_{14}$ (**c**), and $^{15}D^5$, $^1D^{14}$ (**d**)[3]. Optimization of the geometries of molecules **1**—**4** with the above conformations of ten-membered ring showed that all four theoretically possible conformations can exist in nonlinear *trans*-fused germacranolide **1**. The most stable is the conformer of the series **1b** in which the ring *A* has a boat-boat conformation of the type $_{15}D_5$, $_1D_{14}$ (the torsion angles in ten-membered ring are given in Table 1) (Fig. 1, *a*). This conformer is more stable than the others by 1.5—6.5 kcal mol^{-1}, and the probability of its realization is 89.9% with no account of the entropy term.

In the case of *cis*-fused rings only **c**- and **d**-conformations are realized. Of them, the conformer **2c** in which the ten-membered ring has a chair-halfchair conformation of the type $^{15}D^5$, $_1D_{14}$* is the most stable (see Fig. 1, *b*). The probability of the realization of conformation **2c** is 96.2%.

Analysis of the literature data on the crystal structures of *cis,cis*-germacranolides revealed that the ten-membered diene ring in the two non-linear *trans*-fused germacranolides studied previously (langicorine *A*[4] and melrozine *A*[5]) possessed chair—chair conformation of type $_{15}D_5$ and $^1D^{14}$ and boat-boat conformation of type $_{15}D_5$ and $_1D_{14}$ in the structure of *Z,Z*-khanfiline[6], which

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* For Part 1, see Ref. 1.

* The conformations are noted in analogy with 6-membered rings as if a bond exists between the atoms C(5) and C(10). It is necessary to note that these notations are arbitrary, because the distance C(5)...C(10) varies within the range of 3.5—5.0 Å, which substantially exceeds the C—C bond length.

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Table 1. Torsion angles (φ) in the ten-membered ring, conformational barriers (*E*), and the probability (*P*) of realization of conformers in molecules **1**—**4**

Conformer	φ/deg										*E* /kcal mol^{-1}	*P* (%)
	1—2	2—3	3—4	4—5	5—6	6—7	7—8	8—9	9—10	10—1		
1a	122	−123	67	−1	−109	143	−79	85	−97	2	26.7	6.8
1b	−129	54	33	0	−102	140	−62	−41	107	1	27.5	1.7
1c	−110	140	−53	1	−48	148	−68	−62	93	2	27.9	0.9
1d	61	60	−89	2	−46	124	−67	−67	−112	−1	28.8	0.1
1a′	96	−157	96	0	−68	113	−138	117	−71	0	28.2	0.5
1b′	−64	−44	110	−1	−100	120	−66	−47	123	2	25.2	89.9
1c′	−105	146	−85	0	21	76	−154	47	32	0	31.7	<0.1
2c	−86	89	−92	0	120	−27	−47	−39	121	3	26.4	96.2
2d	111	−42	−66	−1	122	−35	−70	115	−100	2	28.5	2.6
2c′	−115	104	−78	1	111	−41	−89	36	71	−1	29.9	0.2
2c″	−50	139	−111	−2	81	−48	−78	155	−52	2	32.8	<0.1
2d′	40	44	−126	0	103	−30	−69	145	−112	0	29.1	0.9
3a	120	−129	71	−1	−102	142	−82	90	−91	2	27.8	43.4
3b	−132	63	26	−1	−95	147	−81	−31	95	1	30.4	0.5
3c	−114	137	−48	1	−45	150	−82	−51	87	−2	31.2	0.1
3d	62	39	−124	−2	44	48	−122	114	−105	0	30.6	0.4
3a′	97	−157	96	1	−70	111	−136	119	−71	0	28.1	25.9
3b′	−65	−48	114	0	−90	117	−84	−31	112	2	28.7	9.3
3c′	−101	141	−98	0	40	51	−152	45	43	0	28.3	18.4
3d′	100	−10	−93	−2	58	56	−122	89	−88	2	29.6	2.0
4a	90	−95	91	−1	−131	59	16	52	−124	−1	25.7	95.5
4b	−113	21	67	1	−133	104	−22	−59	118	−2	30.2	<0.1
4c	−92	152	−70	1	−51	127	−33	−89	93	−2	33.2	<0.1
4a′	59	−144	101	2	−92	75	46	−143	57	−2	31.6	<0.1
4b′	−34	−51	123	−1	−111	55	44	−138	113	1	29.8	<0.1
4b″	−69	−29	108	3	−115	97	−34	−64	133	−1	27.5	4.3
4c′	−69	144	−101	−2	−23	98	−31	−110	105	−1	32.4	<0.1

agrees well with the results of the calculation. Structural data for other *Z*,*Z*-germacranolides are absent.[7]

All four canonical conformers having the conformations **a**—**d** of ring *A* are possible with different probabilities for the linear molecule **3**, while three main conformers having the conformations **a**, **b**, and **c** are possible for compound **4** (see Table 1). The prediction that conformer **4d** cannot exist is based on a probable steric repulsion of the Me-group at the atom C(10) by β-axial-directed O(1) atom of the lactone. It is worth noting that the population of the family of conformational states **a**—**d** is more uniform for molecule **3**, where conformer **3a** dominates, while conformer **4a** with a ten-membered ring in the chair-chair conformation of the type ${}_{15}D_5$, ${}^1D^{14}$ dominates (the probability of its realization equals to 95.5%) (Fig. 2). Thus, the type and

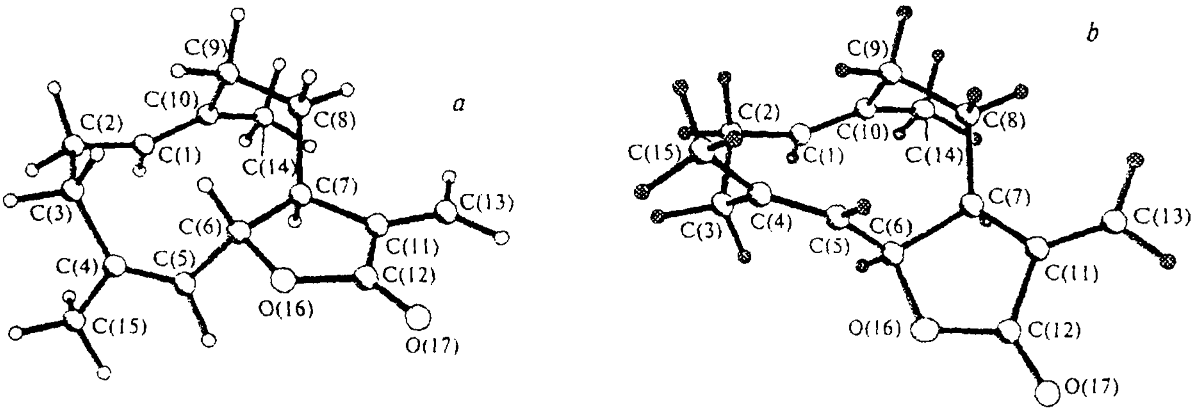

Fig. 1. The most stable conformers of molecules **1** (*a*) and **2** (*b*).

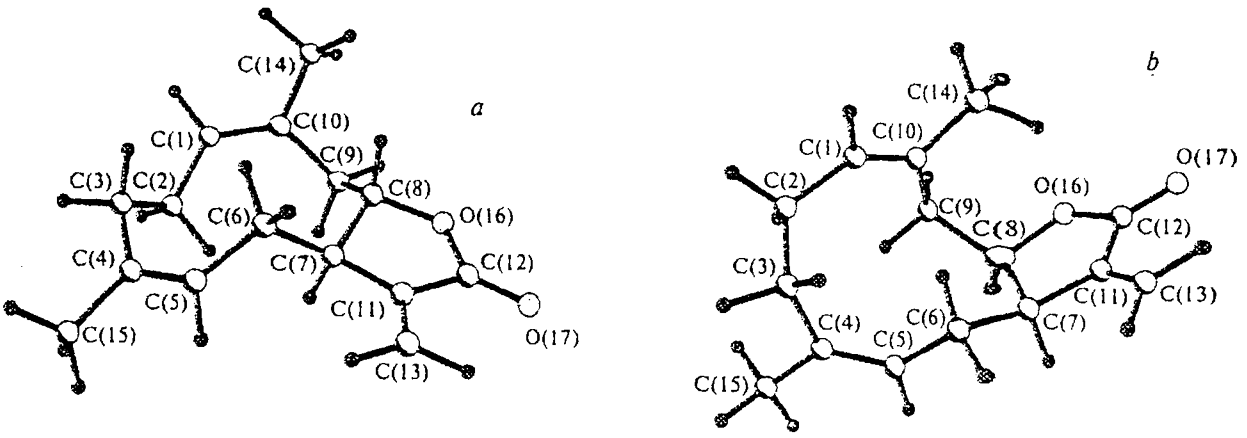

Fig. 2. The most stable conformers of molecules **3** (*a*) and **4** (*b*).

the position of fusion of ten-membered and lactone cycles play an important role in the realization of different conformers of *Z,Z*-germacranolides.

Having determined the main conformers, we considered the conformational transitions in compounds **1**—**4** and estimated their energetic barriers ($\Delta E^{\neq}$). The conformational transitions in ten-membered rings can be simulated by successive rotation of fragments containing endocyclic double bonds, C(1)=C(10) and C(4)=C(5). The optimal transition barriers were found to occur at the angles presented in Figs. 3 and 4. The variations of other torsion angles at the double bonds lead to higher values of $\Delta E^{\neq}$ or the transitions do not take place at all.

As can be seen from Figs. 3 and 4, the barriers to conformational transitions vary within wide limits: 1.7—14.8 kcal mol^{-1} for molecule **1**, 9.1—11.2 kcal mol^{-1} for **2**, 0.9—11.8 kcal mol^{-1} for **3**, and 5.9—9.2 kcal mol^{-1} for **4**. Local minima corresponding to subconformers of the main states are observed for some conformational transitions. As a rule, the probability of their realization does not exceed 2%, excluding subconformers **1b'**, **3a'**, **3b'**, **3c'**, and **4b''**, which are in-

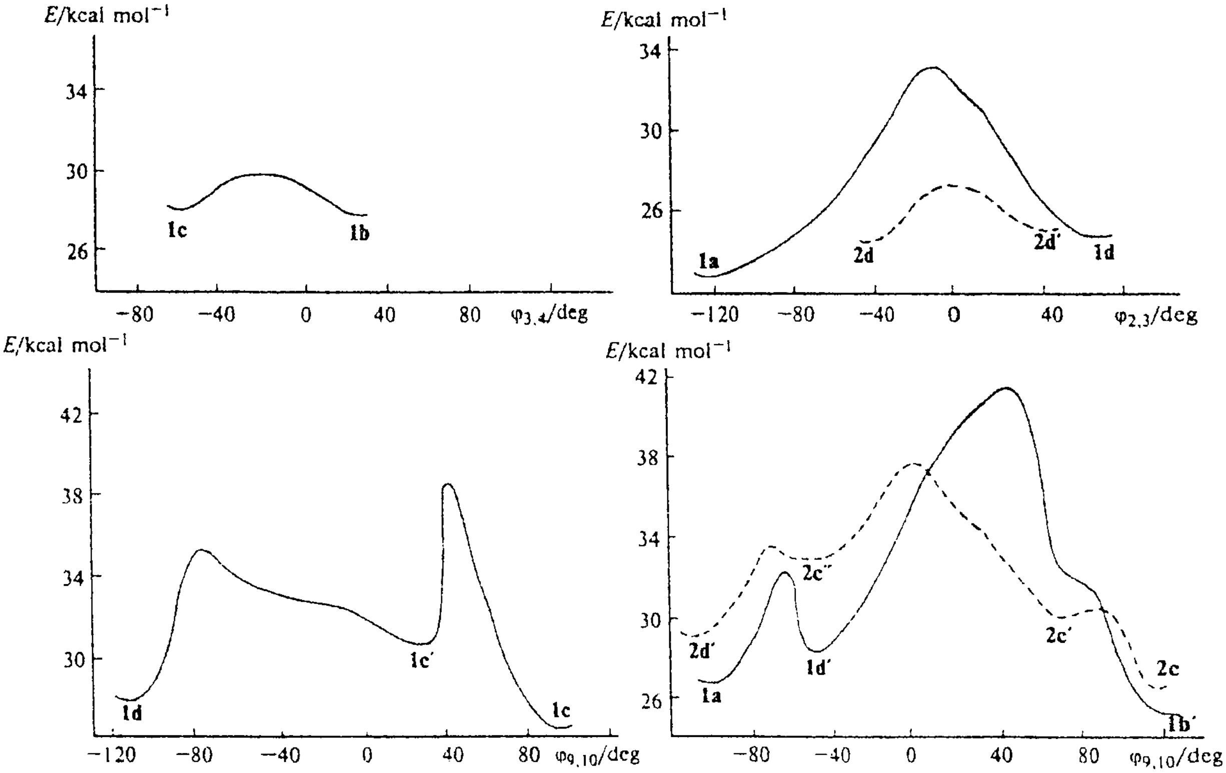

Fig. 3. Energy profiles for the conformational transitions in molecules **1** and **2**.

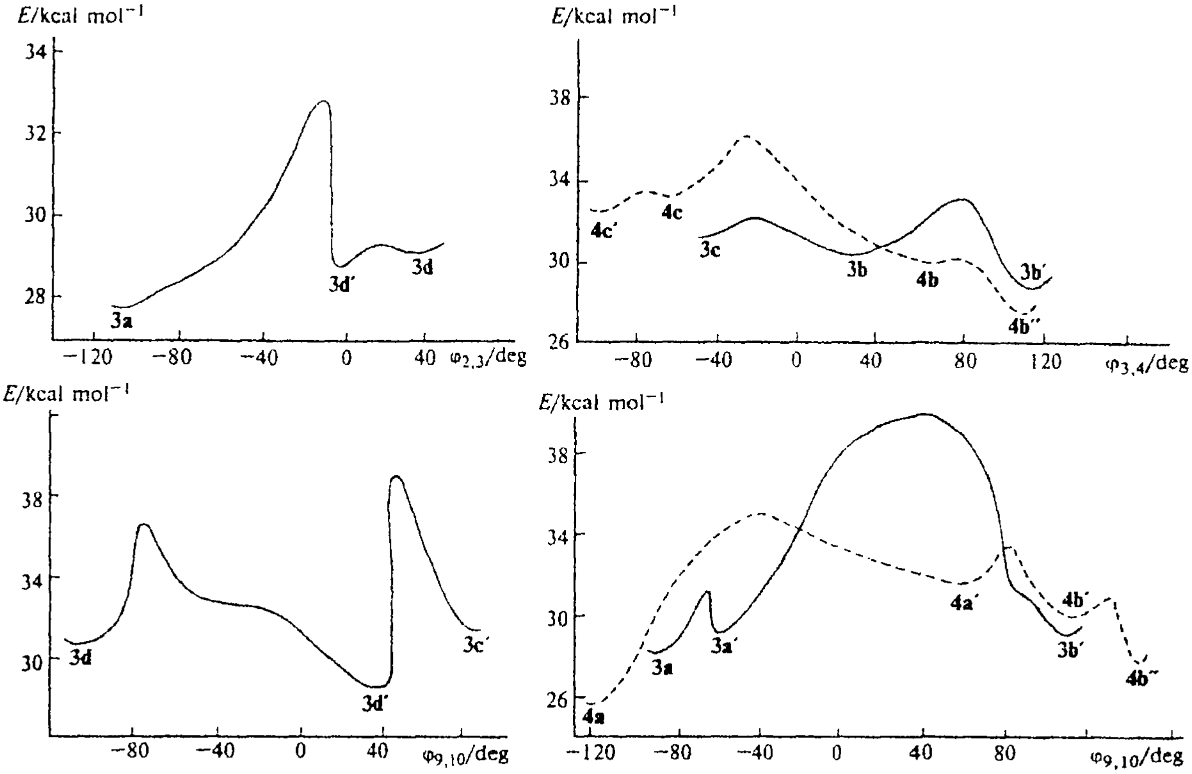

Fig. 4. Energy profiles for the conformational transitions in molecules **3** and **4**.

volved in the cycle of transitions **a**—**b**—**c**—**d**—**a**. Subconformer **1b'** is more stable than the main conformer **1b** by 1.5 kcal mol^{-1}.

To conclude, the probabilities of the realization of different conformers of linear and non-linear Z,Z-germacranolides are estimated with the use of model molecules **1**—**4**; the pathways and energies of conformational transitions are calculated in the first approximation.

References

1. K. M. Turdybekov and T. T. Edil'baeva, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 2890 [*Russ. Chem. Bull.*, 1996, **45**, 2741 (Engl. Transl.)].
2. K. M. Turdybekov, S. V. Lindeman, and Yu. T. Struchkov, *Problemy kristallokhimii* [*The Problems of Crystal Chemistry*], 1993, 118 (in Russian).
3. Z. Samek and J. Harmatha, *Collect. Czech. Chem. Commun.*, 1978, **43**, 2779.
4. A. J. Malcolm, J. F. Carpenter, F. R. Fronczek, and N. H. Fischer, *Phytochemistry*, 1983, **22**, 2759.
5. N. H. Fischer, A. J. Malcolm, E. J. Olivier, F. R. Fronczek, T. J. Delord, and S. F. Watkins, *J. Chem. Soc., Chem. Commun.*, 1982, 1243.
6. K. M. Turdybekov, N. M. Gafurov, S. I. Adekenov, and Yu. T. Struchkov, *Mendeleev Commun.*, 1994, 81.
7. *Cambridge Cristallographic Database*, Release Cambridge, 1995.

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