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EFFECT OF EPOXIDATION OF CARBOCYCLIC DOUBLE BONDS ON CONFORMATIONAL FLEXIBILITY OF 1(10)*E*,4*E*-GERMACRANOLIDES

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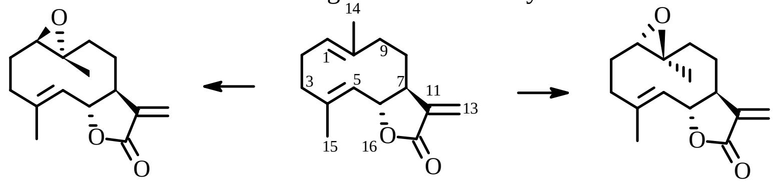
The effect of substitution of double bonds by epoxy groups in 1(10)E,4E-germacranolides is studied by molecular mechanics. The probabilities of forming conformers in the epoxy derivatives are determined. Barriers to possible conformational transitions are estimated.

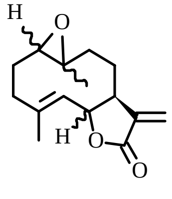
Key words: 1(10)*E*,4*E*-germacranolides, conformations, MMM.

In continuation of our studies of the stereochemistry of 1(10)*E*,4*E*-germacranolides, we examined the effect of replacing the C1=C10 and C4=C5 double bonds by epoxy groups. Epoxidation of the C1=C10 and C4=C5 double bonds in *trans,trans*-germacranolides produces asymmetric centers. For example, epoxidation of nonlinear *trans*-fused *E*,*E*-germacranolide at the C1=C10 bond can form two isomers with different configurations of the asymmetric centers.

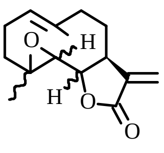


We used molecular mechanics methods (MMM) [1] to calculate the nonlinear *trans*- (**1-8**) and *cis*-fused (**9-16**) and the linear *trans*-fused (**17-24**) *E*,*E*-germacranolides.

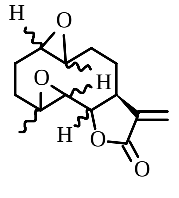
We calculated conformational energies of all four "canonical" conformers **1-24** [2] with conformations chair—chair $^{15}D_5, {}_1D^{14}$ (a), chair—boat ${}_{15}D^5, {}^1D_{14}$ (b), boat—boat ${}_{15}D^5, {}_1D^{14}$ (c), and boat—boat $^{15}D_5, {}^1D_{14}$ (d) of carbocycle *A*. After optimizing the geometries, we found that the configuration of C1,C10 and C4,C5 determined the occurrence of one conformer or another if these atoms contained an epoxy group [3]. Thus, conformers with conformations a,c and b,d can occur for 1R,10R (**1**, **9**, **17**) and 1S,10S-epoxy-*E*,*E*-germacranolides (**2**, **10**, **18**), respectively (torsion angles in the 10-membered ring and conformational energy of conformers of **1-24** are listed in Table 1). Substituting an epoxy into C4=C5 produces conformers with conformations a and d for 4R,5R- (**3**, **11**, **19**) and b and c for 4S,5S-epoxy-*E*,*E*-germacranolides (**4**, **12**, **20**). If both double bonds are epoxidized, only one of the theoretically possible conformers is possible for each stereomer (**5**, **13**, **21**, 1R,10R,4R,5R-; **6**, **14**, **22**, 1S,10S,4S,5S-; **7**, **15**, **23**, 1R,10R,4S,5S-; **8**, **16**, **24**, 1S,10S,4R,5R-configuration of the asymmetric centers) owing to the nonbonding repulsion of the rather bulky epoxy groups [4].



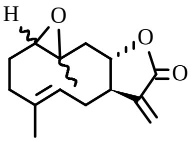
1, 2: 6β(H)
9, 10: 6α(H)



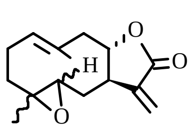
3, 4: 6β(H)
11, 12: 6α(H)



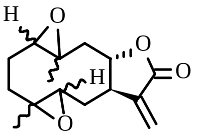
5-8: 6β(H)
13-16: 6α(H)



17, 18: 8β(H)



19, 20: 8β(H)



21- 24: 8β(H)

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TABLE 1. Torsion Angles (φ) in 10-Membered Ring and Conformational Energy (*E*) of Conformers **1-24**

Conformer	φ, deg										*E*, kcal/mol
	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	1-10	
1a	-95	54	-83	169	-142	82	-78	75	-117	158	27.5
1c	-110	32	53	-170	63	80	-92	69	-108	154	30.7
2b	103	-53	84	-169	60	80	-58	-50	123	-145	29.5
2d	80	18	-91	168	-123	76	-106	59	64	-162	34.9
2d′	113	-28	-62	170	-111	73	-113	52	70	-152	35.5
3a	-106	51	-85	149	-136	91	-75	71	-115	174	28.1
3d	75	33	-95	147	-119	84	-102	61	62	-176	30.4
4b	119	-45	92	-148	64	68	-129	48	55	-171	32.0
4c	-77	-29	92	-151	71	72	-107	61	-96	175	31.3
4c′	-73	-36	89	-145	57	78	-38	-44	-20	167	34.0
5a	-102	58	-85	151	-138	90	-76	77	-117	159	32.4
6b	115	-53	92	-149	64	70	-135	52	51	-156	37.9
7c	-79	-21	90	-153	71	73	-110	67	-95	162	36.8
8d	76	27	-94	149	-119	84	-106	63	59	-163	37.9
9a	-96	53	-85	179	-126	53	-75	92	-121	152	32.4
9c	-77	-23	94	-173	101	40	-93	86	-104	157	31.3
9c′	-110	30	59	-177	87	47	-85	89	-114	148	32.7
10b	92	-54	86	-174	111	30	-97	54	77	-158	30.4
10d	106	-34	-56	174	-90	38	-98	62	73	-150	33.6
11a	-103	46	-86	163	-117	61	-75	86	-117	170	34.1
11d	75	31	-93	156	-108	55	-94	73	56	-173	32.8
11a′	-110	44	-87	161	-110	61	-82	91	-108	-169	33.9
12b	108	-51	86	-155	101	29	-105	55	68	-171	30.3
12c	-75	-38	91	-151	100	39	-98	75	-96	174	29.3
13a	-103	51	-89	168	-107	53	-83	107	-112	149	37.6
14b	97	-60	85	-159	109	26	-98	50	80	-159	35.7
15c	-76	-34	91	-154	103	37	-99	82	-95	161	34.7
16d	77	16	-91	161	-100	52	-100	75	60	-159	40.3
17a	-97	52	-85	175	-133	73	-88	86	-112	154	26.6
17c	-78	-22	94	-172	85	61	-109	77	-96	158	27.5
17c′	-113	31	54	174	77	65	-100	81	-104	150	28.3
18b	99	-49	89	-174	88	50	-116	55	66	-157	28.2
18d	80	14	-92	173	-114	64	-110	68	62	-158	30.2
18d′	112	-34	-54	-179	-108	58	-113	61	68	-150	29.5
19a	-111	46	-88	155	-121	84	-92	84	-104	171	28.2
19d	74	31	-95	153	-114	73	-106	68	62	-173	27.4
20b	116	-47	90	-154	78	53	-124	53	59	-172	26.9
20c	-75	-37	93	-151	85	58	-112	70	-92	173	25.8
21a	-104	54	-87	159	-124	79	-90	90	-109	156	32.8
22b	111	-54	90	-155	77	54	-128	56	58	-156	32.9
23c	-76	-31	93	-154	86	57	-113	75	-91	160	31.3
24d	75	23	-95	156	-110	72	-111	70	62	-159	34.5

Comparison of the corresponding intracyclic torsion angles of nonlinear *E*,*E*-germacranolides [5] and epoxy-substituted *E*,*E*-germacranolides showed that epoxidation of the double bond decreases the torsion angle around this bond and increases the torsion angle around the unsubstituted double bond. Thus, torsion angle C2C1C10C9 decreases by 6° and C3C4C5C6 increases by 13° for nonlinear *trans*-fused germacranolide with the ${}^{15}D_{5,1}D^{14}$ chair—chair conformation of the 10-membered ring and C1–C10 epoxidation (conformer **1a**). For conformer **3a**, 4α,5β-epoxy-substituted germacranolide, torsion angle C2C1C10C9 increases by 10° whereas C3C4C5C6 decreases by 7°. Substituting both double bonds in **5a** with 1β,10α;4α,5β-oriented epoxy groups decreases the torsion angles around the substituted bonds by 5°. In general, the corresponding conformers are not significantly distorted.

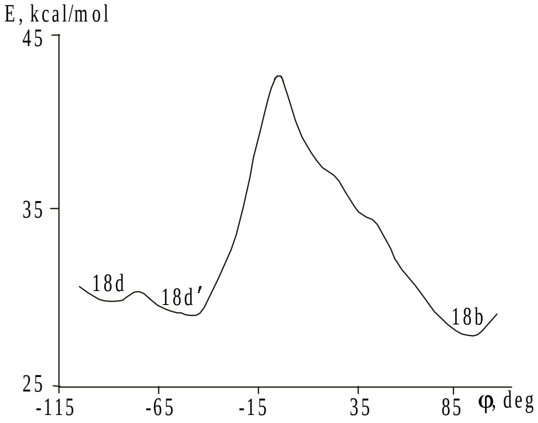

Fig. 1. Conformational pathway of molecule **18**.

Comparison of the conformational energies of epoxy-substituted and 1(10)*E*,4*E*-germacranolides [5] revealed that they are increased by 0.3-7.8 kcal/mol. The highest conformational energies are observed for 1,10;4,5-epoxy derivatives (ΔE = 5.3-7.8 kcal/mol). This is due to the presence of two epoxy groups in the 10-membered ring.

Crystal structures in the literature for *trans*,*trans*-germacranolides show that an epoxy bridge on the C1=C10 bond occurs in the structures of herbolide B [6] and 8β-(2′R,3′S-3′-chloro-2′-hydroxy-2′-methylbutyryloxy)-14-acetoxytithifoline [7]. X-ray structure studies of parthenolide [8, 9] and eupahyssopin diacetate [10] show that the C4–C5 bond is epoxidized. In cordifolia-P2 [11] and (8S)-methacryloxy-1,10;4,5-diepoxycostunolide [12], two epoxy bridges are situated on the C1–C10 and C4–C5 bonds. The epoxys in these molecules have the 1β,10α-, 4α,5β-, and 1β,10α;4α,5β-orientations, respectively. The 10-membered ring in these compounds adopts the $^{15}D_{5},{}_{1}D^{14}$ chair—chair conformation. Comparison of the torsion angles in ring *A* of these compounds and conformers **1a**, **3a**, and **5a**, for which the asymmetric centers have the same configuration, showed that the calculated and experimental values are in excellent agreement ($\Delta\varphi < 17°$). The conformation of ring *A* is significantly distorted from that calculated only for cordifolia-P2 ($\Delta\varphi$ changes from 2 to 46°). In this structure the 10-membered ring has a different conformation that is only qualitatively similar to conformation a.

Crystal structures of nonlinear *cis*-fused epoxy-substituted *E*,*E*-germacranolides have not been reported [13].

According to x-ray structural data and NMR spectroscopy, 10-membered lactone rings in linear *E*,*E*-germacranolides are only *trans*-fused. The chair—chair $^{15}D_{5},{}_{1}D^{14}$ conformation of carbocycle *A* occurs in 1β,10α;4α,5β-diepoxy-*E*,*E*-germacranolides (1β,10α,4α,5β-diepoxy-8β-hydroxyglechoman-8α,12-olide [14], 11,13-dihydroerioline [15], ivaxillin [16], 6α-acetoxy-13-methoxy-1(10),4(5)-diepoxy-1,5,7αH,8,11βH-*E*,*E*-germacr-8,12-olide [17]). The 10-membered ring in known 1β,10α- (pyrethrosin [18]) and 1α,10β-epoxy-*E*,*E*-germacranolides (mucrin [19]) adopts the chair—chair $^{15}D_{5},{}_{1}D^{14}$ and boat—boat $^{15}D_{5},{}^{1}D_{14}$ conformations, respectively. An x-ray structural study of spiciformin acetate [20], a 4β,5α-epoxy derivative, showed that ring *A* has the chair—boat $_{15}D^{5},{}^{1}D_{14}$ conformation. MMM calculations and experimental data are in good agreement.

Conformational transitions in compounds **1-4**, **9-11**, and **17-20** were modeled after the principal conformers were determined. Their energy barriers were estimated qualitatively. It was found that transitions from one conformational state to another are possible for all studied conformers. The heights of the conformational barriers change over rather wide limits, from 10.0 kcal/mol for the 4b↔4c transition of molecule **4** to 17.2 kcal/mol for the 2b↔2d transition of molecule **2**. The fact that barriers to conformational transitions (ΔE) are equal or slightly below these values for previously studied "ideal" model molecules is especially interesting.

Local minima corresponding to subconformers of the ground states are observed on some pathways of conformational transitions. The conformational energies of these subconformers is slightly greater than for the corresponding base conformers. The exception is subconformer **18d′** (Fig. 1), which belongs to the family of conformers with the boat—boat $^{15}D_{5},{}^{1}D_{14}$ conformation of the 10-membered ring, which was observed in mucrin [19]. The conformational energy of the subconformer is 0.7 kcal/mol less than that of **18d**. Comparison of conformers **18d** and **18d′** showed that the second is energetically more favorable than the first owing to a more favorable conformation of the single bonds (ΔE_{tors} = 0.8 kcal/mol).

Thus, epoxidation of one or two double bonds in *E*,*E*-germacranolides decreases the conformational flexibility of the 10-membered ring. The configuration of the epoxy group plays a definite role in the occurrence of one conformer or another, i.e., it is a conformational "anchor." This effect may be used to stabilize the conformation of the 10-membered ring in germacranolides during preparation of new compounds with given conformational characteristics.

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