STEREOCHEMICAL FEATURES OF THE STRUCTURE OF GERMACRANE LACTONES AND THE APPLICABILITY OF GEISSMAN'S RULE IN THIS SERIES

G. P. Moiseeva and B. Kh. Abduazimov

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Stereochemical features of the structure of the germacrane lactones have been investigated. By correlating the circular dichroism and the results of x-ray structural analyses of the germacranolides with different types of linkage of the lactone ring it has been estabished that Geissman's rule is satisfied in the trans-trans-germacra-1(10), 4-dienolide series if the lactone ring has the S-conformation and the decadiene ring the chair-chair conformation in the C_6-trans-lactones and, correspondingly, the A and chair-chair conformations in the C_6-cis compounds. The decadiene ring has the boat-boat conformation if there is an exocyclic double bond at C_{10} in the C_8-trans-germacrolides, and a positive Cotton effect (CE) is observed in the CD spectra in the 220 nm region and a negative one at 200 nm.

Geissman's rule [1], established for sesquiterpene lactones, connects the position and nature of the linkage of the lactone ring with the sign of the Cotton effect (CE) in the 260-250 nm region due to the $n \rightarrow \pi$ transition of the unsaturated lactone chromophore in the following way:

Ring linkage	cis	trans
6–7	+	–
7–8	–	+

Further investigations have shown that the sign of this Cotton effect is determined by the chirality of the $C_D{=}C_C{-}C{=}O$ chromophore (Fig. 1) and the sign of its torsion angle ω_2 ($C_D{=}C_C{-}C{=}O$) [2], ω_2 being interconnected with the torsion angles ω_3 ($C_C{-}C_B{-}C_A{-}O$) and ω_4 ($R_B{-}C_B{-}C_C{-}R_A$) [3, 4], i.e., the $C_D{=}C_C{-}C{=}O$ chirality depends on the conformation of the lactone and decadiene rings.

In the germacranolides, the γ-lactone ring is capable of adopting two main conformations, S and A (Fig. 1). A trans-linked lactone ring has the S-conformation when the torsion angle $\omega_4 \leq 120°$, and the A-conformation when $\omega_4 \geq 120°$ [5, 6].

It can be seen from Fig. 1 that in the C_6-cis-lactones the torsion angle ω_4 ranges between 0 and $\pm 60°$. The A and S conformations of the lactone ring differ by the sign of the torsion angle ω_4. For the A conformation it is positive, and for the S conformation negative (see Fig. 1) [5, 6].

We have previously [7] put forward the hypothesis that Geissman's rule is not observed when the C_6-trans-linked germacranolides have the A conformation and the C_6-cis- and C_8-trans-linked lactones the S conformation.

The CD spectra of C_8-trans-germacranolides considered in [7] (tanakhin, tamirin, and mucrin) showed that these lactones do not obey Geissman's rule and it might therefore be expected that in them $\omega_4 \leq 120°$ and the lactone ring has the S conformation. X-ray structural analyses (XSAs) recently made of mucrin [8] and of tanakhin and tamirin [9] have shown that, in fact, in them the angle $\omega_4 \leq 120°$ and the lactone ring does have the S conformation (see compounds (XIII), (XIV), and (XVII) in Table 1). Thus, our hypothesis has been confirmed by

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TABLE 1. Details of the CD and XSA Spectra of the Germacranolides

Compound	λ_{max}, nm	[θ]	ω, deg	Conformation of the rings		Literature
				lactonic	decadienic	
		C_6-trans-Lactones*				
I. Costunolide	264 220 Below 200	−4690 +69000 (−)- CE	88,6	*S*	Chair-chair $^{15}D_5$, $_1D^{14}$	10,11
II. Eupatolide	261	( )- CE	89,9	"	"	3,12
III. Lactones (III)-(VII) from <u>Eupatorium mikanioides</u>	256 214	−6850 +68000	92,1	"	"	13,14
IV.	256 209	−7170 +89600		"	"	"
V.	255 210	−7170 −62700		"	"	"
VI.	256 214	−7840 +78400		"	"	"
VII.	256 214	−6550 +67400		"	"	"
VIII. Parthenolide	250	−1400	95,8	"	"	1,15
		C_6-trans-Lactone†				
IX. Eupaformonin	264	(+)- CE	135	*A*	Boat-chair	3
		C_6-cis-Lactones				
X. Lactones (X)-(XII) from <u>Montanoa hibiscifolia</u>	254 216 Below 200	+5360 −70200 (+)-CE	28,7	*A*	Chair-boat $_{15}D^5$, $^1D_{14}$	16,17
XI.	260 252 sh 242 224	+730 +850 +1050 −22000	27,9	"	"	"
XII.	250 218	−2900 −48500		"	"	"
		C_8-trans-Lactones†				
XIII. Tanakhin	256 222 207	−5180 +18600 −6850	110	*S*	Boat-boat	7,9
XIV. Tamirin	323 263 211	−2200 −5040 +9800	107,5	"	"	"
XV. Laurenobiolide	253 209	−5660 +43800	—	"	Chair-chair	18,19
XVI. Deacetylaurenobiolide	257 211	−1254 +22836	—	"	"	
XVII. Mucrin	253 213 sh 202	−5480 +20200 +40600	110,6	"	Boat-boat	7,8

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*Lactones obeying Geissman's rule.
†Lactones not obeying Geissman's rule.

XSA. Results published in the literature on the x-ray structural analysis of other germacranolides [3, 10-17] do not contradict our hyopthesis, either.

It can be seen from the information given in Table 1 on the CD and XSA of a series of germacranolides with different types of linkage of the lactone ring that the C_6-trans-lactones obeying Geissman's rule (see compounds (I-VIII) in Table 1) have the S conformation of the lactone ring and $\omega_4 \leq 120°$, but when the angle $\omega_4 \geq 120°$ (see compound (IX) in Table 1) the rule is not observed.

It must be mentioned that compounds (III-VII) differ only by the ester substituent at C_8 and these differences cannot substantially affect the conformation of the molecule, and therefore the torsion angles ω_4 in this group of lactones must be close to one another and to the value of 92° determined by x-ray structural analysis for lactone (III).

According to PMR results [16], the conformation of lactone (XII) differs insignificantly from that of lactone (X) and, consequently, the difference between the torsion angles ω_4 in these compounds will also be insignificant.

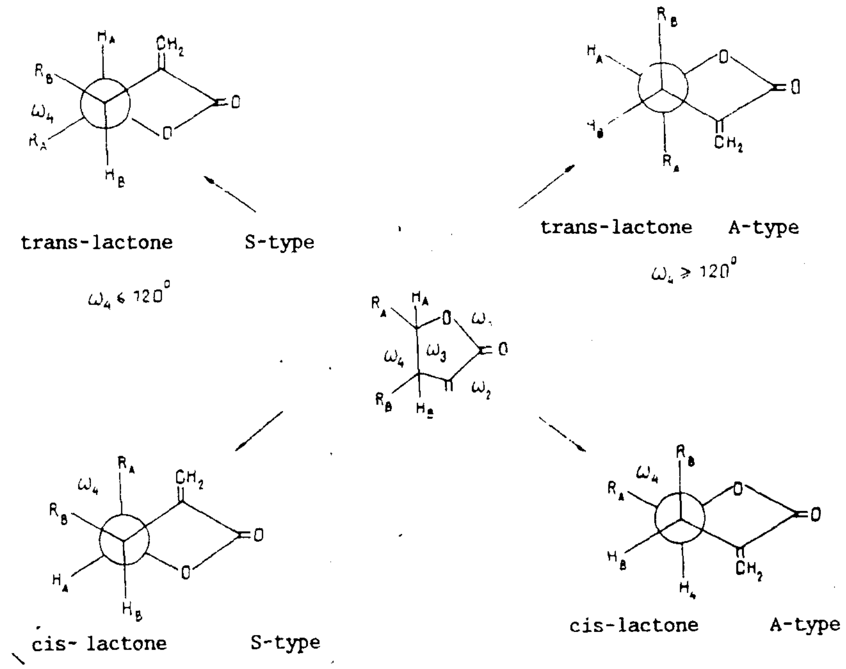


Fig. 1

For the C$_6$-cis-lactones (see compounds (X-XII) in Table 1), the A conformation of the lactone ring was estabished on the basis of the value $J_{7,13}$ = 1 Hz [16, 17], and for them Geissman's rule is satisfied, which again agrees with our hypothesis. Analysis of the facts given in Table 1 did not confirm the hypothesis put forward previously but permitted the following law relative to the conformation of the decadiene ring to be established.

Geissman's rule is observed for the trans-trans-germacra-1(10),4-dienolides if in the C$_6$-trans-lactones (see compounds (I-VII) in Table 1) the ten-membered ring has the chair—chair [$^{15}D_5$, D^{14}] conformation and in the C$_6$-cis compounds (see compounds (X-XII) in Table 1) if it has the chair-boat ($_{15}D^5$, $^1D_{14}$) conformation. At the same time, it must be mentioned that for the C$_8$-trans-lactones (XV) and (XVI), with the preferred chair-chair conformation, Geissman's rule is not observed.

The conformations of the lactonic and ten-membered rings in compounds (XV) and (XVI) were estabished on the basis of NMR results [18, 19].

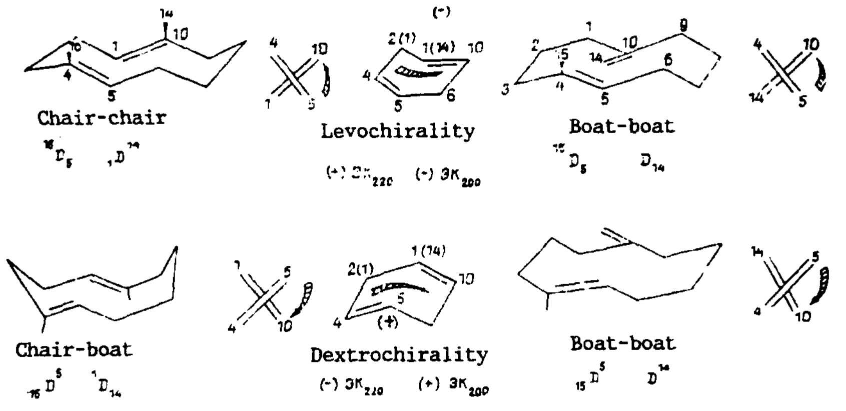


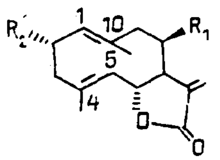
Fig. 2

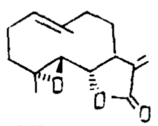
Generalizing what has been said above, it may be concluded that the observance of Geissman's rule in the trans-trans-germacra-1(10), 4-dienolides shows the S conformation of the lactone ring and the chair-chair conformation of the decadiene ring in C_6-trans-lactones and, correspondingly, the A conformation and the chair-boat conformation in the C_6-cis- compounds.

If in the case of one double bond there is an epoxy group in the decadiene ring, the characteristics of the Cotton effects connected with the absorption of the double bonds do not change [20]. In mucrin (XVII), the ten-membered ring has the coat-boat conformation according to XSA results [8], and the epoxy group and the double bond at C_4–C_5 are parallel and there is no trans-angular interaction. In the CD spectrum of mucrin a (+)-CE is observed at 202 nm with an inflection at 212 nm due to the $\pi \rightarrow \pi^*$ transition of the double bond and of the unsaturated lactone group, respectively.

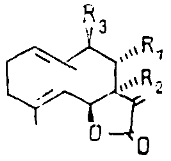
If the double bonds of the ten-membered ring of a germacranolide are skew with respect to one another, then, thanks to dipole-dipole interaction between the electric moments of the $\pi \rightarrow \pi^*$ transitions of the two double bonds, there is an exciton splitting of the Cotton effect connected with this transition into two components, i.e., into two Cotton effects of approximately equal intensity and opposite signs. In the CD spectra of the germacranolides, these Cotton effects are observed in the 220 and 200 nm regions, the latter sometimes being located below 200 nm and not being recorded because of instrumental limitations [11], while the intensities of the observed exciton Cotton effects are not always the same because of the superposition of CEs connected with other electronic transitions.

The sequence of components of the exciton couplet [(+)-CE_{220} and (–)-CE_{200} or (–)-CE_{220} and (+)-CE_{200}] depends on the spatial arrangement of the two double bonds. Thanks to homocoupling, skew double bonds of the ten-membered ring form a chromophoric system approximating in its properties to an internally asymmetric chromophore and constitute a new source of asymmetry – conformational. Two types of conformational asymmetry due to the levo- and dextrochirality of the chromophoric system are distinguished.





VIII



I. $R_1=H$; $R_2=H$

II. $R_1=OH$; $R_2=H$

III. $R_1=O-\underset{\overset{\|}{O}}{C}-\overset{OH}{\underset{CH_2OH}{C}}-\overset{CH_3}{\underset{SH}{CH}}$; $R_2=OH$

IV. $R_1=O=\underset{\overset{\|}{O}}{C}-\overset{CH_2}{\overset{\|}{C}}-\overset{CH_3}{\underset{OH}{CH}}$; $R_2=OH$

V. $R_1=O-\underset{\overset{\|}{O}}{C}-\underset{CH_3}{C}\overset{O}{-}\underset{CH_3}{C}-H$; $R_2=OH$

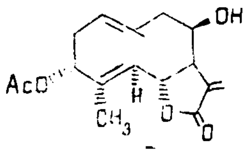
VI. $R_1=O-\underset{\overset{\|}{O}}{C}-\overset{OH}{\underset{CH_2OH}{C}}-\overset{CH_3}{\underset{OH}{CH}}$; $R_2=OH$

VII. $R_1=O-\underset{\overset{\|}{O}}{C}-\underset{CH_2OH}{C}\overset{O}{-}\overset{CH_3}{CH}$; $R_2=OH$

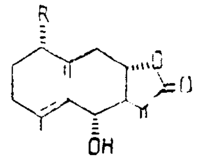
X. $R_1=O-\underset{\overset{\|}{O}}{C}-\underset{CH_3}{C}\underset{O}{-}\overset{CH_3}{CH}$
$R_2=H$
$R_3=O-\underset{\overset{\|}{O}}{C}-CH_3$

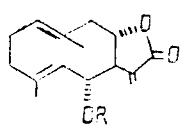
XI. $R_1=O-\underset{\overset{\|}{O}}{C}-\underset{CH_3}{C}\underset{O}{-}\overset{CH_3}{CH}$
$R_2=OH$
$R_3=O-\underset{\overset{\|}{O}}{C}-CH_3$

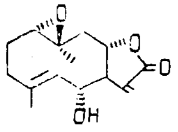
XII. $R_3=O-\underset{\overset{\|}{O}}{C}-\underset{CH_3}{C}\underset{O}{-}\overset{CH_3}{CH}$
$R_2=H$; $R_1=OH$



IX







XIII R = OH

XIV R = O

XV $R = \underset{\underset{O}{\|}}{C}-CH_3$

XVI R = H

XVII

It is generally considered that the system possesses levochirality if the route from the near end to the remove end (i.e., from C_4 along C_4—C_5 in the direction to the C_1—C_{10} bond) takes place counterclockwise, and then the plane in which the C_4—C_5 and C_1—C_{10} double bonds are located possess a negative angle (Fig. 2) [11] and, conversely, if the system has dextrochirality, then the route from the near end to the remote end takes place clockwise and the angle between the planes is positive (see Fig. 2) [16].

According to the facts given above, in the (${}^{15}D_5$, D^{14}) conformers, in which the ten-membered ring has the chair-chair conformation (compounds (I-VII), (XV), and (XVI)), the planes of the C_4—C_5 and C_1—C_{10} double bonds form a negative angle (see Fig. 2), and in the CD spectra at 220 and 200 nm are observed (+)- and (—)-Cotton effects, respectively [11, 16]. In the (${}_{15}D^5$, ${}^1D_{14}$) conformers, the conformation of ten-membered ring is chair-boat (compounds (X-XII)), the angle between the planes of the double bonds is positive (Fig. 2), and, correspondingly (—)-CE_{220} and (+)-CE_{200} are observed [16].

The CD spectrum of tanakhin contains a (+)-CE_{222} and (—)-CE_{207} (see compound (XIII) in Table 1), i.e., the same Cotton effects as in the trans-trans-germacra-1(10), 4-dienolides with the chair-chair conformation of the ten-membered ring. On this basis, an erroneous hypothesis was put forward previously concerning an unimportant change in the cyclodecadiene conformation when an endocyclic double bond was replaced by an exocyclic one [7].

The x-ray structural analysis of tanakhin and tamirin made later showed that the conformation of the ten-membered ring in them was boat-boat [9]. The identity of the sign of the Cotton effect in the 220-200 nm region for tanakhin and compounds of the costunolide type is explained by the identical mutual orientations of the double bonds in space, i.e, the planes of the exocyclic (at C_{10}) and endocyclic (at C_4—C_5) double bonds in compounds (XIII) and (XIV) with the boat-boat conformation form a negative angle just like the endocyclic double bonds (C_1—C_{10} and C_4—C_5) in compounds with the chair-chair conformation of the cyclodecadiene ring (see Fig. 2).

Thus, if in the C_8-trans-germacranolides there is an exocyclic double bond at C_{10} while a (+)-CE and a (—)-CE are observed in the 220 and 200 nm regions respectively, the most probably conformation of the cyclodecadiene system will be boat-boat, which can also be used for the conformation of assignments in germacranolide series. It is obvious that this is also valid for C_6-trans-lactones.

The experimental part has been described previously [7].

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PULCHELLIN C AND INUCHINENOLIDE C FROM *Inula caspica*

S. M. Adekenov, M. A. Abdykalykov,
K. M. Turdybekov, Yu. T. Struchkov,
and A. N. Pushin

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The pseudoguaianolide inuchinenolide C and the eudesmanolide pulchellin C have been isolated for the first time from the flower heads and leaves of *Inula caspica* Blume, and their spatial structures have been established by an x-ray structural experiment as 2α,6β-diacetoxy-6α-hydroxy-1α,7α(H),8β,10β(H)-pseudoguai-11(13)-en-8,12-olide and 2α,3β-dihydroxy-5β,7α,8α(H)-eudesma-4(15),11(13)-dien-8,12-olide, respectively.

The isolation from the epigeal part of the Caspian inula, *Inula caspica* Blume of the sesquiterpene lactones britannin, incaspin, and 3β-hydroxy-2α-senecioyloxyisoalantolactone has been reported previously [1, 2].

On the column chromatographic separation of the lactone fractions, after the compounds mentioned had been obtained, after the compounds mentioned had been obtained, two crystalline substances (I) and (II) were isolated.

Substance (I). $C_{19}H_{26}O_7$, mp 156-158°C (ethanol), $[\alpha]_D$ + 95.5° (c 0.0045; chloroform). The IR spectrum of the substance contained signals at (cm^{-1}) 3540 (OH); 1780 (γ-lactone carbonyl); 1760, 1740 (carbonyls of aceto groups); and 1680. The PMR spectrum of the substances showed the following signals (δ, ppm): 0.90 (3 H, s) – characteristic for an angular methyl; 0.98 (3 H, d) – a secondary methy; 2.02 (3 H, s) and 2.10 (3 H, s) – the methyls of acetyl groups; 3.50 (1 H, dd, J_1 = 3 Hz, J_2 = 8 Hz) – a proton at C_7; 4.44 (1 H, ddd, J = 11 Hz) – a lactone proton; 4.88 (1 H, d, J = 3 Hz) – a hemihydroxylic proton; 4.93 (1 H, m) and 5.60 (1 H, dd, J_1 = 9 Hz, J_2 = 11 Hz) – the hemihydroxylic protons H-2 and H-4, respectively; and 5.97 (1 H, d, J = 3 Hz) and 6.20 (1 H, d, J = 3 Hz) – the protons of an exomethylene group conjugated with the carbonyl of a γ-lactone.

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