

ON THE VALIDITY OF THE "cis/trans" LACTONE RULE
FOR ALLYLIC COUPLING CONSTANTS
OF THE α -EXOMETHYLENE PROTONS
IN NATURAL SESQUITERPENIC α -EXOMETHYLENE γ -LACTONES*

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Received December 28th, 1977

The validity of the empirical rule for the determination of the "cis/trans" configuration of the α -exomethylene γ -lactone ring of type *I* on the basis of the values of allylic coupling constants of α -exomethylene protons, $|^4J|$ (*trans*-lactone) $\geq 3 \geq |^4J|$ (*cis*-lactone), is discussed. A more general rule is derived for the conformational analysis of the lactone ring on the basis of allylic constants, and it is demonstrated that the "cis/trans" rule is its special case. On this basis all exceptions are explained. The validity of the "cis/trans" rule is dependent on conformational factors among which the size and the conformation of the annelated cycle as well as the equatorality of the C_B-C_C bond are of importance. Two configurations of the lactone ring are possible for *trans*-lactones: one with the dihedral angle $\Phi_R = \Phi(R_A, R_B) = \angle R_A-C_A-C_B-R_B \leq 120^\circ$, for which the $|^4J_{BD}| \geq 3$ should be typical, and the second with $\Phi \geq 120^\circ$, for which $|^4J_{BD}| \leq 3$ should be typical. For *cis*-lactones the values $|^4J_{BD}| \leq 3$ should be typical for both ranges of Φ_R . Hence, the conditions for the validity of the "cis/trans" rule are formed where the configuration of R_A and R_B is limited to the range $\Phi_R < 120^\circ$. The question of the regularity of the relation $|^4J_{BD}|$ vs stereochemistry of the lactone ring must be considered for each skeletal type separately.

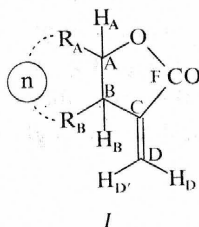
Several years ago we formulated an empirical rule¹ for the determination of the "cis/trans" stereochemistry of the γ -lactone ring of type *I* in natural sesquiterpenic lactones on the basis of the absolute values of allylic coupling constants $|^4J_{BD}|$ and $|^4J_{BD}'|$. For both couplings the rule postulated that

$$|^4J| (\textit{trans-lactone}) \geq 3 \geq |^4J| (\textit{cis-lactone}). \quad (I)$$

Other authors² also have pointed out certain regularities in the values of allylic coupling constants $|^4J_{BD}|$ and $|^4J_{BD}'|$, consistent to a certain extent with the rule (I), that occur in some structural types of standard sesquiterpenic lactones. The formulation of the rule (I) was stimulated by the endeavour to find other criteria supple-

* Part CCLIV in the series On Terpenes; Part CCLIII: This Journal 43, 2779 (1978).

mentary, to the vicinal constant ${}^3J_{BA}$, for more objective determination of the relative configuration of the substituents of the "bridgehead" atoms C_A and C_B in *I*. The vicinal constant ${}^3J_{AB}$ is often little characteristic, owing to the known ambiguity of its dependence on the dihedral angle $\Phi(H_A, H_B) = \angle H_A-C_A-C_B-H_B$. On the other hand, its extraction from the multiplets of the protons H_A and H_B is often very tedious, due to the complexity of the 1H -NMR spectra obtained with the still current 60–100 MHz frequencies. In contrast to this the protons of the exomethylene group have the basic advantage of forming an easily identifiable (a good signal-to-noise ratio) first-order part of the spectrum in consequence of the small geminal coupling $|{}^2J| = 0-2.5$ Hz (ref.^{1,3}) and long-range allylic couplings $|{}^4J| = 0-4$ Hz (ref.^{1,2}) or $|{}^5J| = 0-0.6$ Hz (ref.⁴), and a usually large internal shift $|\delta_D - \delta_{D'}| = 0.5-0.9$ ppm, as well as in view of the proper standard shifts $\delta = 5.4-6.5$ (ref.³). The actual form of the rule (*I*) was evoked mainly by the experimental material available at that time, which was, as was shown later, conformationally too uniform and hence little representative with respect to the extent of the problem. The already existing exceptions, as for example the values of $|{}^4J_{BD}(cis\ lactone)| > 3$ in some pseudoguaianolides, were taken into consideration¹ with a certain reserve in view of the possible experimental errors during the measurements of $|{}^4J_{BD}|$. However, the existence of these exceptions was soon confirmed⁵ and others were found, for example in the form of heliangolides with $|{}^4J_{BD}(trans\ lactone)| < 3$ (ref.^{6,7}) or "open-chain" (with annelated seco homocycle) lactones with $|{}^4J_{BD}(trans\ lactone)| < 3$ (ref.⁸).



As has already been mentioned in connection with the determination of the stereochemistry of the guaianolides grossheimin⁵ and xerantholide⁹, as well as the heliangolides nobilin and its analogues¹⁰, the existence of the relations of type (*I*) is dependent on the existence of conformational factors limiting the flexibility of the γ -lactone ring and its annelated cycle. The role of these conformational factors was partly underestimated during the formulation of the rule (*I*) in consequence of the above mentioned conformational uniformity of the experimental material. On the contrary, the quasirigidity of the lactone ring as a factor limiting the conformation of the annelated cycle was overestimated in consequence of the overestimation of the amount of energy by which the conjugation of the α,β -unsaturated

lactone system should contribute to the stability of the quasiplanar conformation¹. The existence of exceptions could be explained if admitting that the γ -lactone ring of type *I* is fully flexible and that its conformation is determined by standard conformational factors determining the conformation of the annelated cycle or the configuration of R_A and R_B in open-chain lactones. It is then evident that the role of these conformational factors will be different for each structural type of natural sesquiterpenic lactones, and that the formulation of the rules of type (*I*) will be very difficult and in some instances even impossible. Nonetheless, a certain rationalization, in the form of a more general rule, on the basis of a small number of conformational assumptions, extrapolated from current conformational analysis, is possible. Its presentation is the aim of this paper.

The determination of the relation ${}^4J_{BD}$ (${}^4J_{BD'}$) vs "cis/trans" configuration of the lactones ring of type *I* starts with the determination of the relation $\Phi(H_B, C_D)$ vs Φ_{BA} where $\Phi(H_B, C_D) = \angle H_B-C_B-C_C-C_D$ is the allylic angle between the C_B-H_B bond and the plane of the double bond $C_C=C_D$ (Fig. 1), and which determines the value¹¹ of J_{BD} and $J_{BD'}$, and Φ_{AB} is some dihedral angle defining the relative configuration of the fragment C_A-C_B as "cis" or "trans". If an sp^3 -hybridization of the atoms C_A and C_B is assumed, and if their substituents are indicated as $\{A_j\}$ and $\{B_i\}$ ($i, j = 1, 2, 3$; for example the sets $\{A_j\} = \{H_B, R_A, O\}$ or $\{B_i\} = \{H_B, R_B, C_C\}$) then the fundamental set of nine relative dihedral angles (independent of orientation) $\{\Phi_{BA}\} = \{\Phi(B_i, A_j) = \angle B_i-C_B-C_A-A_j, (i, j = 1, 2, 3)\}$ can be defined on the fragment $C_B \rightarrow C_A$ (the arrow indicates the direction of viewing). From these angles the "cis/trans" relation of the centers C_A and C_B is defined by the angles Φ_{23} and Φ_{32} (Fig. 2), i.e. the angles $\Phi_H = \Phi(H_B, H_A) = \angle H_B-C_B-C_A-H_A$ or $\Phi_R = \Phi(R_B, R_A) = \angle R_B-C_B-C_A-R_A$. The pseudorotation around the $C_B \rightarrow C_A$ bond is limited by the accessible maximal puckering of the lactone ring, i.e. by the maximally accessible dihedral angle $\Phi_L = \Phi_{11} = \angle C_C-C_B-C_A-O$.

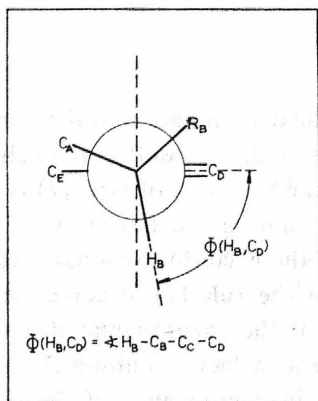


FIG. 1
Definition of the Allylic Angle $\Phi(H_B, C_D)$

If the absolute value of the angle of pseudorotation around $C_B \rightarrow C_A$ is defined as φ_{BA} , then for $\Phi_L \in \langle 0, 60 \rangle$ it applies that $\varphi_{BA} = 0^\circ \pm 60^\circ$. Further if the sign of φ_{BA} is defined by the shortest rotation of the substituents of C_B leading to $\Phi_L = 0^\circ$, then it follows that for *cis*-lactone the ranges are $\Phi_H \in \langle 0, 60 \rangle$ and $\Phi_R \in \langle 0, 60 \rangle$ for both directions of φ_{BA} ; for *trans*-lactone two possibilities exist, *i.e.* the ranges $\Phi_H \in \langle 120, 180 \rangle$ and $\Phi_R \in \langle 60, 120 \rangle$ for $\varphi_{BA} \in \langle 0, +60 \rangle$ or $\Phi_H \in \langle 60, 120 \rangle$ and $\Phi_R \in \langle 120, 180 \rangle$ for $\varphi_{BA} \in \langle 0, -60 \rangle$ (Fig. 2 and 3).

The ranges of the allylic angle $\Phi(H_B, C_D)$ are limited by the range of pseudorotation around the $C_C \rightarrow C_B$ bond. In principle two cases may arise: *a*) pseudorotation around $C_C \rightarrow C_B$ is correlated with the pseudorotation around $C_B \rightarrow C_A$. *b*) pseudorotation around $C_C \rightarrow C_B$ is not correlated with that around $C_B \rightarrow C_A$. The pseudorotation around $C_C \rightarrow C_B$ is limited by the range of the dihedral angle $\Phi_{FA} = \angle C_F-C_C-C_B-C_A$. If assuming that the maximum puckering of the lactone ring is given by the torsion around the $C_B \rightarrow C_A$ bond, *i.e.* by the range of the angle Φ_L , then for the angle Φ_{FA} applies $\Phi_{FA} \leq \Phi_L$. In principle both considered pseudorotations are uncorrelated to a certain extent, in consequence of the possible flipping of the plane of the carbonyl group at constant angle Φ_L . This deviation can be maximum for $\Phi_L = 0^\circ$ and it is minimum for $\Phi_L = 60^\circ$. Hence, for the determination of the extent of the correlation it suffices to consider two extremes only, *i.e.* for

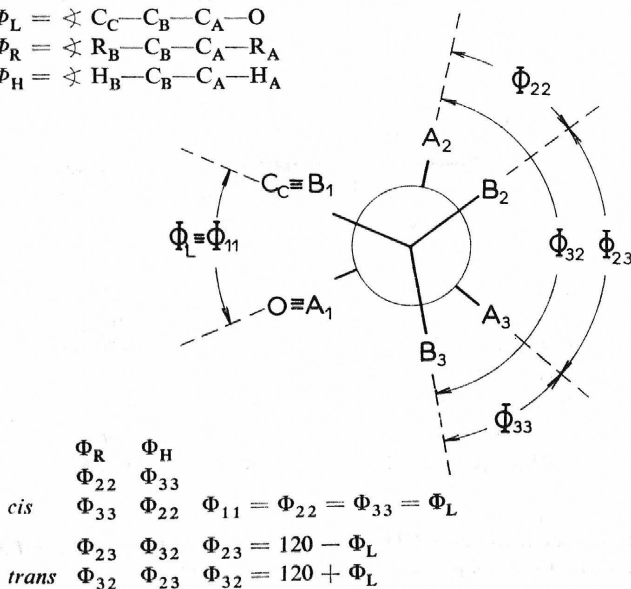
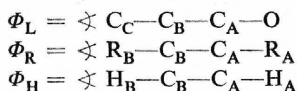


FIG. 2

Definition of Dihedral Angles $\Phi(B_i, A_j) = \angle B_i-C_B-C_A-A_j$ ($i, j = 1, 2, 3$) on the Fragment $C_B \rightarrow C_A$

The arrow indicates the direction of viewing; B_i, A_j are the substituents of the atoms C_B, C_A .

$\Phi_{FA} = \Phi_L = 60^\circ$ and for $\Phi_L = 0^\circ$ and $60^\circ \geq \Phi_{FA} \geq 0^\circ$. If the angle of pseudorotation around $C_C \rightarrow C_B$ is defined as φ_{CB} , then for $\Phi_{FA} \in \langle 0, 60 \rangle$ it applies that $\varphi_{CB} = 0 \pm 60^\circ$. For the allylic angle $\Phi(H_B, C_D)$ it then applies that $\Phi(H_B, C_D) = 60 \pm \Phi_{FA}$, i.e. $\Phi(H_B, C_D) \in \langle 0, 120 \rangle$ (Fig. 3). If the sign of φ_{CB} is defined by the pseudorotation of the substituents of C_C , similarly as in φ_{BA} , then it applies for $\varphi_{CB} = +\Phi_{FA}$ that $\Phi(H_B, C_D) \in \langle 60, 120 \rangle$ and for $\varphi_{CB} = -\Phi_{FA}$ $\Phi(H_B, C_D) \in \langle 0, 60 \rangle$ (Fig. 3). The correlation between φ_{CB} and φ_{BA} can then be derived from the definitions of both angles for the same sign of rotation of the substituents of the atom C_B , i.e. for $\varphi_{BA} = +\Phi_L$ $\varphi_{CB} = -\Phi_{FA}$ and for $\varphi_{BA} = -\Phi_L$ $\varphi_{CB} = +\Phi_{FA}$. In view of the fact that "cis" and "trans" relations are defined both for $+\varphi_{BA}$ and for $-\varphi_{BA}$ the relative angles $\Phi(H_B, C_D)$ and Φ_H or Φ_R cannot be correlated unambiguously independently of the sign of φ_{BA} . Therefore it is useful for further considerations to select for correlation with $\Phi(H_B, C_D)$ (from the values ${}^4J_{BD}$ or ${}^4J_{BD'}$, the absolute sign of this angle cannot be determined, and hence not φ_{CB} either) such an angle among the set of the relative angles $\{\Phi_{BA}\}$ which correlates with its value unambiguously with the

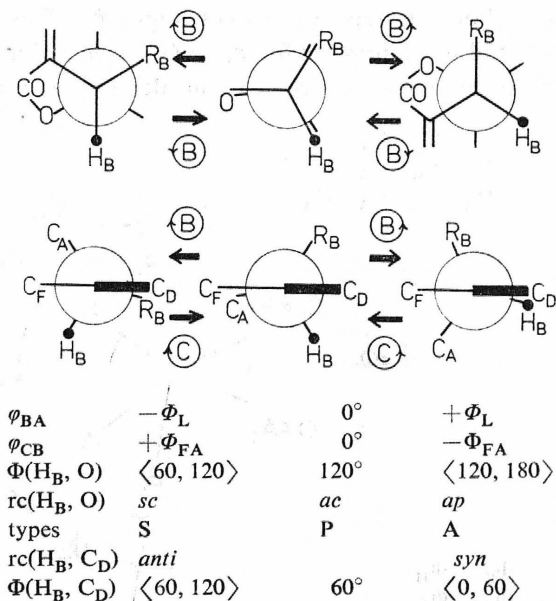


FIG. 3

Definition of Basic Pseudorotational Types of the γ -Lactone Ring of Type I and the Correlation of Pseudorotations on the Fragments $C_B \rightarrow C_A$ and $C_C \rightarrow C_B$

The arrow indicates the direction of viewing, φ_{BA} and φ_{CB} mean absolute angles of pseudorotation. The term rc(X, Y) means the relative configuration of X and Y defined by the usual symbols (*sc* synclinal, *ac* anticlinal, *ap* antiperiplanar). The relative configuration H_B and C_D is defined according to the projections of the fragments $C_B \rightarrow C_A$, where it is distinguished formally only in *syn* and *anti*.

sign of φ_{BA} . From Fig. 2 it may be deduced that for one given absolute configuration C_B only the angles Φ_{21} come into consideration from the subsets of angles $\{\Phi(B_2A_j)\}$ and $\{\Phi(B_3A_j)\}$. The angles Φ_{21} and Φ_{31} are invariant with respect to the permutation of A_2 and A_3 (the angles $\Phi_{22}, \Phi_{23}, \Phi_{32}, \Phi_{33}$ define "cis" and "trans"). It is evident from Fig. 3 as well that the angles Φ_{21} and Φ_{31} , i.e. the angles $\Phi(H_B, O) = \angle H_B - C_B - C_A - O$ or $\Phi(R_B, O) = \angle R_B - C_B - C_A - O$ (mutual complements to 180°), are defined unambiguously for $\varphi_{BA} = \pm 60^\circ$, i.e. as $\Phi(H_B, O) = 60^\circ$ and $\Phi(R_B, O) = 180^\circ$ for $\varphi_{BA} = -60^\circ$, and as $\Phi(H_B, O) = 180^\circ$ and $\Phi(R_B, O) = 60^\circ$ for $\varphi_{BA} = +60^\circ$. For our further considerations the angle $\Phi(H_B, O)$ will be preferred because it has a common definition element with the allylic angle $\Phi(H_B, C_D)$.

The assignment of the pseudorotational extremes of the angles $\Phi(H_B, O)$ and $\Phi(H_B, C_D)$, as well as their ranges, are defined by Fig. 3. A complete stereochemical assignment of the allylic angle for all absolute configurations of the fragment $C_B \rightarrow C_A$ is shown in Fig. 4 (for better insight a 50% transmission of pseudorotation is chosen for the fragment $C_C \rightarrow C_B$, i.e. for $\Phi_L(\max) = 60^\circ$ the angle $\Phi_{FA}(\max) = 30^\circ$). If the abbreviation $rc(X, Y)$ is accepted for the formal expression for "relative" configuration of X and Y", then for the fragment $C_B \rightarrow C_A$ with $\Phi(H_B, O) = 60^\circ$ it applies that $rc(H_B, O) = sc(\text{synclinal})$ and $rc(H_B, C_D) = anti$ (the dihedrality on fragment $C_C \rightarrow C_B$ is distinguished in the Newman projections of the fragment

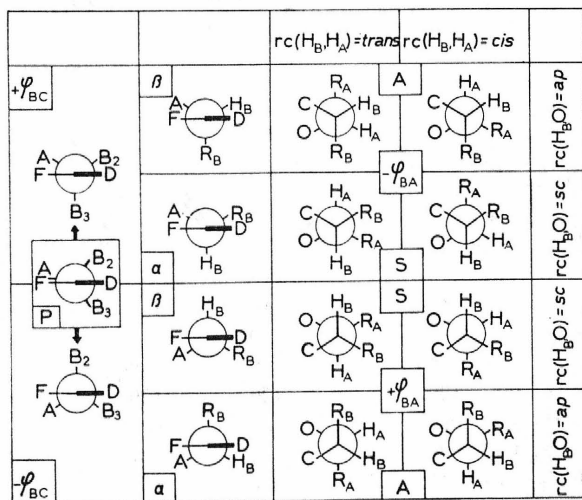


FIG. 4

Complete Stereochemical Assignment of the Allylic Angle $\Phi(H_B, C_D)$ to Extreme Pseudorotational Types A and S (Fig. 3) for All Absolute Configurations of the Fragment $C_B \rightarrow C_A$ For the fragment $C_C \rightarrow C_B$ a case with 50% transmission of $\Phi_L(\max) = 60^\circ$ is shown (for the definition of symbols see Fig. 1–3).

$C_B \rightarrow C_A$ formally only as “*syn*” and “*anti*”) and hence $\Phi(H_B, C_D) = 120^\circ$, and for the fragment with $\Phi(H_B, O) = 180^\circ$ it follows $rc(H_B, O) = ap$ (antiperiplanar) and $rc(H_B, C_D) = syn$ and hence $\Phi(H_B, C_D) = 0^\circ$. The cases of the configuration ranges with $rc(H_B, O) = ac, sc$, for which at the extreme it applies that $rc(H_B, O) = sc$, will be further indicated as S-types (synclinal types), and the cases with $rc(H_B, O) = ac, ap$, having at the extreme $rc(H_B, O) = ap$, will be indicated as A-types (antiperiplanar types). In the anticlinal case with $rc(H_B, O) = ac$ for $\Phi_L = 0^\circ$ it may be at extremes that $\Phi_{FA} = 0^\circ$ and $\Phi_{FA} = 60^\circ$, *i.e.* the same ranges of allylic angles are possible as in the types A and S. In this case the assignment is given by the rotation of the substituents of the atom C_C , and it is shown in Fig. 5. The cases with $\Phi_L = \Phi_{FA} = 0^\circ$ will be indicated as P-types (planar pseudotypes), the cases with $\Phi_L = 0, \Phi_{FA} \in \langle 0, 60 \rangle$ and $rc(H_B, C_D) = syn$ and $\Phi(H_B, C_D) = \langle 0, 60 \rangle$ as P(A)-types (antiperiplanar pseudotypes), and the cases with $\Phi_L = 0, \Phi_{FA} \in \langle 0, 60 \rangle$ and $rc(H_B, C_D) = anti$ and $\Phi(H_B, C_D) \in \langle 60, 120 \rangle$ as P(S)-types (synclinal pseudotypes). For $\Phi_L = 0$ the pseudorotational pathway is degenerated to $E^F \rightleftharpoons P \rightleftharpoons E^E$ (E^E, E^F indicate the envelope conformations, Fig. 5).

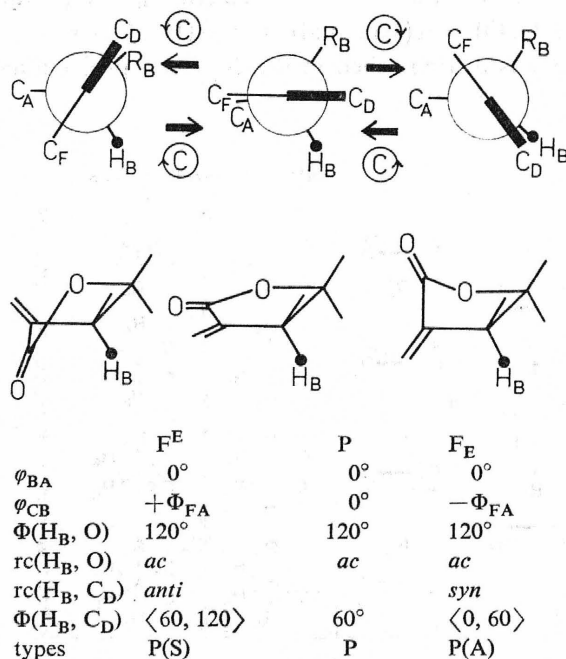


FIG. 5

Definition of Degenerated Pseudorotational Types of the γ -Lactone Ring of Type I

The symbols E^E and E^F indicate envelope-conformations, while the others have the same meaning as in Fig. 3. The symbols P(S) and P(A) express the membership of the P-type to S or A according to $rc(H_B, C_D)$.

On the basis of these definitions it is evident that the relation which applies is

$$\begin{aligned} \Phi(H_B, C_D) (\text{S-type}), \text{P(S-type)} &\geq \Phi(H_B, C_D) (\text{P-type}) \geq \\ &\geq \Phi(H_B, C_D) (\text{A-type}, \text{P(A-type)}) \end{aligned} \quad (2)$$

On the basis of the theory of allylic interaction¹¹ the relationships between $J_{BD} = {}^4J(\text{transoid}) = {}^4J_{\text{trd}}$ and $J_{BD'} = {}^4J(\text{cisoid}) = {}^4J_{\text{csd}}$ and the allylic angle can be approximately (neglecting the cross-over problem) expressed as

$${}^4J_{BD} = {}^4J_{\text{trd}} = {}^4J_{\text{trd}}^{(\sigma)} + {}^4J^{(\pi)} = {}^4J_{\text{trd}}^{(\sigma)} + {}^4J_{\text{max}}^{(\pi)} \cdot \sin^2 \Phi(H_B, C_D), \quad (3)$$

$${}^4J_{BD'} = {}^4J_{\text{csd}} = {}^4J_{\text{csd}}^{(\sigma)} + {}^4J^{(\pi)} = {}^4J_{\text{csd}}^{(\sigma)} + {}^4J_{\text{max}}^{(\pi)} \cdot \sin^2 \Phi(H_B, C_D),$$

where ${}^4J^{(\sigma)}$ and ${}^4J^{(\pi)}$ indicate the contributions from the σ - σ resp. σ - π interactions and ${}^4J_{\text{max}}^{(\pi)}$ the maximum value of the σ - π interaction for $\Phi(H_B, C_D) = 90^\circ$. In the case of lactone rings of the type *I* it applies that ${}^4J_{BD} < 0$, ${}^4J_{BD'} < 0$ (negative sign) and $|{}^4J_{BD}| \geq |{}^4J_{BD'}|$ while usually $\Delta = |{}^4J_{BD}| - |{}^4J_{BD'}| = 0-0.5$ (for the assignment of $H_D(\text{transoid})$ and $H_D(\text{cisoid})$ see ref.^{1,3,5}). The maximum value for $|J_{BD}|$ found so far was 4 Hz (ref.^{12,13}). If estimate ${}^4J_{\text{max}}^{(\pi)} = -3.4$ Hz¹⁰ is accepted and if it is assumed that $\Phi(H_B, C_D) = 90^\circ$ for $J_{BD}(\text{max})$, then from equation (3) it follows that ${}^4J_{\text{trd}}^{(\sigma)} = -0.6$ for ${}^4J_{\text{trd}} = -4$ Hz, and for $\Delta(\text{max}) = 0.5$ for ${}^4J_{\text{csd}} = -3.5$

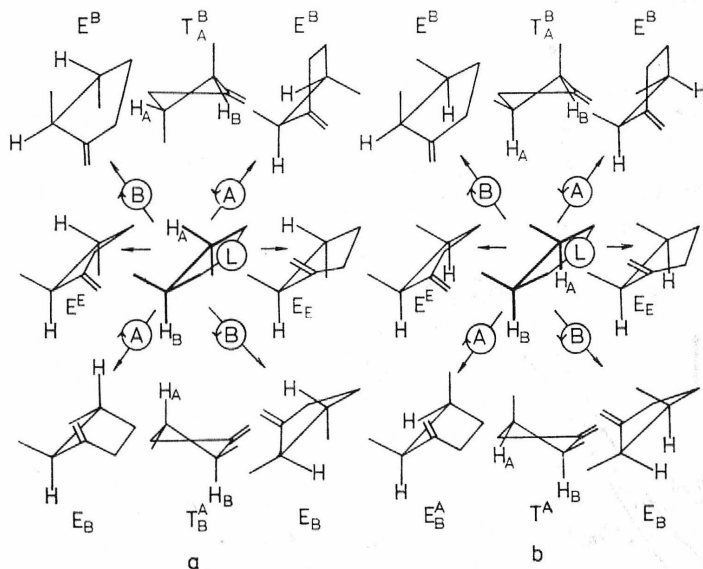


FIG. 6

Basic Conformations of the γ -Lactone Ring of Type *I* for the *trans*- (a) and *cis*-Configuration (b) of the Fragment $C_B \rightarrow C_A$

the σ -contribution ${}^4J_{\text{csd}}^{(\sigma)} = -0.1$. Starting from these estimates and neglecting the angular dependence of ${}^4J^\sigma$ the estimate for $\Phi(\text{H}_B, \text{C}_D) = 60^\circ$ in P-type is obtained, *i.e.* ${}^4J_{\text{csd}}(60) = -2.7$ and ${}^4J_{\text{trd}}(60) = -3.2$. These values agree well with the empirical estimate -3 Hz in the relation (1) (ref. ¹).

If the estimate of 3 Hz is accepted for the value $1/2(|J_{\text{BD}} + J_{\text{BD}'}|)$ in planar conformation, then the relation (2) can be rewritten in the form

$$|{}^4J_{\text{BD}}| |{}^4J_{\text{BD}'}| (\text{S-type, P(S)-type}) \geq 3 \geq |{}^4J_{\text{BD}}| |J_{\text{BD}'}| (\text{A-type, P(A)-type}). \quad (4)$$

As shown in Fig. 7 the function (3) is ambiguous in the range of S-types $\Phi(\text{H}_B, \text{C}_D) \in \langle 60, 120 \rangle$. The sign of inequality in the relation (4) is guaranteed for this range by the fact that the extreme 120° derived for a complete transmission of the maximum puckering 60° from the fragment $\text{C}_B \rightarrow \text{C}_A$ to $\text{C}_C \rightarrow \text{C}_B$ is somewhat unrealistic and has a rather formal meaning. In most cases a smaller range of Φ_{FA} than 60° may be expected, *i.e.* incomplete transmission, even in the case of an extreme torsion on $\text{C}_B \rightarrow \text{C}_A$. However, in the cases of such extreme torsion some deviations from sp^3 -hybridization of the atoms C_A and C_B can be expected which could also condition the extreme variation of $\Phi(\text{H}_B, \text{C}_D) \rightarrow 120^\circ$. A characteristic case of the adaptation of $\Phi(\text{H}_B, \text{H}_D)$ from the range close to the maximum of the function (3), *i.e.* 90° , should be always indicated by both values $|{}^4J_{\text{BD}}| > 3$ and $|{}^4J_{\text{BD}'}| > 3$, and for the opposite extreme $|{}^4J_{\text{BD}}| < 3$ and $|{}^4J_{\text{BD}'}| < 3$. The case of $|{}^4J_{\text{BD}}| > 3$ and $|{}^4J_{\text{BD}'}| < 3$ is not characteristic.

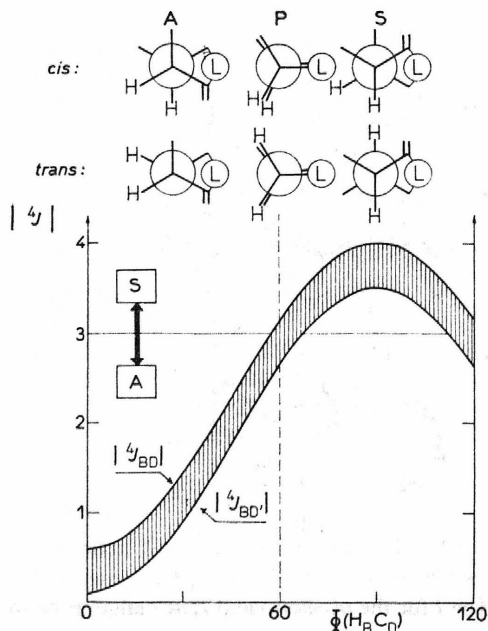


FIG. 7
Graphical Representation of the Function (3) and the Assignment of the Pseudorotational Types for the γ -Lactone Ring of Type I

The relation (4) represents the general rule for conformational analysis of the γ -lactone ring of type I on the basis of the value of allylic coupling, and it permits the interpretation of all observed cases. In dependence on how the *trans* and *cis*-lactones of a given structural type belong to various conformational types A and S according to definition in Fig. 2, various subrelations follow the relation (4).

For the derivation of conformational possibilities of *cis*- and *trans*-lactone ring of type I, annelated with a flexible ring, two basic criteria can be applied in principle; a) the optimum conformations of the annelated n -membered cycle are those in which the lactone ring (*i.e.* the bonds C_B-C_C and C_A-O) is pseudodiequatorial¹⁴, b) in cases when the bonds C_B-C_C or C_A-O can be both axial and equatorial the conformations with an equatorial C_B-C_C bond and an axial C_A-O bond are preferred (in view of the partial delocalization of the lone-pairs the ethereal oxygen atom of the lactone ring can be considered as an effectively sterically less requiring substituent than the exomethylene group $C_D=C_DH_2$). From Fig. 6 it follows that the C_B-C_C and C_A-O bond are in both basic conformations of the *trans*-lactone ring (T_B^A , T_A^B) always pseudodiequatorial. The preference of this or that conformation is determined primarily and exclusively by the factors determining the conformational possibilities of the annelated cycle and limiting the ranges of the "ring-angle" Φ_R . Figs 3 and 6 show that the *trans*-lactones with $\Phi_R < 120^\circ$ (T_B^A) belong to pseudorotational S-types, while the *trans*-lactones with $\Phi_R > 120^\circ$ (T_A^B) belong to pseudorotational A-types. In *cis*-lactones the situation is more complex because the pseudodiequatorial position of the lactone ring (in a general case defined relative to a imaginary plane of the molecule) may be achieved in the case with $\Phi_L \neq 0$ in conformations T_A^B and T_B^A only in such cases where the imaginary plane of the lactone ring (the plane bisecting the dihedral angle Φ_L) is preserved during pseudorotation (with respect to the molecular plane; the pseudodiequatorial position is preserved). In principle this is possible in the case of polycyclic systems only (the plane remains preserved with respect to a plane of a cycle different from that annelated). If considering an n -membered annelated ring as the conformationally determining factor, then in the case of a *cis*-lactone such a pseudorotation of the fragment C_A-C_B may be expected during which just the imaginary plane of the n -membered annelated cycle (the plane bisecting Φ_R) is preserved. From this point of view the substituents R_A and R_B (involved in the annelated ring) in the *cis*-lactone of type I may be expected in pseudodiequatorial positions. For the lactone ring it means a case of "equatorial-axial" arrangement of the C_B-C_C and C_A-O bonds (E^B , Fig. 6) or the case of "axial-equatorial" arrangement (E_B , Fig. 6). According to the above mentioned criterion the equatorial C_B-C_C bond should be preferred. Hence, according to $rc(H_B, O) = anti(C_B-H_B$ and C_A-O are diaxial) it means that the *cis*-lactones should prefer the pseudorotational type A of the lactone ring. On the other hand, for *cis*-lactones it may also be assumed that in view of the torsional interactions R_B and C_D they will have the tendency to assume the conformations with $rc(R_B, C_D) = anti$, *i.e.* $rc(H_B, C_D) = syn$,

ergo $rc(H_B, O) = ap$. This viewpoint leads to the preference of A-types (in this sense the conformation E^B is acceptable).

From the point of view of these conformational considerations it is evident that the regular relationship in the sense of the „*cis/trans*” rule can occur only in cases of the conformations having $\Phi_R < 120^\circ$. Assuming the A-type for the *cis*-lactone, then – in view of the fact that in this case with $\Phi_R < 120^\circ$ the *trans*-lactone belongs to the S-type – the relation (4) is transformed into the „*cis/trans*” rule (1). In this sense the rule (1) represents the dominant subrelation in the set of possible subrelations derivable from the general relation (4).

The range $\Phi_R < 120^\circ$ is typical of small cycles with $n = 5, 6, 7$ in which the alternative $\Phi_R > 120^\circ$, and thus the possibility of the existence of the *trans*-lactone of type A, is *a priori* excluded. In the majority of the standard types of natural sesquiterpenic lactones of this category good conditions occur for the application of the above mentioned conformational criteria in consequence of favourable, biogenetically determined relative distributions of the side chains. Therefore, in such cases, the

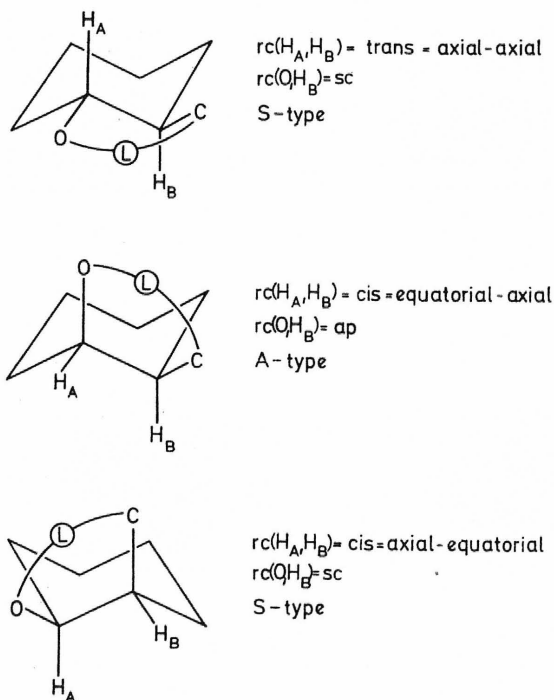


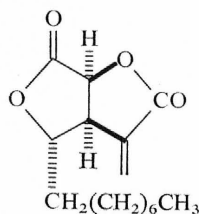
FIG. 8

The Dependence of the Pseudorotational Types of the γ -Lactone Ring of Type I on the Orientation of the $C_B \rightarrow C_C$ Bond in the Case of the “Chair” Conformation of the Annulated Six-Membered Ring

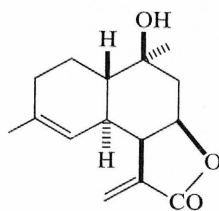
For the definition of the symbols see Fig. 3.

validity of the rule (I) could be observed in the majority of cases (for example eudesman-6,12- and 8,12-olides, eleman-6,12- and 8,12-olides, guaian-6,12- and 8,12-olides and pseudoguaian-8,12-olides ($n = 6, 7$; cf. ref.¹); the *cis*-lactone avenaciolide¹⁵ (II) may serve as an example of a lactone with $n = 5$, with $|^4J_{BD}| = 2.56$, $|^4J_{BD'}| = 2.17$ and $|^3J_{AB}| = 8.53$).

The irregularities in the relation (4), and hence the exceptions from the relation (I), occur always when various conformational types are either restricted or, on the contrary, made possible by the sterical effects. For example, we may have the flexible P-types of *cis*-lactone that can also belong, depending on the conditions, to the P(S)-types with $\Phi_L = 0$ or to S-types with $\Phi_L \neq 0$. This is evidently the case of $C_{(6)}$ -pseudoguaianolides which exhibit the values $^3J_{AB} = J_{6,7} = 8 - 10$ Hz and simultaneously the $|^4J_{BD}|$ values higher and lower than 3 Hz. The variation of $|^4J_{BD}|$ from one range to the other can often be forced by the change of polarity of the solvent, without a change of $^3J_{AB}$ (ref.⁵). Such behaviour corresponds to the variation of either $P(S) \rightleftharpoons P \rightleftharpoons P(A)$ (or $S \rightleftharpoons P \rightleftharpoons A$ in a quasi-planar case). The above mentioned dependence on the relative orientation of the C_B-C_C bond also may be involved. This is shown clearly on the case of the 6-membered ring in Fig. 8. In optimum conformations the C_B-C_C bond is equatorial, which means that the *trans*-lactone is of the S-type and the *cis*-lactone of the A-type, and the relation (I) is valid. In the case of a *cis*-lactone with an axial bond C_B-C_C the lactone is of S-type and the relation (I) becomes invalid. As an example of such a *cis*-lactone the cycloepitulinolide (III) of cadinane type may be mentioned¹⁶, exhibiting $|^4J_{BD}| = 3.2$, $|^4J_{BD'}| = 3.0$ and $^3J_{AB} = 4.8$.



II

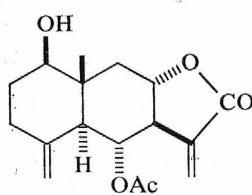


III

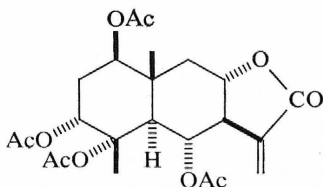
In extreme pseudorotational types of *trans*-lactones, for example in a 6-membered ring, less characteristic cases may also occur when the allylic angle attains a range above 90° , i.e. $90^\circ < \Phi(H_B, C_D) \leq 120^\circ$ and when the values for $|^4J_{BD}|$ again approach the value 3 Hz (Fig. 7). This case takes place probably in $C_{(8)}$ -eudesmanolides, as for example in β -cyclopyrethrosin¹⁷ (IV) with $|^4J_{BD}| = 3.1$ and $|^4J_{BD'}| = 2.9$ and $^3J_{AB} = 11.6$, or in eudesmachamissonin tetraacetate¹⁸ (V) with $|^4J_{BD}| = 3.0$, $|^4J_{BD'}| = 2.8$, and $^3J_{AB} = 12.0$.

In the case when $\Phi_R > 120$ no regularities of the type expressed by the relation (I) can evidently take place, owing to the fact that *trans*-lactones belong to the A-type.

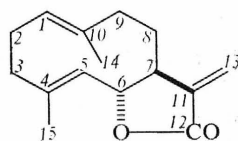
Such conformations with $\Phi_R > 120$ are possible for large cycles only or for "open-chain" lactones ($n \rightarrow \infty$; the annelated ring in *I* is seco). In both cases the driving force is the pseudorotational potential induced by the repulsion $R_A \leftrightarrow R_B$ leading to such a conformation in which R_A and R_B is *trans*.



IV



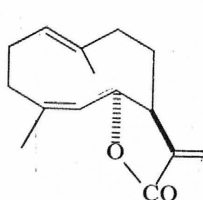
V



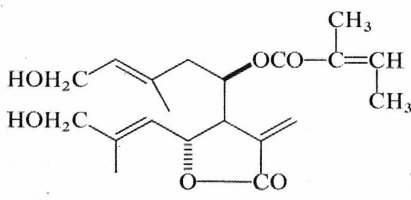
VI

A typical illustration of this is the case of germacradienolides, *i.e.* germacrolides of the type *VI* and heliangolides of type *VII*. It can be easily visualized on Dreiding models that the $C_{(6)}$ -lactones of type *VI* with an *E*-configuration (*trans*) of the $\Delta^{4(5)}$ bond have optimum conformations with $\Phi_R \leq 120$, while the $C_{(6)}$ -lactones of type *VII* with a *Z*-configuration (*cis*) of the $\Delta^{4(5)}$ bond have an optimum conformation with $\Phi_R \geq 120$. This was already mentioned by Herz and coworkers^{6,7}. Therefore it is evident that the validity of the relation (*I*) can be expected in $C_{(6)}$ -germacrolides and not in $C_{(6)}$ -heliangolides. This case also represents a demonstration of the factors limiting the conformation of the annelated cycle. In this case it is the configuration of the $\Delta^{4(5)}$ double bond. The original, erroneous formulation of heliangolides eucannabinolide⁴ and nobilin¹⁹ as germacrolides with a *cis*-configuration of the lactone ring on the basis of the rule (*I*) was also merely a logical consequence of the assumption of the *E*-configuration of the $\Delta^{4(5)}$ double bond.

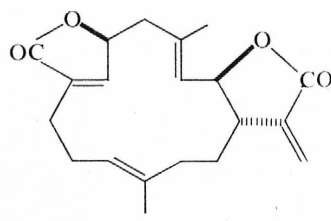
For open-chain lactones ($n \rightarrow \infty$) and lactones annelated with large cycles ($n > 10$) with a *trans*-configuration of the annelation the A-type of the lactone ring should already be quite typical. As an example of an open-chain lactone the pyncnolide (*VIII*) with ${}^4J_{BD} = 2.8$, ${}^4J_{BD'} = 2.6$ and ${}^3J_{AB} = 5.3$ (ref.⁸), and as an example for $n > 10$ ovatotidolide²⁰ (*IX*) with ${}^4J_{BD} = 2.0$ and ${}^4J_{BD'} = 1.8$ and ${}^3J_{AB} = 1.8$ (ref.²⁰)



VII



VIII



IX

can be mentioned. The structure of ovatodiolide was confirmed recently by X-ray analysis²⁰. The determined dihedral angle $\Phi_R = 147^\circ$ is consistent with the A-type.

The given discussion has defined the limits of validity and the utilizability of the relation (1). It is evident that in a general case the "cis/trans" configuration of the lactone ring cannot be deduced unambiguously on the basis of allylic interactions alone. Nonetheless, the dependence on a number of structural factors demonstrates the possibility of applying the general relation (4) in the determination of the stereostructure of the molecules of natural sesquiterpenic lactones, because in the determination of the structure the problem of the "cis/trans" relation appears in the final phase when the majority of the necessary structural factors is already known or estimable. The dependence on these structural factors can be, in principle, utilized for the determination of the character of these factors if the configuration of the lactone ring is known, for example for the determination of the configuration of the double bond $\Delta^{4(5)}$ in germacradienolides and similar. Anyway, the relation of the type (1) can afford a good starting hypothesis for the determination of the stereochemistry of the lactone ring.

The presented discussion of the configurational analysis of the lactone ring of type I based on the allylic interaction $^4J_{BD}$ can be also extended to the vicinal "bridge-head" constant $^3J_{AB}$. However, in this case the situation is no longer as favourable, because the types A and S cannot be separated from each other unambiguously according to the magnitude of $^3J_{AB}$. The basic insight can be obtained from the functional dependence of $^3J_{AB}$ on the dihedral angle $\Phi(H_A, H_B) = \varphi$. It has already been shown (ref.^{21,22}) that the empirical functional form of this dependence should be formulated at least in the form of a four-parameter trigonometric polynomial

$$^3J_{AB}(\varphi) = A + B \cos \varphi + C \cos 2\varphi + D \cos 3\varphi . \quad (5)$$

(The traditional three-parameter Karplus equation²³ ($D = 0$) is a bad model²² from the physical point of view, because in principle it cannot have an extreme (minimum) at $\varphi = 90^\circ$ for $B \neq 0$). The extremes of the function (5) are given by the condition²²

$$\partial J_{AB}(\varphi)/\partial(\varphi) = 0 = B \sin \varphi + 2C \sin 2\varphi + 3D \sin 3\varphi \quad (6)$$

which is always fulfilled for $\varphi = 0$ and 180° (trivial extremes). If assuming that $^3J_{AB}(\min) = ^3J_{AB}(90) = 0$ then from equation (6) it follows that $B = 3D$ (ref.²²). On the basis of the present experimental material the following values could be estimated: $^3J_{AB}(0) = 10-11$ and $^3J_{AB}(180) = 12-13$ (the observed values of $^3J_{AB}(\max)$ are about 10 or 12, respectively). In view of the fact that these values are mostly for angles that are somewhat different from the theoretical extremes 0° and 180° , somewhat higher values must be considered for the determination of the real

estimates of the coefficients of equation (5)). Then the estimates $A = 5.5-6$, $B = -0.75$, $C = 5.5-6$, and $D = -0.25$ are obtained from equation (5) and (6). For these values of the coefficients the function (5) is represented graphically in Fig. 9. Using this dependence and in view of the variability of the dihedral angle $\Phi = 120 \pm \pm 60^\circ$ for *trans*-lactones and $\Phi = 0 \pm 60^\circ$ for *cis*-lactones the following approximate limitations may be formulated:

$$0 \leq {}^3J_{AB}(\text{trans-lactone, A-type}) < 3-4(\text{trans-lactone, P-types}) < < {}^3J_{AB}(\text{trans-lactone, S-type}) \leq 12-13$$

$$2 < J_{AB}(\text{cis-lactone, A + S-types}) < 10-11(\text{cis-lactones, P-types}) \quad (7)$$

On combination of relations (4) and (7) some further information for the determination of "*cis/trans*" relation may be obtained. This applies mainly for extremes.

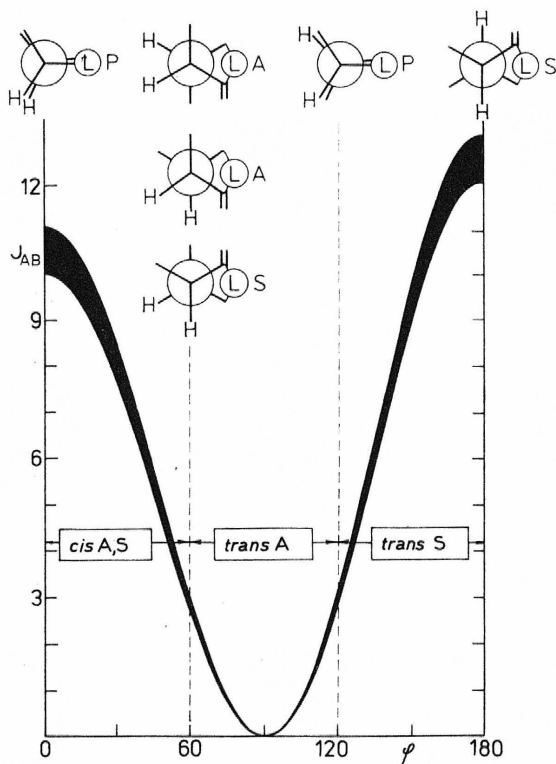


FIG. 9

Dependence of the Vicinal Const. ${}^3J_{AB}$ on the Dihedral Angle $\Phi(H_B, H_A) = \varphi = \angle H_A-C_A-C_B-H_B$, and the Assignment of the Pseudorotational Types of the γ -Lactone Ring of Type I

For example, it is evident that the values $|^4J_{BD}| > 3$ and $^3J_{AB} \approx 8-10$ do not indicate *cis*- and *trans*-lactone, but only the S-type. On the other hand, the values $|^4J_{BD}| < 3$ and $|^4J_{BD'}| < 3$ and $^3J_{AB} \approx 8-10$ are already rather indicative of a *cis*-lactone of P(A)-type. This is typical of the already mentioned $C_{(6)}$ -pseudoguaianolides. The second extreme case is represented by *trans*-lactones of A-type, for which the values $|^4J_{BD}| < 3$ and $|^4J_{BD'}| < 3$ and $^3J_{AB} < 2$ should be indicative.

For the estimation of the applicability of the rules (4) and (7) to the determination of the “*cis/trans*” fusion of the lactone ring in individual structural types of substances, especially for the formulation of empirical ranges of values of allylic vicinal constants the circumstance is still a great handicap that the material for the study is restricted predominantly to natural substances. In consequence of various conformational factors affecting the course of the biogenesis of sesquiterpenic lactones (ref.^{5,24,25}) the palette of the stereoisomers differing in configuration of the annelation of the lactone ring of type I is, however, very poor for a number of structural types. Either *cis*-lactones or, on the contrary, *trans*-lactones are missing. For example for $5\alpha H, 7\alpha H$ -guaian-6,12-olides the *trans*-configuration of the lactone is typical, while for $5\beta CH_3, 7\alpha H$ -pseudoguaian-6,12-olides the *cis*-configuration of the lactone is typical (ref.^{5,24,25}). The lack of *cis*-lactones is especially striking. The predominant occurrence of *trans*-lactones could be explained, in principle, by the already mentioned conformational factors, *i.e.* by optimum conformation of the annelated cycle with the pseudodiequatorial orientation of the lactone ring. The role of these factors is very probable considering that the formation of the lactone ring takes place in heterogeneous phase during the binding of the C_{15} -precursor on some receptor. Here the extended conformation of the precursor with the equatorial position of the lactogenic C_3 -side chain should always be preferred. The preference of the equatorial orientation of the lactone ring closure is then already evident. The pseudodiequatorial orientation of the participating lactonogenic functional groups is also ideal for the formation of a *trans*-lactone ring for the reason that in this case the same conformation of the lactonogenic γ -hydroxy acid and γ -lactone ring may be assumed. In *cis*-lactone, this assumption is no longer evident. It could be rather expected that the conformations would be different and that the formation of the lactone would therefore be connected with the torsion on the lactone bridge formed, and hence, that it would be energetically more favourable than in the case of a *trans*-lactone. In *cis*-lactones the quasi-eclipsed conformation of the lactone bridge (P-type) which may be available is some conformations, as for example in conformations of a seven-membered ring, might be an exception. Naturally, these conformational aspects are only global. In actual cases the concerted or non-concerted formation of both lactonogenic groups will play its role. Of course, the conformational selectivity of the biogenesis is advantageous for the problem under discussion, in that owing to its existence the conformationally unfavourable skeletal types that could potentially have atypical pseudorotational types of the lactone rings with respect to the “*cis*”

/trans" rule (1), are to a certain extent *a priori* eliminated. This preserves the dominant character of the subrelation (1) in the set of all possible subrelations associated to the relation (4), as well as its practical importance.

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Translated by Ž. Procházka.