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POSSIBLE CONFORMATIONS AND RELATIVE STABILITY OF THE 7-MEMBERED RING IN 1α,5β,6,7α(H)- AND 1β,5α,6,7α(H)-GUAI-11(13)-EN-6,12-OLIDES

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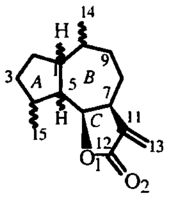
Stereoisomers of 1α,5β,6,7α(H)- and 1β,5α,6,7α(H)-guai-11(13)-en-6,12-olides are calculated using molecular mechanics. The possibility of forming various conformations in the 7-membered ring is examined as a function of the fusion to the 5-membered C-ring. The effect of the methyl orientation on the conformation of the 7-membered ring and the relative stability of the conformers are discussed.

Key words: guaianolides, conformers, conformation of 7-membered ring.

In continuation of conformational studies of sesquiterpene lactones, the structures of *trans*- and *cis*-fused nonlinear guaianolides are calculated by molecular mechanics (MM) in order to determine the possibility of forming various conformations of the 7-membered C-ring and the relative stability of the conformers with various (α- or β-) orientations of the methyls on C4 and C10.

Eight model compounds (**1-8**) with various configurations at chiral atoms C1, C4, C5, and C10 and *cis*-fusion of rings *B* and *C* were selected for the calculation. A preliminary examination of conformations of **1-8** using Dreiding molecular models showed that the 7-membered ring in **1-4** can adopt four chair [6,7α,10β-*C* (*a*), 1α,7,8β-*C* (*b*), 6α,9,10β-*C* (*c*), 1,10α,7β-*C* (*d*)] and two boat [5,8,9β-*B* (*e*) and 7,10,1α-*B* (*f*)] conformations. The 7-membered ring in **5-8** can adopt four chair [10α,6,7β-*C* (*g*), 9,10α,6β-*C* (*h*), 7α,1,10β-*C* (*i*), 7,8α,1β-*C* (*j*)] and four boat [7,1,10β-*B* (*k*), 6,7,10β-*B* (*l*), 5,8,9α-*B* (*m*), 6,9,10α-*B* (*n*)] conformations.



1: 1α, 5β, 14α, 15α
2: 1α, 5β, 14β, 15α
3: 1α, 5β, 14β, 15β
4: 1α, 5β, 14α, 15β

5: 1β, 5α, 14α, 15α
6: 1β, 5α, 14β, 15α
7: 1β, 5α, 14β, 15β
8: 1β, 5α, 14α, 15β

After optimizing the geometries of the six starting idealized conformers *a-f* of **1-4**, it turned out that only four conformers of isomers **2** and **3** are stable. The methyl on C14 in these has the β-orientation. Five conformers are stable for **1** and **4**. These have the C14 methyl with the α-orientation. Conformer *a* of ring *B* is only slightly distorted from the ideal transition to 6,7α,10β-*C* (**1a-4a**). The different orientation of the methyl in **1-4** causes different conformational distortions of the ring from the ideal *C*. Thus, a comparison of torsion angles in ring *B* for **1a-4a** (Table 1) shows that the ring is slightly distorted from ideal 6,7α,10β-*C* [$S_2/(S_S + S_2) = 0.9$, $\Delta C_S^{10} = 4.4$ and 2.4° in **1a** and **4a**, respectively] if the C14 methyl has the α-orientation. If it has the β-orientation, the distortion increases significantly [$S_2/(S_S + S_2) = 0.8$ and 0.5, $\Delta C_S^{10} = 7.9$ and 17.9° for **2a** and **3a**, respectively].

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TABLE 1. Torsion Angles and Ring *B* Conformers in **1**-**4** and Their Conformational Energy *E*

Conformation	Bond angle							*E*, kcal/mol
	C1-C5	C5-C6	C6-C7	C7-C8	C8-C9	C9-C10	C10-C11	
6,7α,10β-*C* (**1a**)	-83	64	5	-71	85	-60	60	33.0
1,5α,10,9β-*TC* (**1b**)	-76	79	-23	-52	90	-69	55	32.4
7,8α,5,6β-*TC* (**1c**)	-94	61	-40	60	88	40	46	34.5
5,8,9β-*B* (**1d**)	-64	65	20	-64	4	59	-21	39.8
8,9α,,1,10β-*TB* (**1e**)	-83	48	38	-52	-24	58	10	38.9
6,7α,10β-*C* (**2a**)	-89	62	9	-72	82	-60	66	34.3
1,5α,10,9β-*TC* (**2b**)	-70	75	-24	-49	90	-70	54	36.2
7,8α,5,6β-*TC* (**2c**)	-93	61	-39	60	-89	40	45	35.4
5,8,9β-*TB* (**2d**)	-58	64	22	-68	4	67	-32	36.7
6,7α,10β-*C* (**3a**)	-92	54	20	-79	78	-56	69	32.2
1,5α,10,9β-*TC* (**3b**)	-77	79	-24	-50	89	-68	56	33.3
7,8α,5,6β-*TC* (**3c**)	-91	62	-38	61	-89	42	42	33.9
5,8,9β-T*B* (**3d**)	-61	64	23	-67	2	67	-29	35.5
6,7α,10β-*C* (**4a**)	-86	65	2	-69	85	-63	64	30.9
1,5α,10,9β-*TC* (**4b**)	-78	81	-24	-51	90	-70	-57	31.0
7,8α,5,6β-*TC* (**4c**)	-91	63	-38	61	-89	41	43	33.0
5,8,9β-*B* (**4d**)	-72	60	27	-60	-8	60	-11	38.2
8,9α,,1,10β-*TB* (**4e**)	-74	53	33	-55	-19	63	-5	38.1

The effect of the β-orientation of the methyl on the conformation of ring *B* is apparent in the significant difference of the corresponding torsion angles ($\Delta\varphi$), reaching 6 and 2°, respectively.

Conformer *b* of ring *B* after optimization is intermediate between 1,5α,9,10β-*TC* and 6,7α,10β-*C* (**1b**-**4b**) [$\Delta C_2^7 = 18.4$, 16.8, 16.9, and 17.1°; $\Delta C_S^{10} = 19.3$, 21.1, 19.4, and 20.1°; $(\Sigma_2/(\Sigma_S + \Sigma_2) = 0.4$, 0.3, 0.4, and 0.4, respectively]. The average scatter in the value of the torsion angles is 1-2° (Table 1). This indicates that the methyl orientation has little influence on the distortion of ring *B* from the ideal *TC*.

Optimization of two starting conformers (*c* and *d*) gives almost ideal 7,8αα,5,6 β-*TC* (**1c**-**4c**) [$\Delta C_2^{10} = 4.9$, 3.7, 1.3, and 2.0°, $\Sigma_2/(\Sigma_S + \Sigma_2) \leq 0.1$, respectively]. The methyl orientation also has little effect on the distortion of ring *B* from ideal *TC*, $\Delta\varphi \leq 1°$ for **1c** and **2c**, **3c** and **4c**. However, $\Delta\varphi = 1\text{-}3°$ for **1c** and **4c**, **2c** and **3c**, which suggests that the effect of the C14 methyl is greater than that of the C15 methyl.

The boat conformers *e* and *f* of **2** and **3**, which have the β-orientation of the C14 methyl, after optimization convert to 5,8,9β-*B* (**2d** and **3d**) [$\Delta C_S^5 = 6.8$ and 3.9°, $\Sigma_2/(\Sigma_S + \Sigma_2) = 0.8$ and 0.9, respectively]. For isomers **1** and **4**, which have the α-orientation of the C14 methyl, conformer *e* is retained (**1d** and **4d**) [$\Delta C_S^5 = 3.0$ and 11.5°, $\Sigma_2/(\Sigma_S + \Sigma_2) = 0.9$ and 0.8, respectively]. However, conformer *f* changes to 8,9α,1,10β-*TB* (**1e** and **4e**) [$\Delta C_2^6 = 20.5$ and 17.9°, $\Sigma_2/(\Sigma_S + \Sigma_2) = 0.3$, respectively], where **1d** is less stable than **1e** by 1.1 kcal/mol whereas **4d** and **4e** are equally probable.

The conformational energies (*E*) of the *C*- and two *TC*-conformers of **1**-**4** indicate that conformers **3a** and **4a** are more stable and **3b** and **4b** are less stable for **3** and **4**, which have the C15 methyl in the β-orientation ($\Delta E = 1.1$ and 0.1 kcal/mol) whereas **3c** and **4c** are much less stable ($\Delta E = 1.7$ and 2.1 kcal/mol). It is noteworthy that conformers **4a** and **4b** are practically equally probable.

Conformer **2a** is also more favorable for **2** than **2b** and **2c** by 1.9 and 1.1 kcal/mol. Conformer **2c** is more stable than **2b** ($\Delta E = 0.8$ kcal/mol).

The most favorable isomer of **1** is **1b**; **1a** and **1c** are less stable ($\Delta E = 0.6$ and 2.1 kcal/mol).

The significant ΔE between stable conformers *C* and *TC* and less stable *B* for the boat conformers **1d**-**4d** suggests that the last is improbable (for **1**-**4** $\Delta E = 7.4$, 3.4, 3.3, and 6.3 kcal/mol, respectively, see Table 1).

A comparison of the conformations of the 7-membered ring calculated by MM for **1**-**4** with the experimental x-ray data indicates that ring *B* in the crystals adopts the 6,7α,10β-*C* conformation in partenin (**9**) [1] or damsin (**10**) [2], 1,5α,9,

TABLE 2. Torsion Angles and Ring *B* Conformers in **5**-**8** and Their Conformational Energy *E*

Conformation	Bond angle							*E*, kcal/mol
	C1-C5	C5-C6	C6-C7	C7-C8	C8-C9	C9-C10	C10-C11	
10α,6,7β-*C* (**5a**)	79	-70	12	57	-87	66	-60	34.3
5,6α,7,8β-*TC* (**5b**)	93	-60	36	-62	89	-37	-48	33.7
10α,6,7β-*C* (**5c**)	89	-63	-5	67	-81	61	-67	33.6
6,7α,8,9β-*TB* (**5d**)	60	-66	-18	61	-1	-65	28	37.4
5,6α,7,8β-*TB* (**5e**)	61	15	-36	-31	86	-33	-57	40.5
10α,6,7β-*C* (**6a**)	80	-70	9	59	-87	67	-61	31.8
5,6α,7,8β-*TC* (**6b**)	91	-60	36	-61	91	-41	-43	32.6
1,5α,7,8β-*TC* (**6c**)	76	-77	20	52	-86	68	-57	31.8
5,6α,1,10β-*TB* (**6d**)	84	-39	-36	30	45	-57	-21	40.0
5,6α,7,8β-*TB* (**6e**)	69	4	-32	-28	88	-39	-53	39.4
10α,6,7β-*C* (**7a**)	88	-65	-1	66	-82	63	-67	33.1
5,6α,7,8β-*TC* (**7b**)	90	-63	39	-64	91	-41	-41	35.0
1,5α,7,8β-*TC* (**7c**)	76	-78	22	50	-88	68	-55	33.6
5,6α,1,10β-*TB* (**7d**)	88	-43	-33	32	41	-54	-23	41.5
6,9α,10α-*B* (**7e**)	42	33	-23	-51	62	19	-84	43.5
10α,6,7β-*C* (**8a**)	87	-64	0	65	-82	62	-66	35.4
5,6α,7,8β-*TC* (**8b**)	92	-61	39	-65	89	-36	-47	36.2
10α,6,7β-*C* (**8c**)	82	-74	15	54	-85	67	-61	36.0
6,7α,8,9β-*TB* (**8d**)	58	-66	-17	61	-2	-65	30	39.1
6,9α,10α-*B* (**8e**)	46	30	-31	-44	80	-11	-67	44.9

10β-*TC* in 1αH,5βH,6αH,7αH,8α-angeloyloxy-10β-acetoxyguaian-6,12-olide (**11**) [3] or guaianolide (**12**) [4], or 7,8α,5,6β-*TC* in confertiflorin (**13**) [5]. This confirms our calculations.

Optimization of the eight initial idealized conformers *g*-*n* for **5**-**8** shows that ring *B* adopts only five conformations. The *g*-conformation of ring *B* is retained in the first (**5a**-**8a**). The torsion angles indicate that ring *B* in the C4 epimers **5a** and **4a**, in which the methyl has the α-orientation, is more distorted from ideal *C* [$\Sigma_2/(\Sigma_S + \Sigma_2) = 0.7$ and $\Delta C_S^2 = 9.5$ and 8.3°] whereas the ring is almost ideal *C* in isomers **7a** and **8a** with the β-orientation [$\Sigma_2/(\Sigma_S + \Sigma_2) = 0.9$ and $\Delta C_S^2 = 4.2$ and 3.7°] (Table 2).

The effect of the C15 methyl on the ring *B* conformation is apparent in the significant difference of the corresponding torsion angle of the C4 epimers (**5a** and **8a**, **6a** and **7a**). The average scatter of the torsion angles ($\Delta\varphi$) reaches 6-7° whereas the C14 methyl orientation has little effect ($\Delta\varphi = 1$-3°) (Table 2).

A different conformation of ring *B* is obtained after optimizing the two initial conformers *h* and *i*, 5,6α,7,8β-*TC* (**5b**-**8b**) [$\Delta C_2^{10} = 5.8$, 1.4, 0.8, and 7.0° and $\Sigma_2/(\Sigma_S + \Sigma_2) \le 0.1$, respectively]. The corresponding torsion angles of **5b**-**8b** indicate that the methyl orientation does not affect the distortion of ring *B* from ideal *TC* ($\Delta\varphi$ for **5b** and **6b**, **7b** and **8b**, **6b** and **7b**, and **5b** and **8b** is 1-2°) (Table 2).

Conformation *j* becomes intermediate between 1,5α,9,10β-*TC* and 10α,6,7β-*C*. The different methyl orientation affects the distortion of ring *B* from ideal *TC* and *C*. Thus, the conformation of ring *B* in isomers **6** and **7**, where the C14 methyl has the β-orientation, deviates toward 1,5α,9,10β-*TC* (**6c** and **7c**) [$\Delta C_2^7 = 19.7$ and 17.8°, $\Delta C_S^{10} = 16.8$ and 18.4°, $\Sigma_2/(\Sigma_S + \Sigma_2) = 0.4$, respectively] whereas in isomers **5** and **8**, where the C14 methyl has the α-orientation, ring *B* deviates toward 10α,6,7β-*C* (**5c** and **8c**) [$\Delta C_S^{10} = 6.2$ and 12.2° and $\Sigma_2/(\Sigma_S + \Sigma_2) = 0.8$ and 0.6, respectively].

For **5** and **8**, with the α-orientation for the C14 methyl, the boat conformers (*k*, *l*, and *m*) after optimization convert to 6,7α,8,9β-*TC* (**5d** and **8d**) [$\Delta C_2^1 = 20.9$ and 18.3° and $\Sigma_2/(\Sigma_S + \Sigma_2) = 0.3$, respectively].

For isomers **6** and **7**, which have the β-orientation of the C14 methyl, conformers *k* and *m* become intermediate between 5,6α,1,10β-*TB* and 7,1,10β-*B* (**6d** and **7d**) [$\Delta C_2^8 = 17.1$ and 15.5°, $\Delta C_S^7 = 16.3$ and 19.7°, $\Sigma_2/(\Sigma_S + \Sigma_2) = 0.5$, respectively] whereas conformer *l* optimizes to 10α,6,7β-*C* (**6a** and **7a**).

For isomers **7** and **8**, which have the β-orientation of the C15 methyl, conformation *n* of ring *B* is slightly distorted from

6,9,10α-*B* (**7e** and **8e**) [$\Delta C_S^6 = 14.9$ and 7.6° and $\Sigma_2/(\Sigma_S + \Sigma_2) = 0.6$ and 0.8, respectively]. However, isomers **5** and **6**, with the α-orientation of the C15 methyl, change after optimization to 5,6α,7,8β-*TB* (**5e**-**6e**) [$\Delta C_2^{10} = 22.0$ and 19.4 and $\Sigma_2/(\Sigma_S + \Sigma_2) = 0.4$ and 0.3, respectively]. The conformational energies (*E*) of the *C*- and *TC*-conformers of **5**-**8** indicate that ΔE for the three (*a*, *b*, and *c*) conformers in **5**, **6**, and **8** are small at 0.7, 0.8, and 0.8 kcal/mol, respectively (see Table 2). For isomer **7**, with the β-orientation of the C14 and C15 methyls, conformers **7a** and **7c** are practically equally probable ($\Delta E = 0.5$ kcal/mol) whereas **7b** is less stable than **7a** by 1.9 kcal/mol.

The significant ΔE for boat conformers **5d**-**8d** and **5e**-**8e** between the more (*C*- and *TC*-) and less stable (*TB*- and *B*-) suggests that the last ones are less probable (for **5**-**8** $\Delta E_1 = 3.8$, 8.2, 8.4, and 3.7 kcal/mol and $\Delta E_2 = 6.9$, 7.6, 10.8, and 9.5 kcal/mol, respectively, see Table 2).

The results from the MM calculations of the conformations of **5**-**8** and the experimental x-ray structures for stramonin-B (**14**) [6] and ambrosin (**15**) [2] indicate that the conformation of ring *B* in these compounds is 5,6α,7,8β-*TC* and agrees with one of those calculated for model isomers **5**-**8**.

The calculations were performed on a PC Pentium using MMX-86 program with full optimization of the molecular geometry.

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