POSSIBLE CONFORMATIONS OF THE SEVEN-MEMBERED
RINGS AND RELATIVE STABILITIES OF THE C10
EPIMERS OF *trans,trans-*, *trans,cis-*, and *cis,trans-*
LINKED PSEUDOGUAI-11(13)-EN-8,12-OLIDES

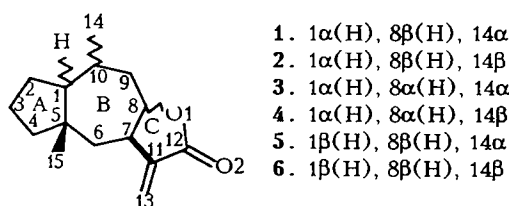K. M. Turdybekov   UDC 547.1'3

A calculation has been made by the molecular mechanics method of the C10-epimers of trans,trans-, trans,cis-, *and* cis,trans-*linked pseudoguai-11(13)-en-8,12-olides. Possible conformations in these compounds and probabilities of their realization have been determined.*

We have previously reported on the analysis by the method of molecular mechanics (MMM) of the spatial structures and conformations of 6,7-linked *trans,trans-* and *cis,trans-*linked guaianolides [1]. Continuing the conformational analysis of sesquiterpene lactones, in the present paper we give the results of a MMM calculation of *trans,trans-*, *trans,cis-*, and *cis,trans-*linked pseudoguaianolides with the aim of finding the possibilities of realization of particular conformers as a function of the type of linkage of the rings and their relative stabilities.

For the calculation we selected compounds (1-6) with different conformations of the chiral centers — the C1, C8, and C10 atoms — modelling the types of skeletons of linear pseudoguaianolides, the molecules of (1) and (2), of (3) and (4), and of (5) and (6) being C10-epimers.

The main canonical forms of the seven-membered rings of the (1-6) molecules were determined from Dreiding molecular models. It was found that in each of the *trans,trans-*linked compounds (1) and (2) the seven-membered ring may assume the conformations $9\alpha,5,6\beta$-C (a), $6,7\alpha,10\beta$-C (b), $5,8,9\beta$-B (c), and $6,7,10\alpha$-B (d), in each of the *trans,cis-*linked compounds (3) and (4) the conformations $1\alpha,7,8\beta$-C (e), $1,10\alpha,7\beta$-C (f), $1,7,8\alpha$-B (g), and $1,7,10\alpha$-B (h), and in each of the *cis,trans-*linked compounds (5) and (6) the conformations $1,5\alpha,8\beta$-C (i), $5\alpha,8,9\beta$-C (j), $6,7,10\alpha$-B (k), $5,8,9\beta$-B (*l*), and $1,5,8\beta$-B (m).

1. $1\alpha(H)$, $8\beta(H)$, 14α
2. $1\alpha(H)$, $8\beta(H)$, 14β
3. $1\alpha(H)$, $8\alpha(H)$, 14α
4. $1\alpha(H)$, $8\alpha(H)$, 14β
5. $1\beta(H)$, $8\beta(H)$, 14α
6. $1\beta(H)$, $8\beta(H)$, 14β

After optimization of the geometries of the four initial conformers of molecules (1) and (2) with conformations a–d of the seven-membered ring (below, 1a, 2a, etc., for brevity), it was established that in (1) they all pass into the stable conformer 1A, intermediate between $1,10\alpha,8,9\beta$-TC and $9\alpha,5,6\beta$-C ($\Delta C_2^6 = 22.5°$, $\Delta C_s^9 = 20.8°$, $\Sigma_2/(\Sigma_s + \Sigma_2) = 0.5$). In the case of the (2) molecule, conformers 2a and 2b pass into the form 2A, which has almost the same conformation of ring B as 1A ($\Delta C_s^9 = 18.2°$, $\Delta C_2^6 = 29.4°$, $\Sigma_2/(\Sigma_s + \Sigma_2) = 0.5$) (the torsional angles are given in Table 1). On optimization, conformers 2c and 2d pass into form 2B, in which ring B assumes the conformation of a flattened $1,10\alpha,9\beta$-TB considerably

TABLE 1. Torsional Angles (degrees) in Ring B, Conformational Energies E (kcal/mole), and Probabilities of Realization P (%) of Molecules (1-6)

Conformer	Bond angle							E	P
	1–5	5–6	6–7	7–8	8–9	9–10	1–10		
1 A	−77	19	54	−94	71	−53	73	35.4	100.0
2 A	−72	11	57	−94	72	−54	73	39.4	99.99
2 B	−65	35	54	−81	2	50	−4	45.2	0.01
3 A	−70	79	−50	−14	69	−78	67	37.1	8.27
3 B	−84	62	−40	56	−78	38	40	40.6	0.03
3 C	−68	−16	69	−14	−66	43	48	35.7	91.70
4 A	−66	77	−54	−9	65	−74	62	41.8	0.08
4 B	−76	65	−44	55	−79	47	27	43.3	0.02
4 C	−64	−17	70	−16	−67	49	41	37.7	99.90
5 A	−19	−47	85	−78	69	−78	72	39.0	99.99
5 B	14	25	23	−89	50	40	−74	44.7	0.01
6 A	−18	−45	83	−79	70	−74	66	39.9	86.80
6 B	−6	32	29	−87	36	53	−66	41.0	13.10

distorted in the direction of 1,7,10α-B (ΔC_2^6 = 14.4°, ΔC_s^9 = 26.1°, $\Sigma_2/(\Sigma_s + \Sigma_2)$ = 0.3), this conformer being 5.8 kcal/mole less stable than 2A, with a probability of realization of only 0.01% (here and below, probabilities are given without taking the entropy factor into account).

For the (1) molecule the theoretical impossibility of realization of the 1,10α,8,9β-TB conformation for ring B (analogous to 2B) is apparently due to steric repulsion not only between the pseudoaxially β-oriented C15 Me group and the axially β-oriented H8 and H9 atoms (the C15···H8 and C15···H9 distances are 2.98 and 2.93 Å) but also between the axially α-oriented C14 Me group and the H1 and H7 atoms (estimated C14···H1 and C14···H7 distances 2.27 and 2.17 Å).

A comparison of the torsional angles (see Table 1) in ring B of the corresponding conformers 1A and 2A (intermediate between twist-chair and chair) shows that they are practically identical, with the exception of the angles C1C5C6C7 ($\Delta\varphi$ = 7°), C10C1C5C6 ($\Delta\varphi$ = 5°) and C5C6C7C8 ($\Delta\varphi$ = 3°). The difference in these angles is obviously connected with the fact that in 2A the β-syn- orientation of the two C14 and C15 Me groups leads to steric repulsion between them (the C14···C15 distance is 3.17 Å). In actual fact, according to the results of the MMM calculation, conformer 2A is more strained than the epimeric conformer 1A (ΔE= 4.0 kcal/mole), its steric hindrance appearing also in the values of the valence angles C15C5C1 (114.2°), C15C5C4 (107.5°) and C14C10H10 (104.4°), deviating to a substantially greater degree from the ideal tetrahedral angle (109.6°) than the corresponding valence angles C15C5C1 (112.2°), H10C10C1 (108.5°) and H10C10C4 (106.7°) in conformer 1A.

Of all trans,trans-linked pseudoguaianolides with a β-oriented C14 Me group, only the molecule of allodesacyl-confertiflorin (7) has been investigated experimentally [2]; however, the conformation of ring B in this proved to be identical with that calculated as most suitable (2A). In the case of the α-orientation of the same Me group, ring B may change from 1,10α,8,9β-TC in britannin (8), for example, through an intermediate state to 9α,5,6β-C in 11,13-dibromopulchellin (9) [4]; i.e., an effect of pseudorotation [5] is observed.


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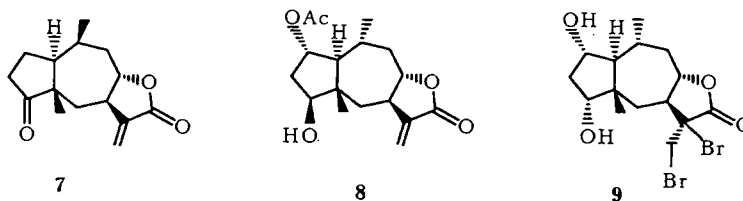
In each of compounds (3) and (4), in contrast to (1) and (2), three identical conformations of the seven-membered ring are realized. Optimization of the initial conformers 3e and 4e leads to conformers 3A and 4A, that of conformers 3f and 4f to 3B and 4B, and that of 3(h,g) and 4(h,g) to 3C and 4C, respectively (see Table 1). A comparison of corresponding conformers of the (3) and (4) molecules shows that the latter are more highly strained (E = 2.0-4.6 kcal/mole) because of the β-syn- orientation of the C14 and C15 Me groups. This leads to the appearance between them of nonvalent contacts (3.40 Å in 4A, 3.67 Å in 4B, and 3.46 Å in 4C) that are shorter than the sum of the van der Waals Me···Me radii (4.06 Å) [6]. In the molecule of (3), having the α-orientation of the C14 atom, the corresponding repulsion between the C15 Me group and the H10 atoms is considerably less (2.83 Å in 3A, 3.01 Å in 3B, and 2.90 Å in 3C). The influence of the β-oriented C14 Me group

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is also shown appreciably on the "distortion" of the conformation of ring B in the corresponding conformers. The mean value of the scatter of the intracylic torsional angles in the ring ($\Delta\varphi$) amounts to 3-6° (see Table 1).

Unexpectedly, of all the conformers of the molecules (3) and (4) the most stable proved to be 3C and 4C, assuming the conformation 7,8α,5,6β-TB (ΔC_2^{10} = 3.3°, $\Sigma_2/(\Sigma_s + \Sigma_2)$ = 0.1 in 3A and ΔC_2^{10} = 5.0°, $\Sigma_2/(\Sigma_s + \Sigma_2)$ = 0.1 in 4A). The least stable, with a probability of realization of less than 1% proved to be conformers 3B and 4B, having the same form of ring B as 3B and 4B [sic], but only for a twist-chair — 7,8α,5,6β-TC — while for 4B the conformation of the seven-membered ring is considerably distorted in comparison with the ideal twist form (ΔC_2^{10} = 5.0°, $\Sigma_2/(\Sigma_s + \Sigma_2)$ = 0.1 in 3B and ΔC_2^{10} = 13.50°, ΔC_s^7 = 19.6°, $\Sigma_2/(\Sigma_s + \Sigma_2)$ = 0.3 in 4B. In this concrete case, such a small probability of realization of these conformers is due to the presence of nonvalent contact of the axially oriented C15 and H9a atoms with the atoms of the lactone ring C15...C11 3.53 and 3.49 Å, C15...C13, 3.50 and 3.44 Å, H9a...C11 2.75 and 2.77 Å on 3B and 4B, respectively, while in conformers 3C and 4C these contacts are absent because of the equatorial orientation of ring C (C15...C11 4.96 and 4.95 Å, C15...C13 5.71 and 5.76 Å, H9a...C11 and 3.76 Å 3B and 4B, respectively). Slightly more favorable than 3B and 4B are conformers 3A and 4A, in which ring B assumes a conformation intermediate between 9,10α,1,5β-TC and 1α,7,8β-C but closer to the latter (ΔC_2^7 = 22.1 and 27.8°, ΔC_s^1 = 11.1 and 7.0°, $\Sigma_2/(\Sigma_s + \Sigma_2)$ = 0.6 and 0.7 for 3A and 4A, respectively). The smaller population of this conformational state than of the formally less favorable twist-boat (3C and 4C) is due to the axial β-syn- orientation of the C15 Me group and of the atoms of the lactone ring. The contacts C15...C11 (3.08 Å in 3A and 3.09 Å in 4A) and C15...C12 (3.34 Å in 3A and 3.52 Å in 4A) are considerably smaller than the sum of the van der Waals radii (3.9 Å), which leads to an increase in the conformational energy of the molecules. Passage of these conformers into the more favorable twist-chair conformation is impossible because of the resulting repulsion between the C15 and O16 atoms (3.55 Å in 3A and 3.80 Å in 4A).

A comparison of the results of the MMM calculations with experimental x-ray-structural results shows that, in fact, in the seven-membered ring of trans-cis-linked pseudoguaianolides the 7,8α,5,6β-TB conformation is realized most frequently — for example, in autumnolide (10) [7]. The conformations 9,10α,1,5β- and 7,8α,5,6β-TC, are also realized — for example, in radiation (11) [8] and helenalin (12) [9]. Consequently, in spite of the low probability of realization of the last two conformers in the model molecules (3) and (4), their stabilization is possible through the presence of other groupings, usually keto, hydroxy, and ester groupings.


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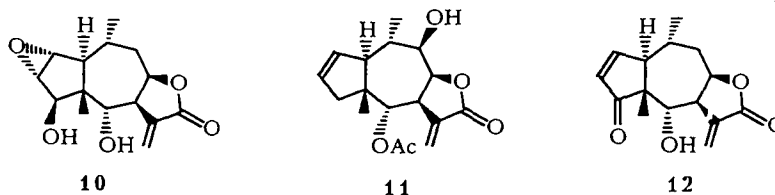
In compounds (5) and (6) with the cis,trans-ring linkage, on geometry optimization conformers 5i and 6i pass into 5A and 6A, and the others (5(j-m) and 6(j-m)) into 5B and 6B (see Table 1). In conformers 5A and 6A, ring B assumes a conformation intermediate between 7,8α,9,10β-TC and 1,5α,8β- C (ΔC_2^6 = 17.8 and 18.6°, ΔC_s^8 = 15.9 and 14.2°, $\Sigma_2/(\Sigma_s + \Sigma_2)$ = 0.5 and 0.5. As was to be expected, the axial β-orientation of the C14 atom in 6A leads to repulsion between C14 and C15 (3.68 Å) and between C14 and H8 (2.73 Å), in consequence of which this epimer in the given conformation is less stable than 5A by 0.9 kcal/mole (the corresponding contacts H10$\cdots$C15 and H10$\cdots$H8 amount to 3.37 and 2.40 Å, respectively).

The other two conformers, 5B and 6B, are minor ones and are realized with probabilities of 0.01 and 13.1%, respectively. The conformation of ring B is a highly flattened 6,7α,1,5β-TB with a deviation in the 1,8,9-B direction that is not very considerable in 5B (ΔC_2^9 = 11.6°, $\Sigma_2/(\Sigma_s + \Sigma_2)$ = 0.2) and is more pronounced in 6B (ΔC_2^9 = 25.6°, ΔC_s^5 = 32.7°, $\Sigma_2/(\Sigma_s + \Sigma_2)$ = 0.4). At the same time the (5) molecule in this conformation is less stable than (6), while in compounds (1-4) the epimers with an α-orientation of the C-14 Me group are always more stable. This is a result of the pseudoaxial orientation of the C14 atom and the resulting 1,6-repulsion between C14 and H7 (2.72 Å) in 5B. The corresponding contact in 6B, H10$\cdots$H7 (2.16 Å) is close to the sum of the van der Waals radii.

The only pseudoguaianolide with this type of linkage that has been investigated by the x-ray structural method is 3-bromoanhydrodehydrodihydropulchellin (13) [10], in which ring B assumes the 7,8α,9,10β-TC conformation.

However, the possibility of realization of a minor conformer as well is not excluded, since the population of the conformational states depends to a considerable degree on the presence of any substituents, the nature of the solvent, etc. [11].
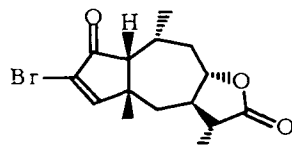
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The conformational calculations were made on an AT-286 personal computer by the MMX program using the potential parameters existing in this version and with full optimization of molecular geometries.

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