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STEREOCHEMISTRY OF SESQUITERPENES OF THE GERMACRANE TYPE

B. Tashkhodzhaev[a] and B. Kh. Abduazimov[b]

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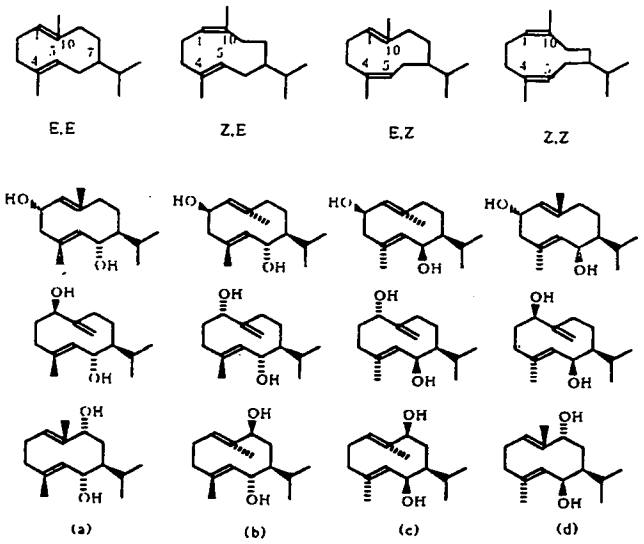
An analysis has been made of the conformations of the 10-membered ring in the known sesquiterpene E,E-germacranes and a relationship has been established between the realization of one of the four conformers and the positions and orientations of substituents in the 10-membered ring. A relationship is presented between the conformational states of the germacrolides and the structures of their bicyclic derivatives — guaianes and eudesmanes.

Among sesquiterpenes, the most common in Nature and the most intensively studied from all-sided stereochemical aspects are the monocyclic germacranes, of which the bicyclic sesquiterpenes eudesmanes, guaianes, carotanes, and others are considered to be biogenetic derivatives [1, 2].

The germacrane skeleton of these natural compounds is based on the carbon skeleton of cyclodecane with two endocyclic double bonds in the 1(10) and 4(5) positions and methyl groups at C4 and C10 and an isopropyl group at C7, in accordance with the isoprene rule. However, examples are found in which one of the double bonds in the germacranolides is shifted into the 9=10 position [3], has been replaced by an epoxide group [4], or is absent [5]. Depending on the *cis-* or *trans-*configurations of the endocyclic double bonds (or their substituting epoxide groups) in the 1(10) and 4(5) positions of the cyclodecadiene system, they are classified as representatives of four possible geometric isomers [1, 6]:



Scheme 1. Realization of predominant conformations in the germacranes according to the positions and orientations of substituents.

a) Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent, fax (3712) 40 64 75. *b*) Tashkent Pharmaceutical Institute. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 497-506, July-August, 1997. Original article submitted January 15, 1996.

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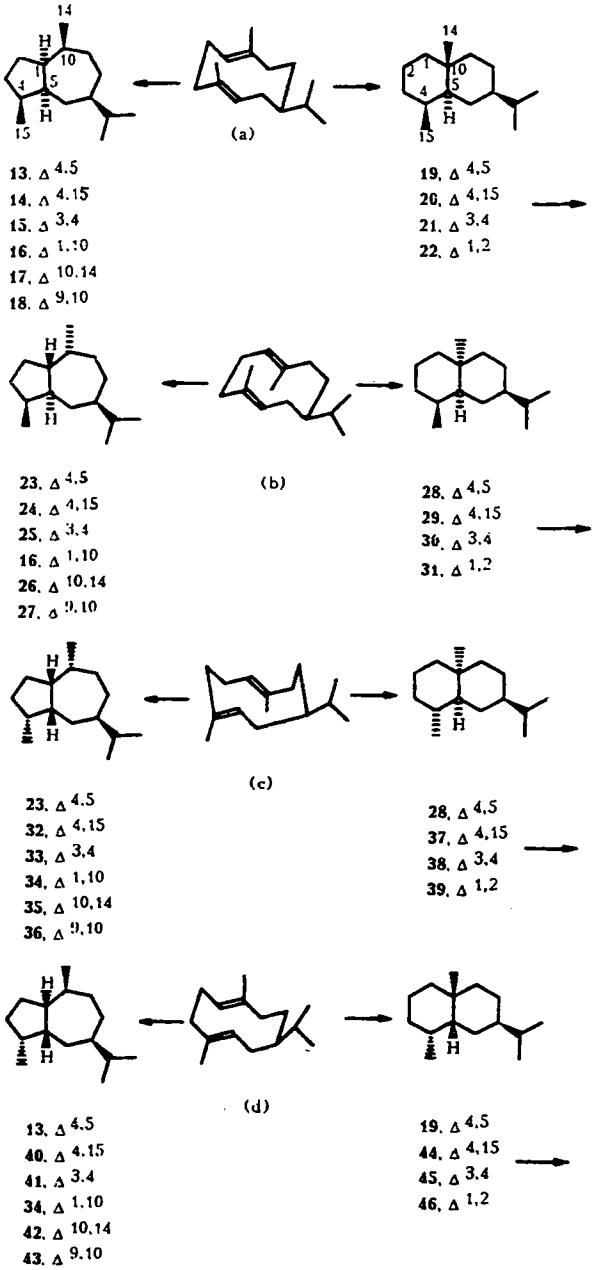
Among the types shown in Scheme 1, the group of *trans,trans-* (E,E)-germacranes is the most representative. Their structures have been studied fairly thoroughly in the stereochemical aspect [7-10].

Our task was to analyze the existing literature material (on the basis of the Cambridge Crystallographic Data Centre) and to reveal the main characteristics of the realization of the conformers in the E,E-germacranes.

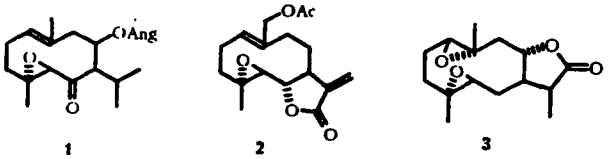
Conformational Analysis of E,E-Germacranes (Germacrolides)

The basic ideas on the conformation of cyclodecadiene were first introduced in Samek's classical work on the structure of the carbon backbone of sesquiterpene γ-lactones [11]. According to Z. Samek, characteristic conformations are realized for the E,E-germacranolides — germacrolides — in solution: chair-chair, chair-boat, and two types of boat-boat forms, which are denoted by the respective symbols ${}_1D^{14},{}^{15}D_5$ (**a**), ${}^1D_{14,15}D^5$ (**c**), ${}^1D_{14},{}^{15}D_5$ (**b**), and ${}_1D^{14},{}_{15}D^5$ (**d**). Perspective views of these conformations are given in Scheme 2.



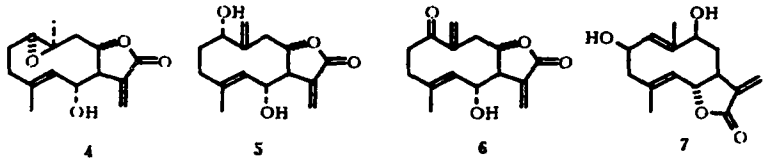
Scheme 2. Probable structural types of guaianes and eudesmanes formed from the four conformers of germacranes as the result of cyclization.

The chair-chair conformation (**a**) with the $_1D^{14},^{15}D_5$ configuration is frequently found in natural germacranes. For example, a comparison of the corresponding intracyclic torsion angles in such different types of molecules as the ester shiromodiol (ugamdiol) (**1**) [4], the 6,7-*trans*-lactone sachosin (**2**), which we have investigated [12], and the 7,8-*trans*-lactone ivaxillin (**3**) [13] shows that they possess close values and have the same chair-chair conformation with the $_1D^{14},^{15}D_5$ configuration. Here the methyl groups at C4 and C10 are *β-syn*-directed and the double bonds are in a skew position.



1 **2** **3**

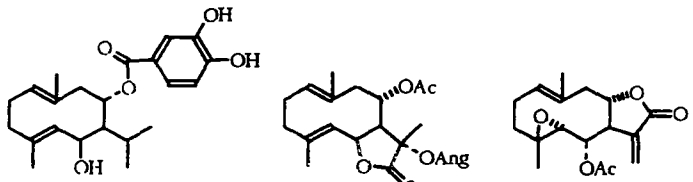
The following conformation, boat-boat (**b**) with the $^1D_{14},^{15}D_5$ configuration according to NMR spectroscopy and XSA is found mainly in the *trans*-linked linear germacrolides. The 7,8-lactonized sesquiterpene germacrolides mucrin (**4**), tanachin (**5**), and tamirin (**6**) [14, 15] are examples of such a conformation. Here the methyl (methylene in compounds (**5**) and (**6**)) group at C10 of the relatively planar germacrane ring has the α-, and the methyl group at C4 the β-, orientation; the bonds corresponding to the double bonds in the basic skeleton are parallel. The absence of an endocyclic C1=C10 double bond in compounds (**5**) and (**6**) is reflected in a decrease in the C2C1C10C9 torsion angle in comparison with that observed in (**4**) and (**7**).



4 **5** **6** **7**

It must be mentioned that the detection in montafrusin A (**7**) [16] of a cyclodecadiene conformation in the boat-boat form (type **b**) disproves the opinion that, as a rule, *trans*-6(7)-lactonized germacrolides assume the chair-chair configuration [9].

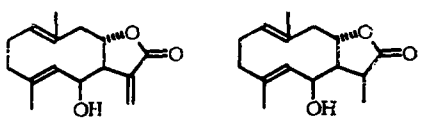
The third type of conformation, chair-boat (**c**) with the $^1D_{14},_{15}D^5$ configuration, has examples in all sesquiterpenoids with germacrane skeletons. According to the literature it is frequently found in nonlactonized germacrolides [sic]. The c conformation is found exclusively in nonlinear *cis*-linked germacrolides with γ-lactone rings. As examples of this we may give the ester chimganidin (**8**) [17, 18], the 6(7)-lactone laserolide (**9**) [19], and the linear germacrolide acetate spiciformin (**10**) [20].



8 **9** **10**

Here the methyl groups at C4 and C10 of the relatively planar germacrane ring are α-oriented and in the *syn*-relationship, while the double bonds (or the C4−C5 bond of the epoxy group) are in a skew position. In (**10**), there is an epoxy group in place of the double bond at C4−C5; nevertheless the intracyclic torsion angles C3C4C5C6 in compounds (**8**), (**9**) and (**10**) scarcely differ. The main difference is observed in the values of the angles at −C5−C6−, −C6−C7−, and −C7−C8− connected with the linkage of the lactone ring

According to the literature, the last conformation (**d**), boat-boat with the $_1D^{14},_{15}D^5$ configuration is found fairly rarely. This conformation has not so far been detected among sesquiterpene esters and 6,7-lactonized germacrolides. It has been found only in the linearly lactonized germacrolides 6-*epi*-deacetylaurenobiolide (**11**) [21] and hallerol (**12**) [22].



11 **12**

It is possible to trace a characteristic feature in the structures of compounds (**11**) and (**12**): the methyl groups at C10 and C4 have the anti arrangement relative to the plane of the germacrane ring (β an α, respectively) and the endocyclic double bonds are parallel.

From the analysis of the conformation of cyclodecadiene given above, it can be noted that the replacement of a double bond (4(5) or 1(10)) by an epoxide bridge does not lead to appreciable changes of conformation. However, when the 4(5) double bond is absent, the conformation of the 10-membered ring within the framework of the four assumed is not preserved, as a rule [23, 24]. Such deviation from the nominal "standard" conformations is also found when the 1(10) double bond is absent, in 9,10-dihydroxy-8-(2′-methylbutyl-2′-enoyloxy)germacra-4-dien-6,12-olide [26]. However, the analogous absence of the 1(10) double bond in tanachin (**5**) and tamirin (**6**) does not lead to conformational changes in comparison with mucrin (**4**).

Realization of the Predominant Conformations in the Germacranes

Analysis of the spatial structures and values of the torsion angles of known E,E-germacranes shows that the geometries of conformational states **a** and **b** (or **c** and **d**) of cyclodecadiene are identical in the C3−C8 section. Conformers **a** and **b** are realized predominantly in E,E-germacranes with the α-orientation of a substituent in the C6 position. This can be traced by using as examples the structures of 6,7-lactones: hanphyllin, salonitenolide, and sachosin (**a**) and montafrusin A (**b**); and of 7,8-lactones: mucrin, tanachin, and tamirin (**b**), etc. In compounds with an α-oriented substituent in the C6 position, conformations **c** and **d** are hindered, apparently because of steric repulsion of the *syn*-directed C15-methyl group and the α-oriented substituent at C6 [27]. When a substituent OR at C6 is β-oriented, conformations **c** and **d**, where the C15-methyl group is oriented α-axially, become predominant. This clearly shows a structure with a βOH group at C6: chimganidin and ugaferin, where conformation **c** is realized, or 6-epideacetylaurenobiolide and hallerol, with the **d** conformation.

Analysis has shown that the realization of one of the conformers **a** or **b** in germacranes with a 6α-, or **c** and **d** in germacranes with a 6β-, -hydroxy group depends largely on the orientation of a substituent (hydroxy group) in the C2 position. Where a hydroxy group in the C2 position has the α-orientation, the C14 methyl group is β-oriented relative to the cyclodecadiene plane, and, consequently, conformation **a** is observed, while if the C2 substituent has the β-orientation the C14 methyl group is α-oriented and conformation **b** is realized [for example, (**28**) and (**29**)]. In sesquiterpenes with a 6β-hydroxy group, the realization of conformations **c** and **d**, respectively, is more likely.

Another determining factor in the realization of one of the two conformers — **a** or **b** in germacranes with a 6α- and **c** or **d** in germacranes with a 6β-hydroxy group — is an OH group at C1. When it is β-oriented, the C14 methyl group is also β-oriented relative to the cyclodecadiene plane and, consequently, conformation **a** is realized. Where the hydroxy group at C1 is α-oriented the methyl group at C14 is also α-oriented and, consequently, conformation **b** is observed [14, 15].

When epoxy groups are present in place of the 1(10) and 4(5) double bonds, a decisive role in the realization of one conformation or another is played by the configuration of the epoxy compound. That conformation is realized for which the intra-annular repulsion is a minimum [27] and it does not depend on the orientation of adjacent hydroxy groups [30, 31].

The above-noted correlation — the predominance of a preferred conformation according to the positions and orientations of substituents — is not observed in the melampolide, heliangolide, and Z,Z-germacranolide series.

Thus, as analysis of the experimental material (including our own x-ray structural results) shows, in the crystal the realization of one of the four conformers in the E,E-germacranes depends on the presence and orientation of hydroxy groups in the C6, C2, and C1 positions. In all E,E-germacranes with a 6α-hydroxy group the $_1D^{14},{}^{15}D_5$ (**a**) or the $^1D_{14}$, $^{15}D_5$ (**b**) conformation is realized. In germacranes with a 6β-hydroxy group, conversely, the $^1D_{14},{}_{15}D^5$ (**c**) or the $_1D^{14},{}_{15}D^5$ (**d**) conformation is realized. The alternative nature of the realization of a conformation disappears when hydroxy groups are also present at C1 and C2 and depends on their orientation. A decisive role in the realization of a particular conformation is played by the configuration of epoxy groups replacing double bonds.

All that has been said about the dependence of the realization of a predominant conformation in the germacranes on the position and orientation of substituents is reflected in Scheme 1 (rows 1 and 2). In addition, this scheme includes cases with a hydroxy group in the C9 position (row 3).

The realization of a predominant conformation of the cyclodecadiene nucleus in solution has been shown in two NMR-spectral investigations on laurenobiolide. Tori et al. [32] showed the presence of two conformers on the basis of the results of an investigation of laurenobiolide under various temperature regimes and established by using the Overhauser effect that

conformers **a** (80%) and **b** (20%) existed in solution. Later, in a ^{13}C NMR study of laurenobiolide, the same authors [10] reported the presence in solution at −15°C of four conformers of the germacrane ring (**a**, **b**, **c**, and **d**) in a ratio of 5:4:3:1, respectively. It must be mentioned that these conclusions [10] to some extent contradict the above-mentioned hypothesis of the realization of predominant conformations in the germacranolides. Therefore, in our opinion, the observed splitting of the ^{13}C NMR signals of laurenobiolide must be linked not with the fixation of the four conformers of the germacrane ring but with a possible hindrance to the free rotation of the OAc group at C6. This means that, as stated in [32], in solution the two conformers **a** and **b** of the germacrane ring with two predominant positions of the planar OAc group are realized, with the result that four signals appear from each carbon atom. This interpretation of the splitting of the signals agrees well with our hypotheses. Their confirmation (or refutation) requires additional NMR investigations of different germacranolide derivatives with a variation of the temperature regime.

Conformational States and Products of the Cyclization of Germacrolides

The determination of the conformation of an E,E-germacranolide through its cyclization products is another approach permitting the supplementation of spectral methods [33-37], since, in many cases, on passing from monocyclic (germacrane) to bicyclic (five-, seven-, or six-membered) systems the configurations of the asymmetric centers of the initial substances are retained, and the structure of the end-product depends on the conformation of the 10-membered ring [38-41]. This means that the formation of one bicyclic system or another depends on precisely in which (out of the four possible) conformations the germacrolide is present at the time of cyclization, although on intramolecular cyclization in the germacrolides the migration of functional groups, the cleavage of individual bonds, and other processes are possible [42-45].

The positions of the H1 and H5 atoms and of the angular methyl group in guaianolides and of the H5 atom in eudesmanolides are the key factors in determining the conformation of a germacrolide through an analysis of cyclo products. Since the linkage of rings *A/B* in guaianolides and eudesmanolides is determined by the positions of the H1 and H5 atoms and the methyl group (at C10), and the orientations of H1 and H5 themselves are linked with the always α-directed H7 proton, these orientations are not usually shown in structural formulas of the germacrolide, although they determine the conformation of the cyclodecadiene ring.

Unfortunately, researchers assuming the orientation of the αH5 proton in eudesmanolides but not having determined the orientation of the methyl group at C10 frequently assume the α- or the β- orientation for it. They then make use of the fact that eudesmanolides are formed from a germacrolide having the chair-chair conformation with the *trans*- type of linkage. This would be correct if the orientation of the H5 protons were determined unambiguously. However, the determination of the orientation of H5 on the basis of the SSCCs $J_{5,6}$ and $J_{6,7}$ is not always reliable [46-50].

Scheme 2 gives probable structural types of the guaianolides and eudesmanolides that can be formed from germacrolides. Here, structural types connected with the migration of functional groups are not taken into account in cyclization, but it is assumed that on the cyclization of germacrolides the methyl groups may change into exomethylene groups and the positions of the double bonds may be different [51, 52].

If it is assumed that on the cyclization of a germacrane with the chair-chair conformation (conformer **a** with the $_1D^{14},^{15}D_5$ configuration) the orientations of the methyl groups and olefinic protons do not change, guaianolides with the *cis*-linkage of the five-and seven-membered rings and eudesmanolides with the *trans*-linkage of the six-membered rings may be formed (see the first row of Scheme 2).

The second row of Scheme 2 shows possible products of the cyclization of a germacrolide with the boat-boat conformation (conformer **b** with the $^1D_{14},^{15}D_5$ configuration). In contrast to the preceding conformer **a**, here the H1 and H5 protons are β- and α-oriented, respectively, and on cyclization, therefore, *trans*-guaianolides and *cis*-eudesmanolides are formed. In this case, guaianolide (**16**) is also present in the cyclization products from conformer **a**. Conformer **b** is characteristic for linearly lactonized germacrolides. The key asymmetric center of the cyclization product is 1βH in the guaianolides and the α-methyl group at C10 in the eudesmanolides. The formation of the different types is affected by the presence of a γ-lactone ring at C7−C8 or C6−C7 and also by hydroxy, carbonyl, and acyl groups at C1, C3, C6, and C8. The same factors determine the existence and stability of the germacrolide conformers themselves.

The presence of the chair-boat conformer (conformer **c** with the $^1D_{14},_{15}D^5$ configuration) is characteristic for germacrolides with the *cis*-linkage of a γ-lactone ring at C6−C7, where the olefinic protons at H1 and H5 are β-oriented. It

is therefore natural to expect the formation of the cyclization products shown in the third row of Scheme 2. Of the suggested cyclization products, guaianolide (**31**) and eudesmanolide (**36**) are given in the second row of Scheme 2 and guaianolide (**25**) in the fourth row [sic]. The cyclization of conformer **c** forms *cis*-guaianolides and *trans*-eudesmanolides, just like the cyclization of conformer **a**. But in this case the orientation of the methyls at C10 and C4 and, consequently, of the H1 and H5 protons differ from that of the cyclization products shown in the first row of Scheme 2.

The third [sic] row of Scheme 2 gives the presumed products of the cyclization of a germacrolide with the rarely found boat-boat conformation (conformer **d** with the $_1D^{14},_{15}D^5$ configuration). In contrast to the cyclization products of conformer **a**, in this case a *trans*-guaianolide (1α,5βH) and a *cis*-eudesmanolide (14α,5βH) are formed. Of the cyclization products given in the fourth row, guaianolide (**13**) and eudesmanolide (**19**) are also included in the second [sic] row of Scheme 2 because of the absence of orientation of the methyl groups at the double bonds (C10 and C4).

Thus, without taking migrations and rearrangements into account, six guaianolides and four eudesmanolides with different configurations can be formed from each germacrolide conformer. After the elimination of some structural coincidences, 34 types of guaianolide and eudesmanolides can be formed from the four conformers of a germacrolide.

Guaianolides with the 1α,5αH-*cis*-linkage of rings *A* and *B* are formed from germacrolides with the chair-chair-conformation (**a**), and guaianolides with the 1β,5βH-*cis*-linkage from germacrolides with the chair-boat conformation (**c**). Guaianolides with the 1β,5αH-*trans*-linkage are formed from germacrolides with the boat-boat conformation and the $^1D_{14},^{15}D_5$ configuration (**b**) and those with the 1α,5βH-*trans*-linkage from germacrolides with the boat-boat conformation and the $_1D^{14},_{15}D^5$ configuration (**d**).

Eudesmanolides with the 14β,5βH-*cis*-linkage of rings *A* and *B* are formed from germacrolides with the boat-boat conformation and the $_1D^{14},_{15}D^5$ configuration (**d**), and those with the 14α,5αH-*cis*- linkage from germacrolides with the boat-boat conformation and the $^1D_{14},^{15}D_5$ configuration (**b**). Eudesmanolides with the 14β,5αH-*trans*-linkage are formed from germacrolides with a chair-boat conformation (**c**), and those with a 14α,5βH-*trans*-linkage from germacrolides with the chair-chair conformation (**a**).

In conclusion, the possibility must be mentioned of the formation of these types of guaianolides and eudesmanolides from heliangolides and melampolides, as well, although some structural characteristics of the melampolides (presence of a carboxy group at C10) or the heliangolides (presence of a hydroxy or carbonyl group at C3) make it possible [sic] to determine a biogenetic precursor.

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