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CONFORMATIONAL ANALYSIS OF GERMACRANE SESQUITERPENE LACTONES. 1(10)Z,4E- AND 1(10)E,4Z-GERMACRANOLIDES

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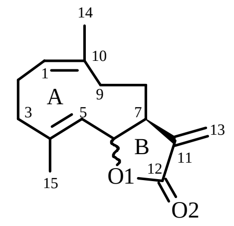
Molecular mechanics was used to study the structures of 1(10)Z,4E- and 1(10)E,4Z-germacranolides. Possible conformers, their probabilities, and barriers to conformational transitions were determined.

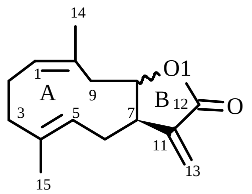
Key words: 1(10)Z,4E- and 1(10)E,4Z-germacranolides, conformational analysis.

We previously reported on the conformational analysis of *trans,trans*- and *cis,cis*-isomers of natural germacrane sesquiterpene lactones [1, 2].

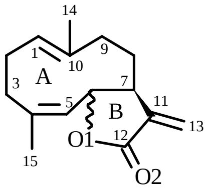
In continuation of the study of the stereochemistry of germacranolides, we performed a conformational analysis using molecular mechanics of several model *cis,trans*- (**1-4**) and *trans,cis*-isomers (**5-8**):



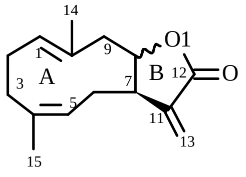
1: 6β (H); **2:** 6α (H)



3: 8β (H); **4:** 8α (H)



5: 6β (H); **6:** 6α (H)



7: 8β (H); **8:** 8α (H)

The 10-membered ring (*A*) in these compounds can 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 [3]: for Z,E-germacranolides, chair—chair $_{15}D^{5},{}^{1}D_{14}$ (**a**), boat—boat $_{15}D^{5},{}_{1}D_{14}$ (**b**), chair—boat $^{15}D_{5},{}_{1}D_{14}$ (**c**), and boat—chair $^{15}D_{5},{}^{1}D^{14}$ (**d**); for E,Z-germacranolides, boat—chair $^{14}D_{1},{}_{5}D_{15}$ (**a**), chair—chair $_{14}D^{1},{}_{5}D_{15}$ (**b**), boat—boat $_{14}D^{1},{}^{5}D^{15}$ (**c**), and chair—boat $^{14}D_{1},{}^{5}D^{15}$ (**d**).

Molecular-mechanics calculations using the program MMX86 and its standard parameters [4] showed that **1-8** adopt all four theoretically possible conformers (torsion angles in the 10-membered ring, conformational energies, and probabilities of **1-8** are listed in Table 1). The starting conformers of **1-8** were obtained from Dreiding molecular models.

For the nonlinear *A/B-trans*-fused germacranolide **1**, conformers **1b** and **1c** are most stable. In these, ring *A* adopts the chair—boat $_{15}D^{5},{}_{1}D_{14}$ and chair—boat $^{15}D_{5},{}_{1}D_{14}$ conformation, respectively. For **2** with *cis*-fusion of rings *A* and *B*, conformers **2a** and **2d** are stable. In these, the 10-membered ring adopts the chair—chair $_{15}D^{5},{}^{1}D^{14}$ and boat—chair $^{15}D_{5},{}^{1}D^{14}$ conformations, respectively. For linear **3** (*trans*-fusion of the 10-membered and lactone rings), conformer **3d** is most stable and is energetically more favorable than the others by 0.9-2.0 kcal/mol with a probability of 70.2% (not considering the entropy factor). Ring *A* in this conformer adopts the boat—chair $^{15}D_{5},{}^{1}D^{14}$ conformation. In linear **4** with *A/B-cis*-fusion, only conformer **4c** is in fact possible with the chair—boat $^{15}D_{5},{}_{1}D_{14}$ conformation of the 10-membered ring. Its probability is 98.4%.

For nonlinear *A/B-trans*-fused **5**, conformers **5a** and **5b** are most stable. Ring *A* in them adopts the boat—chair $^{14}D_{1},{}_{5}D_{15}$ and chair—chair $_{14}D^{1},{}_{5}D_{15}$ conformations, respectively. For nonlinear *A/B-cis*-fused **6**, conformer **6d** is stable. In it, ring *A* has the chair—boat $^{14}D_{1},{}^{5}D^{15}$ conformation.

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TABLE 1. Torsion Angles (φ) in 10-Membered Ring, Conformational Energy (E), and Probability (P) of Conformers of **1-8**

Conformer	φ/deg										E, kcal/mol	P, %
	1–2	**2–3**	**3–4**	**4–5**	**5–6**	**6–7**	**7–8**	**8–9**	**9–10**	**10–1**		
1a	101	-68	77	-165	56	71	-77	88	-124	2	27.9	0.6
1b	-103	50	62	-165	61	74	-67	-56	124	-1	25.6	33.2
1c	-94	71	-86	165	-121	80	-60	-53	133	2	25.2	66.1
1d	107	-46	62	164	-135	70	-71	101	-124	3	29.1	<0.1
1a′	2	51	7	-159	57	63	-76	110	-117	1	38.1	<<0.1
1c′	2	-52	-14	159	113	73	-67	-52	118	-1	33.5	<<0.1
2a	87	-87	93	-174	83	36	-82	129	-124	-2	26.6	59.7
2b	-99	44	70	-172	78	48	-59	-52	128	-2	28.1	4.5
2c	-90	66	-83	173	-106	51	-49	-47	134	1	30.7	<0.1
2d	94	-58	-67	173	-88	36	-79	143	-113	-1	26.9	35.6
2b′	-29	69	16	-167	86	28	-80	145	-96	1	32.7	<<0.1
2b′′	-115	51	70	-163	85	37	-117	42	71	-5	32.9	<<0.1
2c′	-107	70	-76	167	-86	30	-95	47	79	-3	30.4	<0.1
2c′′	2	53	-127	165	-87	35	-76	160	-109	1	33.5	<<0.1
3a	96	-76	85	-172	73	55	-91	111	-119	-1	25.2	14.9
3b	-104	47	64	-169	74	64	-81	-38	118	-1	25.3	12.6
3c	-93	66	-87	171	-109	73	-77	-30	122	2	26.3	2.2
3d	97	-57	-69	173	-102	55	-93	137	-109	-1	24.3	70.2
3b′	-20	67	12	-169	75	44	-91	138	-98	-1	31.9	<0.1
3c′	-6	-48	-14	163	-102	62	-80	-31	112	-2	31.9	<0.1
4a	95	-63	78	-171	57	51	-50	76	-129	2	30.9	<0.1
4b	-101	53	61	-171	66	58	-47	-70	126	-1	28.0	1.5
4c	-96	73	-74	170	-125	63	-40	-67	137	1	25.6	98.4
4d	106	-40	-60	167	-115	61	-42	79	-127	4	30.8	<0.1
4a′	12	43	9	-164	58	43	-43	85	-122	3	38.5	<<0.1
4a′′	-68	69	48	-165	117	-36	-34	143	-73	4	38.4	<<0.1
4c′	4	-55	-6	163	-117	55	-46	-66	120	-2	34.3	<<0.1
4c′′	76	-68	-55	164	-119	41	38	-142	60	-3	34.8	<<0.1
5a	82	57	-91	1	118	-137	82	-59	94	-173	23.9	86.8
5b	-93	64	-90	-1	128	-111	85	-51	-59	174	25.0	13.1
5c	-95	-61	103	-1	-40	-71	140	-40	-51	163	33.3	<<0.1
5d	86	-75	104	-1	-51	-72	114	-50	92	-164	32.2	<<0.1
5a′	147	-54	1	-1	104	-149	80	-58	89	-166	30.9	<0.1
5b′	-37	-27	-21	-2	123	-109	76	-53	-46	167	35.5	<<0.1
5d′	87	-67	96	1	-26	-90	47	34	34	-162	33.4	<<0.1
6a	92	50	-97	-3	119	-41	-77	62	47	-171	31.0	<0.1
6b	-97	54	-92	-5	121	-66	61	-69	-24	169	34.0	<<0.1
6c	-96	-52	108	3	-77	-31	128	-48	-55	164	30.6	<0.1
6d	93	-57	90	2	-132	34	65	-66	100	-170	25.8	91.2
6b′	-91	58	-92	-2	127	-32	-63	74	-103	169	27.8	2.9
6d′	89	-58	99	6	-70	-48	42	34	22	-161	35.7	<<0.1
6d′′	95	-57	94	4	-108	-8	95	-69	86	-170	27.4	5.8
7a	81	59	-93	-1	113	-138	91	-61	93	-172	25.4	65.9
7b	-94	63	-94	-2	125	-103	90	-59	-52	172	26.1	19.8
7c	-83	-46	97	1	-123	44	81	-62	-60	170	27.4	2.1
7d	96	-56	91	1	-124	25	80	-80	93	-169	28.5	0.3
7c′	-98	-55	108	2	-61	-52	140	-43	-53	163	29.1	0.1
7d′	90	-66	104	4	-79	-42	114	-62	82	-165	26.4	11.8
8a	72	72	-78	2	-49	137	-43	-46	104	-163	36.6	<<0.1
8b	-89	65	-98	-2	33	79	-37	-44	-26	162	33.6	<0.1
8c	-81	-54	94	2	-129	76	48	-61	-43	171	27.2	95.6
8d	92	-62	91	1	-139	60	36	-61	105	-170	29.0	4.3
8c′	-144	42	17	2	-123	73	56	-41	-57	166	36.0	<0.1
8d′	36	30	18	2	-127	61	46	-63	100	-164	36.2	<<0.1

For linear *A/B-trans*-fused **7**, conformers **7a** and **7b** are most stable. In these, the 10-membered ring adopts the boat—chair ${}^{14}D_{1},{}_{5}D_{15}$ and chair—chair ${}_{14}D^{1},{}_{5}D_{15}$ conformations, respectively. Their probabilities without considering the entropy factor are 65.9 and 19.8%, respectively. In linear *A/B-cis*-fused **8**, conformers **8c** and **8d** are the most stable. In them, the 10-membered ring adopts the boat—boat ${}_{14}D^{1},{}^{5}D^{15}$ and chair—boat ${}^{14}D_{1},{}^{5}D^{15}$ conformations, respectively.

In our opinion, the preference for one conformer or another for all model molecules is due primarily to the orientation of the lactone ring relative to the 10-membered ring. Thus, O1 of the lactone ring in conformers **1b** and **1c** of **1** and **2a** and **2d** of **2** is equatorial in contrast with the axial orientation in the others (**1a**, **1d**, **2b**, and **2c**). As a result, the nonbonding repulsion between O1 and the carbocycle atoms is significantly decreased. The greater stability of **1c**, which has 66.1% probability, compared with **1b** (ΔE = 4 kcal/mol) results from the more favorable configuration of the single bonds (ΔE = 1.0 kcal/mol).

It should be mentioned that this difference in the conformational energies is slightly compensated by the nonbonding repulsion between the C4 methyl and H6 in conformer **1c**. The C15....H6 distance calculated for **1c** is 2.76 Å whereas the sum of the van-der-Waals radii is 3.16 Å [5]. We note for comparison that the C15**....**H6 distance in **1b** is 4.2 Å. In *cis*-fused nonlinear **2**, conformer **2b** with 59.7% probability is more stable than **2a** owing to the smaller distortion of the bond angles (ΔE = 0.6 kcal/mole).

We note that linear Z,E-germacranolides, in contrast with the nonlinear ones, have the α-oriented lactone O1 in the equatorial position for *trans*-fused rings for all canonical conformers whereas the β-oriented atom for *cis*-fused rings is only axial.

For the C8-epimer **3**, the probability of four conformers is more likely compared with the corresponding conformers of model molecule **4**. This indicates that **4** is conformationally strained owing to the forced axial orientation of O1, the exception to which is conformer **4c**, the conformational energy of which is comparable to that of **3** (Table 1).

Comparison of conformers **5a** and **5b** shows that the first is more favorable than the second for all factors (ΔE_{bond} = 0.5 kcal/mol, $\Delta E_{\text{nonbond}}$ = 0.2 kcal/mol, ΔE_{tors} = 0.4 kcal/mol) and is determined by the equatorial orientation of O1. For *cis*-fused rings in **6**, conformers **6a** and **6b** have O1 axial relative to the 10-membered ring whereas **6c** and **6d** have the more energetically favorable equatorial orientation. However, conformer **6d** is more favorable (by 4.8 kcal/mol) than **6c** for all factors (ΔE_{bond} = 0.6 kcal/mol, $\Delta E_{\text{nonbond}}$ = 1.6 kcal/mol, ΔE_{tors} = 2.8 kcal/mol).

The equatorial orientation of O1 in conformers **7a** and **7b** (*trans*-fused) and **8c** and **8d** (*cis*-fused) also favors these conformers. Comparison of conformers **7a** and **7b** indicates that the first if more favorable (by 0.7 kcal/mol) than **7b** owing to the smaller distortion of the torsion angles (ΔE_{tors} = 1.4 kcal/mol) whereas **7b** has a more favorable conformation of the single bonds (ΔE_{tors} = 1.1 kcal/mol) than **7a**. In **8** with *cis*-fused C7–C8, conformer **8c** is energetically more favorable (by 1.8 kcal/mol) than **8d** owing to the more favorable conformation of the single bonds (ΔE_{tors} = 2.8 kcal/mol). However, the bond angles in **8d** are less distorted (ΔE_{bond} = 0.7 kcal/mol).

Conformational analysis of ring *A* in **1-4** indicates that the torsion angles in them are qualitatively the same for each conformer. These angles are significantly different only for the C5....C9 portion ($\Delta\varphi_{5,6}$, $\Delta\varphi_{6,7}$, $\Delta\varphi_{7,8}$, $\Delta\varphi_{8,9}$) for conformations **a**, **b**, and **c** (27, 35, 41, 53°; 12, 26, 22, 32°; and 19, 29, 37, 37°, respectively). Even greater differences of the torsion angles in this portion are found in conformer **d** ($\Delta\varphi_{5,6}$ = 47°, $\Delta\varphi_{6,7}$ = 34°, $\Delta\varphi_{7,8}$ = 51°, $\Delta\varphi_{8,9}$ = 64°). The reason for these differences is the way in which the rings are fused. Changing the fusion at the C6–C7 bond from *trans*- in **1** to *cis*- in **2** changes the intracyclic torsion angle of the lactone ring from -35 to 29°. For this, the fused torsion angle in the carbocycle should theoretically change by approximately 60°. However, the Newman projection shows that the torsion angle changes only from 71 to 36° along the C6–C7 bond in **1** and **2** (carbocycle conformation **a**) (Fig. 1a and b) because the unfavorable eclipsed configuration would be obtained if this angle were changed to 11°. The insufficient twist around this bond is redistributed along the C5–C6 and C7–C8 bonds owing to the flexibility of the 10-membered ring. In **3** and **4**, changing the O1C7C8C11 angle from 25 to -32° similarly causes the C6C7C8C9 angle to change from -91 to -50° (Fig. 1c and d). As a result, the configuration along the C7–C8 and C8–C9 bonds changes. In the same way, changing the mode of fusion causes the torsion angles in the C5...C9 portion to differ in other conformers of **1-4**.

Conformational analysis of the 10-membered ring of the E,Z-isomers has showed that nonlinear fusion of the *A* and *B* rings (**5** and **6**) retains qualitatively conformations **b** and **c** whereas the scatter of torsion angles for conformations **a** and **d** is significant ($\Delta\varphi_{6,7}$ = 96°, $\Delta\varphi_{7,8}$ = 159°, $\Delta\varphi_{8,9}$ = 121°, $\Delta\varphi_{9,10}$ = 47°; $\Delta\varphi_{5,6}$ = 81°, $\Delta\varphi_{6,7}$ = 107°, $\Delta\varphi_{7,8}$ = 49°, respectively). A similar comparison of the corresponding conformers for **7** and **8** has found that all conformations are significantly distorted.

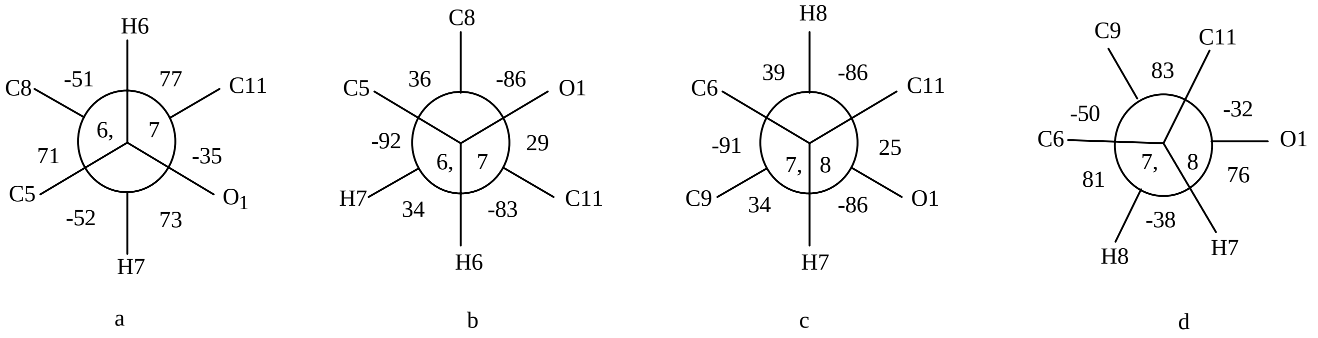

Fig. 1. Newman projection along the C6–C7 bond for **1** and **2** and C7–C8 for **3** and **4** (carbocycle conformation **a**).

A comparison of the intracyclic torsion angles with a different site but same type of *A/B* ring fusion indicates that conformations **a** and **b** in **5** and **7** with *trans*-fusion are practically the same ($\Delta\varphi_{\max} = 9^{\circ}$ and $\Delta\varphi_{\max} = 8^{\circ}$ for **a** and **b**, respectively). The scatter of torsion angles for **c** and **d** conformations of these molecules is significant for C5...C8 ($\Delta\varphi_{5,6}$ = 83 and 88, $\Delta\varphi_{6,7}$ = 115 and 132, $\Delta\varphi_{7,8}$ = 59 and 78° for **c** and **d**, respectively). Only conformation **d** does not differ qualitatively for *cis*-fusion in **6** and **8** whereas the torsion angles in **a**, **b**, and **c** are significantly different. The differences in the torsion angles in the C5....C10 portion of **6** and **8** for conformation **a** and in the C5....C8 portion for conformations **b** and **c** are large. Thus, whereas the values for conformations **b** and **c** are $\Delta\varphi_{5,6}$ = 89 and 52, $\Delta\varphi_{6,7}$ = 145 and 107, and $\Delta\varphi_{7,8}$ = 98 and 80°, respectively; the values for conformation **a** are $\Delta\varphi_{5,6}$ = 168, $\Delta\varphi_{6,7}$ = 178, $\Delta\varphi_{7,8}$ = 34, $\Delta\varphi_{8,9}$ = 108, and $\Delta\varphi_{9,10} = 57^{\circ}$. Thus, the site and type of fusion has a significant effect on the conformation of the 10-membered ring in E,Z-germacranolides.

An analysis of the literature data and our results indicates that the majority of Z,E- and E,Z-germacranolide structures have a *trans*-fused γ-lactone ring at the C6–C7 bond. Only the chair—boat $^{15}D_{5},{}_{1}D_{14}$ conformation is found for the 1,5-diene ring in the Z,E-isomers [1(10)-*cis*-costunolide [6], melampodin [7], etc.]. The same conformation is observed in subchrysin, which we studied [8]. The conformation of the 10-membered ring in E,Z-isomers is boat—chair $^{14}D_{1},{}_{5}D_{15}$ (heliangolidin [9], euparhombin [10], etc.).

This same conformation occurs in epoxides that we studied: argolide [11], deacetylajanolide A and epoxyajanolide A [12], and ketopelenolide B [13]. Structural data are lacking for *cis*-fused nonlinear Z,E- and E,Z-germacranolides [14]. Two linear Z,E-germacranolides (frutescin [15] with *trans*-fusion and schkuhriolide monohydrate [16] with *cis*-fusion) and one E,Z-germacranolide (scorpioidine with *A/B-trans*-fusion [17]) have been studied by x-ray methods. In these, the 10-membered ring adopts the boat—chair $^{15}D_{5},{}^{1}D^{14}$, chair—boat $^{15}D_{5},{}_{1}D_{14}$, and chair—boat $_{14}D^{1},{}_{5}D_{15}$ conformations, respectively. These data agree well with the results of our calculations.

Conformational transitions in **1-8** were modeled and their energy barriers were estimated after determining the principal conformers. The barriers and pathways of conformational transitions were obtained by sequential rotation around one or two of the sp^3–sp^3 or sp^3–sp^2 bonds by 5° with optimization of the molecular geometry after each step. The barriers to conformational transitions ($\Delta E^{\neq}$) vary over broad limits: from 13.0 for the **1c-1d** transition to 26.5 kcal/mol for the **1d-1c** transition of **1**, from 80.7 for **2c-2d** to 13.7 for **2a-2b** for **2**, from 10.2 for **3c-3d** to 24.4 for **3d-3c** for **3**, from 9.1 for **4a-4b** to 33.7 for **4b-4a** for **4**, from 5.8 for **5c-5b** to 19.0 for **5a-5b** for **5**, from 10.7 for **6c-6d** to 27.5 for **6b-6c** for **6**, from 3.6 for **7c-7d** and **7d-7c** to 28.4 for **7a-7d** for **7**, and from 6.8 for **8a-8d** to 25.8 for **8b-8a** for **8**.

Local minima were observed on certain pathways of conformational transitions. These corresponded to subconformers of the ground states. Their probabilities, as a rule, were <0.1%, except for subconformers **6b′**, **6d″**, and **7d′**. Subconformers **6b′** and **7d′** were more favorable than the ground conformers by 6.2 and 2.1 kcal/mol, respectively.

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