STRUCTURE OF SESQUITERPENIC LACTONES OF SOME SPECIES OF SUBTRIBE *Centaureinae* DUMORT.*

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The authors describe in full the elucidation of complete structures of guaianolide and germacranolide lactones, isolated from some species of genera *Centaurea* L., *Chartolepis* CASS. and others belonging to subtribe *Centaureinae* DUMORT. The structures were determined mainly on the basis of detailed analysis of ^{1}H NMR and CD spectra. The structure of linichlorin B (*XV*) was determined by X-ray diffraction analysis.

For many years, sesquiterpenic lactones, isolated from species of subtribe *Centaureinae* DUMORT. (family *Asteraceae*, syn. *Compositae*, tribe *Cardueae*, syn. *Cynareae*), represent a subject of our investigations (refs[1 – 11]).** As early as ten years ago we published correct structures of earlier described guaianolides – repin (*I*), acroptilin (*II*), janerin (*III*), chlorohyssopifolin B (*IV*), chlorohyssopifolin D (*V*), chlorohyssopifolin E (*VI*), linichlorin A (*VII*) and chlorojanerin (*VIII*) – on the basis of detailed analysis of their ^{1}H NMR spectra and published structural correlations[1]. In the present communication we describe in extenso a detailed determination of complete structures of sesquiterpenic lactones *I* – *VIII* and other structurally related lactones which we isolated from *Centau-*

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**In refs[4,5] the name "cebelin C" should be changed for "chlorojanerin" and the name "cebelin D" for "8-deacetylcentaurepensin-8-*O*-(4′-hydroxy)tiglate".

rea bella TRAUTV. and other species of subtribe *Centaureinae*, e.g. genus *Centaurea* L., *Chartolepis* CASS. and others (ref.[11]).

From *Centaurea bella* TRAUTV. we obtained repin[2] (*I*), m.p. 163 – 165 °C, $[\alpha]_D$ +98.4°, composition $C_{19}H_{22}O_7$, which was identical with the compound isolated earlier from species *Acroptilon repens* (L.) DC. (ref.[12]) and *Centaurea hyrcanica* BORNM. (refs[13,14]), as confirmed by comparison of physical constants and IR and ^{1}H NMR spectral data. From *C. bella* we further isolated[2] acroptilin (*II*), m.p. 195 – 198 °C, $[\alpha]_D$ +93.8°, composition $C_{19}H_{23}ClO_7$. Comparison of physical constants, IR and ^{1}H NMR spectra has shown that this compound is identical with acroptilin isolated by Soviet authors from species *Acroptilon repens*[12,15] and *Centaurea hyrcanica*[14], and obtained as chlorohyssopifolin C by Spanish authors[16] from species *C. hyssopifolia* VAHL.*

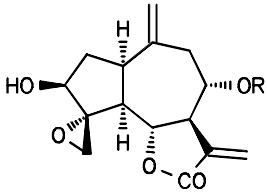
Another compound isolated by us from *C. bella* was noncrystalline janerin[2] (*III*) of composition $C_{19}H_{22}O_6$ and $[\alpha]_D$ +75.4°. We proved its identity with janerin, obtained by Gonzáles and coworkers[17] from the species *C. janeri* GRAELLS, again by comparison of physical constants and ^{1}H NMR and IR data.

From *C. bella* we also obtained centaurepensin[4] (chlorohyssopifolin A) (*IX*), m.p. 216 – 218 °C, composition $C_{19}H_{24}Cl_2O_7$, which was isolated practically simultaneously from *Centaurea repens* L. (ref.[18]) and *C. hyssopifolia* (ref.[19]). The identity of our compound with the earlier described[14] centaurepensin (chlorohyssopifolin A) was confirmed by comparison of physical constants and IR and ^{1}H NMR data.

Later on, the sesquiterpenic lactones *I* – *III* and *IX* were also found in other plant species (see, e.g., refs[4 – 6, 20]).

We derived[1] stereostructures of the lactones *I* – *III* from the described partial data on their structure, detailed analysis of ^{1}H NMR spectra and comparison with data on subluteolide (*X*) which was the first lactone of the 1αH,3αH,5αH,6βH,7αH,8βH-3,8-dihydroxy-4α,15-epoxyguai-10(14),11(13)-dien-6,12-olide type (*XI*) whose stereostructure was fully elucidated[21] as early as in 1977. The correctness of structures *I* – *III* was confirmed by correlation with centaurepensin (*IX*) the structure of which (including the absolute configuration) was determined by X-ray diffraction[18] as well as by chemical correlation with α-santonin[23] (*XIII*) via cynaropicrin[22] (*XII*). Acroptilin (chlorohyssopifolin C) (*II*) was converted into centaurepensin (chlorohyssopifolin A) (*IX*) by reaction with hydrogen chloride[16]. In view of the mechanism of epoxide opening under the given conditions, this fact shows that the structure of acroptilin, including absolute configuration, is represented by formula *II*. Acroptilin (*II*) was chemically correlated with repin (*I*) via compound *XIV* (ref.[24]) and therefore both compounds *I* and *II* have identical sesquiterpenic part. After characterization of the ester part, it was possible to

* We are indebted to Professor A. G. Gonzales and Dr J. Bermejo for copies of ^{1}H NMR and IR spectra of acroptilin, chlorohyssopifolin C, janerin and some other lactones.

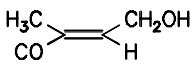


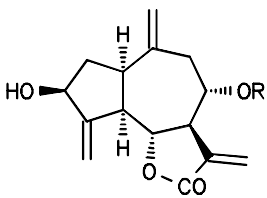
I, R = CO–C(CH3)(O)–CH2

II, R = CO–C(CH3)(OH)–CH2Cl

III, R = CO–C(CH3)=CH2

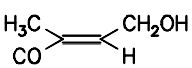
X, R = CO–C(CH3)(O)–CH2

XXVII, R = 



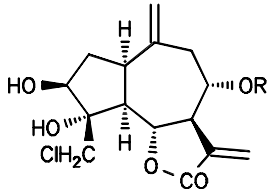
XII, R = CO–C(CH2OH)=CH2

XV, R = CO–C(CH3)(OH)–CH2Cl

XIX, R = 

XXXI, R = CO–C(CH3)(O)–CH2

XLI, R = CO–C(CH3)(OH)–CH2OH



IV, R = H

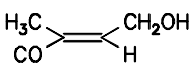
V, R = CO–C(CH3)(OCH2CH3)–CH2OH

VI, R = CO–C(CH3)(OH)–CH2OH

VII, R = CO–C(CH3)=CH2

VIII, R = CO–C(CH2OH)=CH2

IX, R = CO–C(CH3)(OH)–CH2Cl

XXVIII, R = 

XXX, R = CO–C(CH3)(O)–CH2

derive formula *I* for repin, including the absolute configuration. The structure *I* for repin has been recently confirmed by X-ray diffraction analysis[25]. The structure of janerin (more precisely, the completion of the stereostructure suggested[17] for this compound previously) was derived from correlation of ^{1}H NMR spectra of repin (*I*) and acroptilin (*II*) on the one side and janerin (*III*) on the other. We clarified the absolute configuration of the latter compound by comparison of CD spectra and specific rotation of compounds *I* – *III* (Table I) and thus the formula *III* describes also the absolute configuration of janerin.

For all sesquiterpenic lactones that were correlated with some of the lactones *I* – *III* and *IX* (either chemically or by ^{1}H NMR spectra) it was possible to derive correct stereostructures: this concerns e.g. chlorohyssopifolin B (*IV*) (ref.[19]), chlorohyssopifolin D (*V*) (ref.[16]), chlorohyssopifolin E (*VI*) (ref.[16]), linichlorin A (*VII*) (ref.[26]) (which, as indicated by Russian authors[27], is very probably identical with elegin from *Saussurea elegans* LEDEB.), linichlorin B (*XV*) (ref.[26]) and chlorojanerin (*VIII*) (ref.[17]). The stereostructures of sesquiterpenic lactones *I* – *III* were directly or indirectly verified by results of other authors (e.g. refs[28 – 33]) and especially by X-ray diffraction analysis of acroptilin[34] (*II*) and repin[25] (*I*). In order to verify the stereostructures of lactones *I* – *III* and lactones correlated with them, we performed an X-ray diffraction study of acroptilin (*II*), with results identical with those of Stevens and Wong[34], and of linichlorin B (*XV*).

The X-ray diffraction analysis of linichlorin B (*XV*) (its molecule is depicted in Fig. 1, heavy atoms coordinates, bond lengths and valence and torsion angles are given in Tables II – V) afforded the following results: *cis*-annelation of the five- and seven-

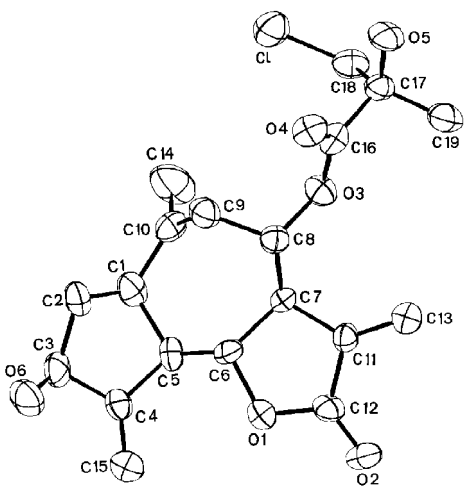


FIG. 1
View of a single molecule of linichlorin B (*XV*). Thermal ellipsoids are drawn at the 40% probability level; hydrogen atoms are omitted for clarity

TABLE I

CD spectra of guaianolides *I – III*, *VIII – X*, *XV – XXV*, *XXVII – XXXII* and germacranolides *XXVI*, *XXXIII – XXXVI*

Compound	nm	Δε	nm	Δε	nm	Δε
			Guaianolides			
I[a]	–	–	228	–0.9	259	–0.5
II[b]	–	–	227	–1.3	260	–0.4
III[c]	–	–	–	–	267	–0.2
VIII	209	+6.1	–	–	259	–0.3
IX	203	+13.1	228	–1.8	257	–0.5
X[d,e]	–	–	225	–6.5	264	–0.3
XV	201	+22.9	225	–2.2	256	–0.6
XVI	205	+16.3	228	–1.4	–	–
XVII	205	+16.9	228	–1.4	–	–
XVIII	214	+2.5	–	–	264	–0.3
XIX	205	+7.1	–	–	268	–0.1
XX	210	+6.1	–	–	265	–0.3
XXI	205	+8.0	227	+1.4	275	–0.2
XXII	210	+3.2	–	–	265	–0.3
XXIII[f]	208	+6.3	237	–0.8	–	–
XXIV	210	+4.0	226.5	–2.6	257	+0.3
XXV	210	+3.5	225	–1.6	260	–0.2
XXVII	–	–	232	+0.6	270.5	–0.1
XXVIII[g]	205	+4.6	237	+0.4	268	–0.2
XXIX	205	+14.1	–	–	266	–0.2
XXX[h]	210	+3.0	230.5	–0.2	–	–
XXXI	205	+18.6	226	–1.2	258	–0.4
XXXII	210	+4.8	–	–	265	–0.4
			Germacranolides			
XXVI	205.5	–0.7	226.5	+0.6	–	–
XXXIII	–	–	218	+31.1	259	–1.8
XXXIV	–	–	228	0	252	–2.0
XXXV	210	–3.2	–	–	255	+0.6
XXXVI	210	–5.9	–	–	252	–1.0

Specific rotations $[\alpha]_D$: [a] +98.4; [b] +93.8; [c] +74.5; [d] +54.0 (from ref.[21]). Data taken from: [e] ref.[21]; [f] ref.[9]; [g] ref.[30]; [h] ref.[37].

membered homocycles, *trans*-annelation of the γ-lactone ring, α-orientation of hydrogen atoms in positions 1, 3, 5 and 7, and β-orientation of hydrogen atoms in positions 6 and 8. The seven-membered ring assumes a distorted twist-chair conformation of approximate C_2 symmetry, the C_2 axis passing through C(8) and the midpoint of the C(1)–C(5) bond. Both five-membered rings exist in almost ideal half-chair conformation. In the methylenecyclopentanol ring, the approximate C_2 axis passes through C(4) and midpoint of the C(1)–C(2) bond. The average value of the five endocyclic torsional angles is 24.6°. In the γ-lactone ring, the approximate C_2 axis passes through C(12) and the

TABLE II
Atomic positional parameters for linichlorin B (*XV*)

Atom	*x*	*y*	*z*
C(1)	0.1932(6)	0.3649(3)	0.5722(8)
C(2)	0.3004(6)	0.3961(3)	0.6512(8)
C(3)	0.2526(6)	0.4405(3)	0.7851(8)
C(4)	0.1425(6)	0.4039(3)	0.8244(8)
C(5)	0.1112(5)	0.3480(3)	0.7108(8)
C(6)	0.1259(6)	0.2739(3)	0.7732(7)
C(7)	0.0981(6)	0.2140(3)	0.6535(7)
C(8)	0.2063(6)	0.1869(3)	0.5793(7)
C(9)	0.2816(6)	0.2445(4)	0.5107(8)
C(10)	0.2161(6)	0.3075(3)	0.4539(8)
C(11)	0.0259(5)	0.1646(3)	0.7486(7)
C(12)	–0.0113(6)	0.2007(3)	0.8956(8)
C(13)	–0.0064(7)	0.1005(3)	0.7198(8)
C(14)	0.1860(9)	0.3131(4)	0.3056(9)
C(15)	0.0905(6)	0.4142(3)	0.9673(9)
C(16)	0.2493(5)	0.0948(3)	0.3953(7)
C(17)	0.2081(6)	0.0502(3)	0.2531(8)
C(18)	0.1678(6)	0.0966(4)	0.1204(7)
C(19)	0.1104(6)	0.0049(3)	0.3054(8)
O(3)	0.3314(4)	0.4536(2)	0.9125(6)
O(6)	0.0422(4)	0.2644(2)	0.9025(5)
O(8)	0.1692(3)	0.1396(2)	0.4503(5)
O(12)	–0.0790(4)	0.1826(2)	0.9988(5)
O(16)	0.3471(4)	0.0910(2)	0..4447(5)
O(17)	0.3015(4)	0.0085(2)	0.2065(5)
Cl	0.2773(2)	0.1548(1)	0.0528(2)

TABLE III
Selected bond lengths (Å) in linichlorin B (*XV*)

Atoms	Bond length	Atoms	Bond length
C(1)–C(18)	1.777(7)	C(4)–C(5)	1.533(8)
O(1)–C(6)	1.464(7)	C(4)–C(15)	1.282(9)
O(1)–C(12)	1.366(7)	C(5)–C(6)	1.522(8)
O(2)–C(12)	1.217(7)	C(6)–C(7)	1.558(8)
O(3)–C(8)	1.464(7)	C(7)–C(8)	1.494(8)
O(3)–C(16)	1.342(7)	C(7)–C(11)	1.492(8)
O(4)–C(16)	1.205(7)	C(8)–C(9)	1.530(8)
O(5)–C(17)	1.395(7)	C(9)–C(10)	1.502(9)
O(6)–C(3)	1.426(8)	C(10)–C(14)	1.297(10)
C(1)–C(2)	1.524(9)	C(11)–C(12)	1.479(8)
C(1)–C(5)	1.534(9)	C(11)–C(13)	1.305(8)
C(1)–C(10)	1.504(9)	C(16)–C(17)	1.543(9)
C(2)–C(3)	1.514(9)	C(17)–C(18)	1.499(8)
C(3)–C(4)	1.508(9)	C(17)–C(19)	1.489(9)

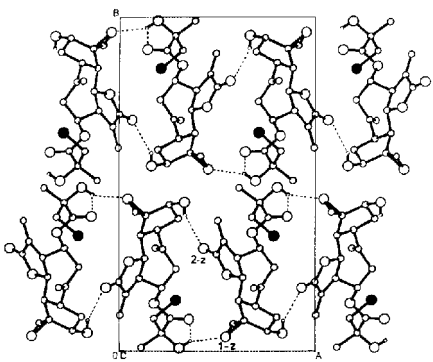


FIG. 2
The packing arrangement of the molecules of acroptilin (*II*) in crystal (along the *z*-axis)

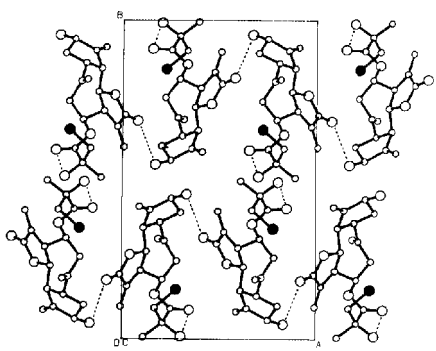


FIG. 3
The packing arrangement of the molecules of linichlorin B (*XV*) in crystal (along the *z*-axis)

midpoint of C(6)–C(7) bond. The average value of the five endocyclic torsion angles in the γ-lactone ring is 11.0°. The C(3)-hydroxyl group probably participates in intermolecular hydrogen bonding to the lactone oxygen atom O(2) of the neighbouring molecule, the distance between O(6) and O(2) being 2.90 Å. The only potential intramolecular hydrogen bond may involve the hydroxyl on C(17) which strongly interacts with carbonyl oxygen of the ester group (distance O(5)...O(4) = 2.60 Å) and may also interact with the chlorine atom (distance O(5)...Cl = 3.094(4) Å). According to our X-ray diffraction data for acroptilin (*II*), the analogous hydroxy group forms an intermolecular

TABLE IV
Selected bond angles (deg) in linichlorin B (*XV*)

Atoms	Angle	Atoms	Angle
C(6)–O(1)–C(12)	112.2(6)	C(7)–C(8)–C(9)	111.6(6)
C(8)–O(3)–C(16)	116.1(5)	C(8)–C(9)–C(10)	114.9(6)
C(2)–C(1)–C(5)	104.6(6)	C(1)–C(10)–C(9)	117.7(6)
C(2)–C(1)–C(10)	115.5(7)	C(1)–C(10)–C(14)	121.8(8)
C(5)–C(1)–C(10)	117.1(6)	C(9)–C(10)–C(14)	120.4(8)
C(1)–C(2)–C(3)	104.3(7)	C(7)–C(11)–C(12)	108.2(6)
O(6)–C(3)–C(2)	115.1(6)	C(7)–C(13)–C(11)	131.0(7)
O(6)–C(3)–C(4)	114.4(7)	C(12)–C(11)–C(13)	120.8(7)
C(2)–C(3)–C(4)	104.5(7)	O(1)–C(12)–O(2)	120.9(7)
C(3)–C(4)–C(5)	109.7(7)	O(1)–C(12)–C(11)	108.7(7)
C(5)–C(4)–C(15)	125.9(8)	O(2)–C(12)–C(11)	130.3(7)
C(1)–C(5)–C(4)	102.8(6)	O(3)–C(16)–O(4)	124.4(7)
C(1)–C(5)–C(6)	112.9(6)	O(3)–C(16)–C(17)	114.1(6)
C(4)–C(5)–C(6)	112.9(6)	O(4)–C(16)–C(17)	121.4(7)
O(1)–C(6)–C(5)	107.3(6)	O(5)–C(17)–C(16)	107.2(7)
O(1)–C(6)–C(7)	104.6(5)	O(5)–C(17)–C(18)	111.7(6)
C(5)–C(6)–C(7)	116.1(6)	O(5)–C(17)–C(19)	109.6(5)
C(6)–C(7)–C(8)	111.2(6)	C(16)–C(17)–C(18)	110.0(6)
C(6)–C(7)–C(11)	103.6(5)	C(16)–C(17)–C(19)	109.1(6)
C(8)–C(7)–C(11)	117.5(6)	C(18)–C(17)–C(19)	109.2(7)
O(3)–C(8)–C(7)	106.4(5)	Cl–C(18)–C(17)	112.8(6)
O(3)–C(8)–C(9)	109.3(5)		

hydrogen bond with the epoxide oxygen atom O(7) (distance O(5)...O(7) = 2.88 Å, O(5)H...O(7) = 2.23 Å and angle O(5)–H...O(7) = 143°). In linichlorin B, of course, this interaction is not available. Our inability to locate the hydrogen atoms associated with these hydroxyl groups in linichlorin B prevents us from making a more definite assessment of the hydrogen bonding in the crystal. Interestingly, crystals of linichlorin B (*XV*) and acroptilin (*II*) are isomorphous which illustrates the stereostructural simi-

TABLE V
Selected torsion angles (deg) in linichlorin B (*XV*)

Atoms	Angle	Atoms	Angle
C(10)–C(1)–C(2)–C(3)	–168.9	C(6)–C(7)–C(8)–C(9)	–51.0
C(5)–C(1)–C(2)–C(3)	–38.6	C(6)–C(7)–C(8)–O(3)	–170.2
C(1)–C(2)–C(3)–O(6)	156.9	C(11)–C(7)–C(8)–O(3)	70.7
C(1)–C(2)–C(3)–C(4)	30.7	C(11)–C(7)–C(8)–C(9)	–170.1
C(2)–C(3)–C(4)–C(5)	–11.8	C(7)–C(8)–C(9)–C(10)	–29.8
C(2)–C(3)–C(4)–C(15)	162.3	O(3)–C(8)–C(9)–C(10)	87.6
O(6)–C(3)–C(4)–C(15)	35.6	C(8)–C(9)–C(10)–C(1)	89.3
O(6)–C(3)–C(4)–C(5)	–138.5	C(8)–C(9)–C(10)–C(14)	–94.1
C(3)–C(4)–C(5)–C(1)	–11.5	C(9)–C(10)–C(1)–C(5)	–66.7
C(3)–C(4)–C(5)–C(6)	110.4	C(9)–C(10)–C(1)–C(2)	57.3
C(15)–C(4)–C(5)–C(6)	–63.5	C(14)–C(10)–C(1)–C(2)	–119.3
C(15)–C(4)–C(5)–C(1)	174.6	C(14)–C(10)–C(1)–C(5)	116.7
C(4)–C(5)–C(1)–C(2)	30.3	C(6)–C(7)–C(11)–C(12)	13.7
C(4)–C(5)–C(1)–C(10)	159.6	C(6)–C(7)–C(11)–C(13)	–167.3
C(6)–C(5)–C(1)–C(10)	37.6	C(8)–C(7)–C(11)–C(13)	–44.2
C(6)–C(5)–C(1)–C(2)	–91.7	C(8)–C(7)–C(11)–C(12)	136.7
C(1)–C(5)–C(6)–C(7)	–62.7	C(7)–C(11)–C(12)–O(1)	–5.9
C(1)–C(5)–C(6)–O(1)	–179.2	C(13)–C(11)–C(12)–O(1)	174.9
C(4)–C(5)–C(6)–O(1)	64.7	C(7)–C(11)–C(12)–O(2)	172.4
C(4)–C(5)–C(6)–C(7)	–178.8	C(13)–C(11)–C(12)–O(2)	–6.7
C(5)–C(6)–C(7)–C(8)	98.6	C(11)–C(12)–O(1)–C(6)	–5.4
C(5)–C(6)–C(7)–C(11)	–134.3	O(2)–C(12)–O(1)–C(6)	176.1
O(1)–C(6)–C(7)–C(11)	–16.2	C(12)–O(1)–C(6)–C(7)	13.8
O(1)–C(6)–C(7)–C(8)	–143.3		

larity of both compounds. The packing arrangement of the molecules of acroptilin (*II*) and linichlorin (*XV*) is shown in Figs 2 and 3.

The X-ray diffraction and ^{1}H NMR data for linichlorin B enabled us to compare its conformation in crystal and in solution. The dihedral angles between C–H bonds in the five- and seven-membered homocycles, found by X-ray diffraction, were compared with the values calculated from the corresponding vicinal coupling constants using a modified Karplus equation (for a detailed description see our previous paper[35]). The obtained good accord (Table VI) (estimated error of the NMR determination is ±10°) shows that conformational features in crystal and solution are similar. Greater differences, found for dihedral angles about the C(8)–C(9) bond, could be due to an increased flexibility and averaging of the values of *J*(H8,H9) in solution.

In addition to the mentioned lactones *I* – *III* and *IX*, we isolated from species *Centaurea bella* other sesquiterpenic lactones[4]: cebelin A (*XVI*), cebelin B (*XVII*), cebelin E (*XVIII*), cebelin F (*XIX*), cebelin G (*XX*), cebelin H (*XXI*), cebelin I (*XXII*), cebelin J (*XXIII*) (ref.[9]), cebelin K (*XXIV*), cebelin L (*XXV*), cebelin M (*XXVI*), cebelin P (*XXVII*) (which, or its enantiomer, was already isolated[36] from *Berkheya carlinopsis* WELW. ex HOFFM. ssp. *magalismontana* (H.BOL.) ROESSL.), 8-deacetylcentaurepensin-8-*O*-(4-hydroxy)tiglate[5] (*XXVIII*) (obtained previously[30] from *C. imperialis* HAUSSKN.), repdiolide[4] (*XXIX*) (found previously[28] in *C. repens* L.), lactone *XXX* (of known structure[37]; obtained previously from *Centaurea aegyptica*) and chlorojanerin (*VIII*) which was found for the first time in *C. janeri*[17] and later by us in some other species of the studied subtribe[9].

We studied in detail the structure of all the sesquiterpenic lactones mentioned (except those of known structure), as well as of the following undescribed lactones isolated by us within the framework of systematic investigation of species of subtribe *Centaureinae*[1 – 11]: 15-deoxyrepin (*XXXI*), obtained from many species of genus *Centaurea* L. (ref.[6])*, pterocaulin (*XXXII*) from two species of genus *Chartolepis* CASS. (ref.[5]), stenophyllolide (*XXXIII*)** (ref.[39]) from *Centaurea sphaerocephala* subsp. *lusitanica* (BOISS. et REUTER) NYMAN (ref.[9]), and three germacranolides *XXXIV* – *XXXVI* from *Stizolophus balsamita* (LAM.) CASS. ex TAKHT. (ref.[10]). A recent paper[40] reports the isolation and structure of further two hitherto undescribed guaianolides – cebelin N and cebelin O.

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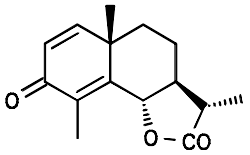
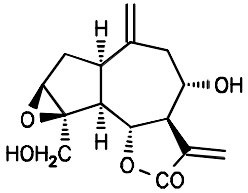
* One of recent papers[38] described, inter alia, the isolation of an allegedly undescribed sesquiterpenic lactone which was named salograviolide C. However, a compound of structure *XXXI*, named 15-deoxyrepin, had been found already earlier in many species of genus *Centaurea* L. (ref.[6]), and its structure had been determined[6,11]. Therefore, compound *XXXI* should be named 15-deoxyrepin instead of salograviolide C.

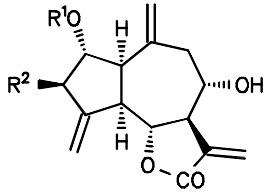
**In our previous communication[9], this compound is erroneously described as 3α,15-dihydroxycostunolide; its correct structure is *XXXIII*.



XIII



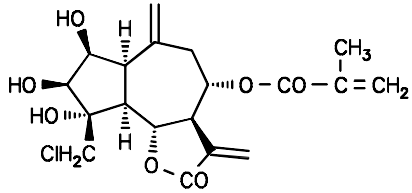
XIV



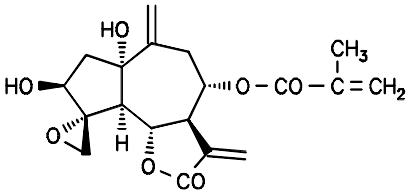
XVI, $R^1 = COCH(CH_3)CH_2CH_3$; $R^2 = OH$

XVII, $R^1 = COCH(CH_3)_2$; $R^2 = OH$

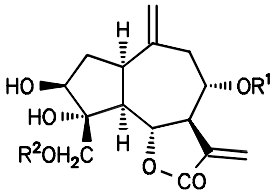
XXIV, $R^1 = COCH(CH_3)CH_2CH_3$; $R^2 = H$



XVIII



XXII

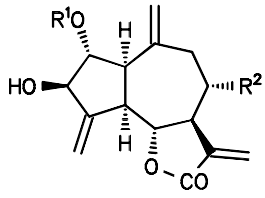


XX, $R^1 = CO-C(CH_2OH)=CH_2$; $R^2 = COCH_3$

XXI, $R^1 = CO-C(CH_3)=CH-CH_2OH$; $R^2 = COCH_3$

XXIII, $R^1 = CO-C(CH_3)(OH)-CH_2Cl$; $R^2 = H$

XXXII, $R^1 = CO-C(CH_3)=CH_2$; $R^2 = H$



XXV, $R^1 = COCH(CH_3)CH_2CH_3$; $R^2 = H$

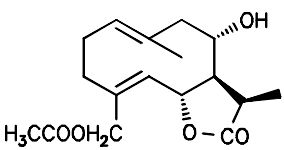
XXIX, $R^1 = H$; $R^2 = OCO-C(CH_3)=CH_2$

DISCUSSION

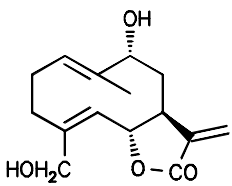
NMR Spectra

The structures of all the studied guaianolides and germacranolides were derived from detailed analysis of ^{1}H NMR data (Tables VI – X) and their comparison within series of structurally related compounds. In the case of hydroxy derivatives, we made use of in situ TAI-acylation and structural information gained from NMR spectra of the TAC-derivatives.

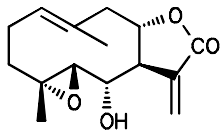
Complete structural assignment of proton signals and their coupling constants has shown that all the discussed guaianolides can be described by the general formula *XLII*. The seven-membered ring thus differs only in the substituent in position 8. The presence of exomethylene groups is proved by the characteristic signals of olefin protons: the doublets of H-13 and H-13′ at $\delta \approx 6.25$ and 5.60 with $J(13,7) > J(13',7) > 3.0$ Hz and $J(13,13') = 0$ for compounds with R^8 = OCOR or H are transformed into doublets of doublets with a significant downfield shift of the H-13′ signal (δ 6.16) and nonzero $J(13,13')$ in compounds where R^8 = OH (*XVI*, *XVII* and *XXIV*). Signals of exomethylene protons H-14 and H-14′ appear in the region δ 4.8 – 5.2 with charac-



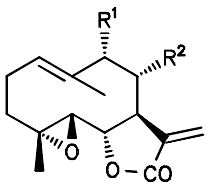
XXVI

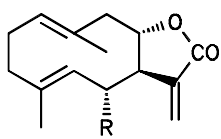


XXXIII



XXXIV





XXXV, $R^1 = R^2 = OH$

XXXVI, R^1 = OH; $R^2 = O-CO-CH=C(CH_3)-CH_2OH$

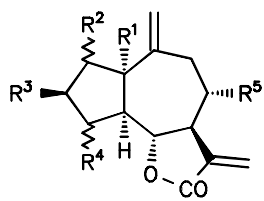
XXXVII, $R^1 = R^2 = H$

XXXVIII, R^1 = OH; R^2 = H

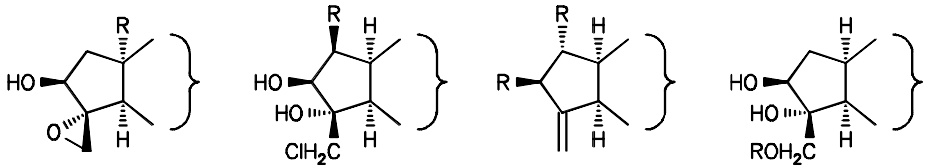
XXXIX, R = OH

XL, R = $OCOCH_3$

teristic geminal interaction $J(14,14')$ = 1.5 – 2.0 Hz. The relative configurations in positions 5, 6, 7 and 8 follow from the high values of $J(5,6)$, $J(6,7)$ and $J(7,8)$ = 9 – 11.5 Hz, which indicate mutual *trans*-orientation of protons in these positions. In a differential NOE experiment with linichlorin B (*XV*), saturation of H-6 signal resulted in NOE of H-8 and one of the methylene protons in positions 2 and 9; this enabled us to assign α- and β-protons in these positions. According to the Samek's rule[41], also the above-mentioned values of $J(13,7)$ and $J(13',7)$ are compatible with *trans*-annelation of the five-membered exomethylene-γ-lactone. The *cis*-annelation of the five- and seven-membered homocycles was indicated by values of $J(1,5)$ (about 8.5 Hz throughout the whole series of the guaianolides studied) as well as by NOE between H-1 and H-5 in linichlorin B (*XV*), and was confirmed by the X-ray diffraction data (vide supra). Except for cebelin L (*XXV*), all the discussed guaianolides have a free or esterified hydroxy group in position 8. The presence of free hydroxyl in compounds *XVI*, *XVII* and *XXIV* was indicated by the signal of H-8 (δ about 4.0) and confirmed by in situ TAI-acylation (characteristic downfield shift of the H-8 signal for about 1.2 ppm). The nature of the ester group was determined from the characteristic shifts and multiplicities of the ^{1}H NMR signals[42].



XLII



A *B* *C* *D*

According to the substitution in position 4, the discussed guaianolides can be divided into four groups, corresponding to partial formulae *A* – *D*. The presence of a 4α,15-epoxy group in compounds of group *A* (*I* – *III*, *X*, *XXII* and *XXVII*; for ^{1}H NMR data see Table VII) is indicated by characteristic signals of oxirane protons (doublets of

H-15 and H-15′ at δ 3.35 and 3.07 with J(15,15′) = 4.5 Hz). The almost identical chemical shifts and coupling constants of the five-membered ring protons indicate identical configurations of the 4,15-epoxide and the 3-OH group in the whole group of compounds. The accord with ^{1}H NMR data for subluteolide (*X*; for comparison, its data[21] are given in Table VII), for which the configuration 4α,15-epoxy-3β-hydroxy has been unequivocally established, makes possible the assignment of configuration in positions 3 and 4 in compounds *I* – *III*, *XXII* and *XXVII*. Cebelin I (*XXII*) is the only compound containing one more hydroxyl, in position 1α, as shown by the absence of H-1α proton and a marked downfield shift (0.5 ppm) of the H-5 signal.

For compounds of the group *B* (*VIII*, *IX*, *XVIII*, *XXVIII* and *XXX*; for ^{1}H NMR data see Table VIII), the presence of the 4α-hydroxy-15-chloro grouping is manifested by signals of the CH_2Cl group (doublets of H-15 and H-15′ at δ 4.30 and 3.95 with J(15,15′) = 11.8 Hz). The presence of a hydroxy group in position 3 is indicated by a signal of the corresponding CH–O proton at δ 4.18. The almost identical NMR parameters of the five-membered ring protons in compounds *VIII*, *IX*, *XXVIII* and *XXX* prove identical configurations of substituents in positions 3 and 4, confirmed for centaurepensin (*IX*) by X-ray diffraction[18]. In cebelin E (*XVIII*) there is another OH group in position 2β (H-2 signal at δ 3.98 with J(2,1) = 5.8 and J(2,3) = 2 Hz), as proved by TAI-acylation. The arising 2,3,4-tri-TAC derivative shows characteristic acylation shifts of the α-protons (H-2: 1.36 ppm and H-3: 1.59 ppm) and markedly different

TABLE VI
Comparison of the conformation of linichlorin B (*XV*) (defined by interproton dihedral angles $\Phi(H_i,H_j)$) found in crystal (X-ray) and in solution (NMR)

H_i,H_j	$\Phi(H_i,H_j)$, X-ray	J (H_i,H_j)	$\Phi(H_i,H_j)$, NMR[a]
1,2α	–46	7.0	32
1,2β	–167	11.5	163
1,5	–1	8.6	10
2α,3	35	7.6	18
2β,3	150	7.4	144
5,6	176	10.6	172
6,7	–140	9.0	156
7,8	–174	9.6	161
8,9α	90	3.0	57
8,9β	–21	5.1	41

[a] The sign of interproton dihedral angle cannot be determined due to the periodicity of Karplus relation.

TABLE VII

Proton NMR parameters of 4α,15-epoxy guaianolide derivatives *I*, *II*, *III*, *X*, *XXII*, and *XXVII* in $CDCl_3$

Protons	Chemical shifts, ppm/Signal multiplicities					
	I	*II*	*III*	*X*[a]	*XXII*	*XXVII*
H-1	3.34 q	3.38 q	3.36 q	3.40 m	–	3.35 q
H-2α	2.48 ddd	2.51 ddd	2.49 ddd	2.48 ddd	2.22 m	2.48 ddd
H-2β	1.81 ddd	1.81 ddd	1.84 ddd	1.86 ddd	2.22 m	1.84 ddd
H-3	3.98 dd	3.99 m	4.00 bdd	4.00 dd	4.04 dd	4.01 ddd
H-5	2.06 dd	2.02 dd	2.08 dd	2.08 dd	2.57 d	2.09 bdd
H-6	4.63 dd	4.68 dd	4.65 dd	4.62 dd	4.33 dd	4.63 dd
H-7	3.07 tt	3.08 tt	3.11 tt	3.12 m	3.13 tt	3.10 tt
H-8	5.13 ddd	5.24 ddd	5.18 ddd	5.04 ddd	5.11 ddd	5.14 ddd
H-9α	2.37 dd	2.49 dd	2.43 dd	2.34 dd	2.47 dd	2.40 dd
H-9β	2.73 dd	2.71 dd	2.78 dd	2.80 dd	2.64 dd	2.76 dd
H-13	6.22 d	6.24 d	6.22 d	6.25 d	6.23 d	6.21 d
H-13′	5.57 d	5.57 d	5.61 d	5.72 d	5.63 d	5.59 d
H-14	5.20 b	5.21 d	5.20 b	5.19 b	5.27 bd	5.19 b
H-14′	4.98 d	5.11 d	4.97 d	4.96 b	5.10 bd	4.96 d
H-15	3.32 d	3.34 d	3.34 d	3.34 d	3.42 d	3.35 d
H-15′	3.07 d	3.07 d	3.07 d	3.08 d	3.09 d	3.07 d
Ester protons						
CH_2O	2.82 d, 3.16 bd	–	–	2.84 d, 3.20 d	–	–
CH_2Cl	–	3.88 d, 3.65 d	–	–	–	–
CH_2OH	–	–	4.39 b	–	–	4.42 dq
$=CH_2$	–	–	6.34 d, 5.96 q	–	6.20 p, 5.70 p	–
=CH	–	–	–	–	–	6.92 tq
CH_3	1.62 bs	1.55 s	–	1.64 s	2.00 dd	–
Protons	Coupling constants, Hz					
1,2α	9.5	9.5	9.5	9	–	9.5
1,2β	9.7	9.7	9.7	9.5	–	9.8
1,5	8.3	8.2	8.5	9	–	8.6
2α,2β	14.6	14.4	14.5	14	[c]	14.4
2α,3	7.1	7.3	7.1	7	6.0	7.0
2β,3	4.1	3.7	4.2	4.5	2.4	4.3
5,6	11.3	11.3	11.2	11	11.2	11.3
6,7	9.2	9.3	9.2	9	9.1	9.1

TABLE VII
(*Continued*)

Protons	Coupling constants, Hz					
	I	*II*	*III*	*X*[a]	*XXII*	*XXVII*
7,8	9.5	9.4	9.4	10	9.6	9.6
7,13	3.5	3.5	3.4	3.5	3.4	3.5
7,13′	3.1	3.2	3.2	3	3.1	3.2
8,9α	3.5	2.7	3.5	3	3.4	3.6
8,9β	5.0	5.2	4.9	5	5.0	5.0
9α,9β	14.9	15.2	15.0	14	15.0	14.6
14,14′	1.5	1.6	1.3	[b]	1.6	1.6
15,15′	4.3	4.2	4.3	4.5	4.9	4.3

[a] Data taken from ref.[21]. [b] The value is not given in ref.[21]. [c] The value of parameter could not be determined.

effects in the β-positions (H-1: 0.23 ppm and H-5: 0.97 ppm), in accord with the *trans*- or *cis*-orientation of the acylated hydroxyl relative to the corresponding proton. A compound of the same structure was described later as repensolide[31]. Very similar NMR parameters were described also for chlororepdiolide which, however, has been shown by X-ray diffraction[43] to have α-configuration of the 2-hydroxyl.

The third group, *C*, consists of nine compounds (*XII*, *XV – XVII*, *XIX*, *XXIV*, *XXV*, *XXIX* and *XXXI*; for ^{1}H NMR data see Table IX) with exomethylene group in position 4, characterized by signals of H-15 and H-15′ at δ 5.6 and 5.4, each with two allylic interactions (with protons H-3 and H-5) and zero value of *J*(15,15′). The CH–O multiplet at δ 4.5 corresponds to the hydroxyl in position 3; this has been proved also by TAI-acylation of compounds *XII*, *XVII* and *XIX* (acylation downfield shift of H-3 signal: 1.1 ppm). The only exception is the 3-deoxy derivative *XXIV*, with allylic protons H-3 and H-3′ at δ 2.94 and 2.48, which both interact with the exomethylene protons H-15 and H-15′. Compounds *XVI*, *XVII*, *XXIV*, *XXV* and *XXIX* contain further oxygen functionality (OH in *XXIX* and OCOR in the remaining compounds) in position 2. The configuration 2α follows from comparison with the published ^{1}H NMR data[28] for repdiolide (*XXIX*), and the internal consistency of the data indicated the same configuration throughout the whole group of the discussed compounds.

Group *D* comprises guaianolides containing substituents 4α-OH-15-OAc (*XX*, *XXI*) or 4α,15-di-OH (*XXIII*, *XXXII*); their data are given in Table X. The presence of CH_2OAc group is characterized by markedly nonequivalent methylene signals at δ 5.0 and 4.2 with *J*(15,15′) = 12.6 Hz and by an OAc singlet at δ 2.17; the C(3)H–O proton

TABLE VIII

Proton NMR parameters of 4α-hydroxy-15-chloroguaianolide derivatives *VIII – X*, *XVIII*, *XXVIII*, and *XXX* in $CDCl_3$

Protons	Chemical shifts, ppm/Signal multiplicities				
	VIII	*IX*	*XVIII*	*XXVIII*	*XXX*
H-1	3.62 dt	3.63 dt	3.34 dd	3.60 m	3.61 dt
H-2α	2.55 ddd	2.56 ddd	3.98 bd	2.54 ddd	2.54 ddd
H-2β	1.60 ddd	1.58 ddd	–	1.60 ddd	1.58 ddd
H-3	4.18 um	4.18 dd	4.08 b	4.18 bd	4.18 m
H-5	2.33 bdd	2.32 ddd	2.59 m	2.33 bdd	2.32 ddd
H-6	4.73 dd	4.74 dd	4.65 dd	4.73 dd	4.72 dd
H-7	3.17 tt	3.14 tt	3.14 tt	3.15 tt	3.13 tt
H-8	5.17 ddd	5.22 ddd	5.10 ddd	5.12 m	5.13 ddd
H-9α	2.45 dd	2.50 bdd	2.50 dd	2.43 dd	2.40 dd
H-9β	2.67 bd	2.66 d	2.57 bd	2.64 bd	2.62 bd
H-13	6.21 d	6.23 d	6.22 d	6.20 d	6.23 d
H-13′	5.62 d	5.58 d	5.63 d	5.59 d	5.58 d
H-14	5.14 d	5.17 d	5.25 b	5.14 bd	5.16 d
H-14′	4.83 d	5.02 d	4.97 b	4.82 d	4.86 d
H-15	4.34 d	4.34 d	4.24 d	4.34 d	4.33 d
H-15′	3.96 d	3.97 d	3.93 d	3.96 d	3.96 d
Ester protons					
CH_2O	–	–	–	–	3.18 d, 2.82 d
CH_2Cl	–	3.88 d, 3.66 d	–	–	–
CH_2OH	4.39 bd	–	–	4.42 bd	–
$=CH_2$	6.34 q, 5.96 q	–	6.20 b, 5.69 p	–	–
=CH	–	–	–	6.91 tq	–
CH_3	–	1.56 s	2.00 bs	1.89 q	1.62 s
Protons	Coupling constants, Hz				
1,2α	11.2	11.1	5.8	11.0	11.1
1,2β	8.0	8.0	–	7.6	7.5
1,5	8.6	8.5	9.3	8.5	8.6
2α,2β	15.0	15.2	–	15.0	15.0
2α,3	6.6	6.6	<2	6.5	6.6
2β,3	<2	1.5	–	<2	1.6
5,6	11.3	11.3	11.3	11.3	11.2
6,7	9.0	9.0	9.1	9.1	9.1
7,8	9.8	9.6	9.5	9.7	9.6
7,13	3.4	3.5	3.5	3.5	3.4

TABLE VIII
(*Continued*)

Protons	Coupling constants, Hz				
	VIII	*IX*	*XVIII*	*XXVIII*	*XXX*
7,13′	3.0	3.1	3.1	3.0	3.0
8,9α	2.0	1.6	2.4	2.0	1.9
8,9β	5.0	5.2	4.8	5.0	5.0
9α,9β	15.2	15.3	14.7	15.0	15.2
14,14′	1.9	2.0	<2	1.8	1.7
15,15′	11.9	11.8	11.8	11.8	11.9

appears at δ 3.8. In the case of the CH_2OH group, the methylene protons are equivalent (broad two-proton singlet at δ 4.0) and the C(3)H–O signal is shifted to δ 4.2. On TAI-acylation, compound *XXXII* afforded 3,4,15-tri-TAC derivative with nonequivalent protons C(15)-H_2 (doublets δ 5.31 and 4.97 with J(15,15′) = 13.0 Hz) and marked acylation shifts of protons H-3 (1.48 ppm) and H-5 (1.10 ppm). The values of vicinal interactions prove the same configuration in position 3 and 4 throughout the whole group of compounds.

Germacranolides *XXVI*, *XXXIII – XXXVI* represent the last group of compounds studied; their ^{1}H NMR spectral data are in Table XI. Proton 1D- and 2D-COSY NMR spectra (500 MHz) of cebelin M enabled us to assign signals of all protons and their J(H,H), and thus to formulate the structure *XXVI*. The β-configuration of C(11)–CH_3 follows from the value of J(7,11) = 7.1 Hz, which indicates *cis*-orientation of protons H-7 and H-11. The relative *trans*-arrangement of hydrogen atoms in positions 6, 7 and 8 follows from the large coupling constants J(6,7) and J(7,8) (10 Hz). Also compound *XXXIII* has the same germacra-1(10),4(5)-diene skeleton. The presence of a *trans*-annelated exomethylene-γ-lactone, closed at C(6), is proved by signals of exomethylene protons H-13 and H-13′ at δ 6.28 and 5.64 with J(13,7) = 3.5 Hz and J(13′,7) = 3.3 Hz, and by interactions of protons H-5, H-6 and H-7. The hydroxy groups in positions 9α and 15 (signals of H-9 at δ 4.16 and of H-15, H-15′ at δ 4.25 and 4.02) were confirmed by TAI-acylation (in the 9,15-di-TAC derivative the signal of H-9 is at δ 5.34, and that of H-15, H-15′ at δ 4.83). The configuration at C(9) follows from the value of coupling constant J(9,8) (10.8 and 2.7 Hz) for the germacradiene ring conformation derived from vicinal coupling constants of protons. The suggested structure *XXXIII* corresponds to stenophyllolide (isolated from *Centaura aspera* var. *stenophylla*[39]) and the identity of

TABLE IX

Proton NMR parameters of 4,15-dehydroguaianolide derivatives *XII*, *XV* – *XVII*, *XIX*, *XXIV*, *XXV*, *XXIX*, and *XXXI* in $CDCl_3$

Protons	Chemical shifts, ppm/Signal multiplicities								
	XII	*XV*	*XVI*[d]	*XVII*[d]	*XIX*	*XXIV*[a]	*XXV*[b]	*XXIX*	*XXXI*
H-1	2.98 ddd	3.00 ddd	2.98 m	2.98 m	2.99 ddd	3.00 m	2.93 dd	3.04 dd	2.98 ddd
H-2α	2.23 ddd	2.23 ddd	–	–	2.25 ddd	–	–	–	2.24 ddd
H-2β	1.74 dt	1.72 dt	4.98 dd	4.96 dd	1.73 dt	5.26 q	4.94 dd	3.72 dd	1.72 dt
H-3	4.57 tt	4.58 tt	4.43 dt	4.43 dt	4.57 tt	2.94 ddq	4.41 dt	4.32 dt	4.56 tt
H-5	2.84 bt	2.82 ddt	2.98 m	2.98 m	2.85 tt	3.00 m	3.01 tt	2.82 dd	2.84 tt
H-6	4.27 dd	4.28 dd	4.16 dd	4.16 dd	4.25 dd	4.01 dd	4.16 dd	4.20 dd	4.23 dd
H-7	3.20 tt	3.17 tt	2.81 tt	2.81 tt	3.19 tt	2.84 tt	2.88 m	3.21 tt	3.16 tt
H-8	5.15 ddd	5.21 ddd	4.01 m	4.01 ddd	5.11 ddd	3.95 m	2.25 m	5.12 ddd	5.10 ddd
H-9α	2.40 dd	2.47 dd	2.31 dd	2.32 dd	2.37 dd	2.31 dd	2.25 m	2.49 m	2.36 dd
H-9β	2.72 dd	2.70 dd	2.71 dd	2.70 dd	2.70 dd	2.75 dd	2.47 m	2.49 m	2.68 dd
H-13	6.22 d	6.25 d	6.29 dd	6.29 dd	6.21 d	6.30 dd	6.25 d	6.24 d	6.24 d
H-13′	5.62 d	5.58 d	6.16 dd	6.16 dd	5.60 d	6.18 dd	5.52 d	5.62 d	5.58 d
H-14	5.15 d	5.18 d	5.12 bd	5.11 d	5.14 d	5.02 d	4.98 b	5.22 b	5.16 d
H-14′	4.94 d	5.09 d	5.03 bd	5.03 d	4.94 d	5.00 d	4.93 b	5.02 b	4.97 d
H-15	5.49 d	5.51 t	5.66 dd	5.66 dd	5.51 t	5.40 q	5.52 t	5.70 t	5.49 t
H-15′	5.37 d	5.38 t	5.47 dd	5.47 t	5.37 t	5.14 q	5.44 t	5.43 t	5.37 t
Ester protons									
CH_2OH	4.39 b	–	–	–	4.42 dq	–	–	–	–
CH_2Cl	–	3.65 d, 3.88 d	–	–	–	–	–	–	–
CH_2O	–	–	–	–	–	–	–	–	3.17 dq, 2.83 d
$=CH_2$	6.36 q, 5.97 q	–	–	–	–	–	–	6.24 m, 5.70 m	
CH_2	–	–	1.63 m 1.51 m	–	–	1.64 m 1.45 m	1.67 m 1.48 m	–	–

TABLE IX
(*Continued*)

Protons	Chemical shifts, ppm/Signal multiplicities								
	XII	*XV*	*XVI*[d]	*XVII*[d]	*XIX*	*XXIV*[a]	*XXV*[b]	*XXIX*	*XXXI*
Ester protons									
⟩CH–	–	–	2.42 m	2.58 h	–	2.34 h	2.40 m	–	–
=CH	–	–	–	–	6.91 tq	–	–	–	–
CH_3	–	1.56 s	1.15 d, 0.69 t	1.17 d, 1.16 d	1.89 q	1.11 d, 0.88 t	1.16 d, 0.90 t	2.00 dd	1.62 bs
Protons	Coupling constants[c], Hz								
1,2α	7.3	7.0	–	–	7.2	–	–	–	7.4
1,2β	10.7	11.5	9.3	9.0	10.5	6.9	6.5	10.6	10.7
1,5	8.6	8.6	[e]	[e]	9.6	[e]	9.8	9.8	8.5
2α,2β	13.2	13.4	–	–	13.1	–	–	–	13.2
2α,3	7.3	7.6	–	–	7.2	–	–	–	7.4
2β,3	7.6	7.4	7.2	7.2	7.6	7.3	5.8	8.0	7.6
5,6	10.4	10.6	10.2	10.1	10.3	10.0	9.8	10.5	10.5
6,7	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.1	9.2
7,8	9.8	9.6	9.0	9.2	9.8	9.2	[e]	9.8	9.7
7,13	3.5	3.6	3.5	3.5	3.5	3.5	3.6	3.4	3.5
7,13′	3.1	3.1	3.2	3.2	3.0	3.1	3.2	3.1	3.1
8,9α	3.8	3.0	3.0	3.0	4.0	4.4	[e]	[e]	4.0
8,9β	5.2	5.1	5.4	5.3	5.1	5.4	[e]	[e]	5.0
9α,9β	14.6	15.0	14.6	14.6	14.5	14.2	[e]	[e]	14.6
14,14′	1.6	1.7	1.6	1.7	1.6	1.4	[e]	[e]	1.6
15,15′	0	0	0	0	0	0	0	0	0

[a] H-3′: 2.48 ddt; $J(2\beta,3\beta)$ = 6.8, $J(3\alpha,3\beta)$ = 17.1 Hz. [b] H-8′: 1.51 m. [c] Additional long-range coupling present in whole series of compounds – $J(3,15) \approx J(3,15') \approx$ 1.8 to 2.7 Hz and $J(5,15) \approx J(5,15') \approx$ 1.5 to 2.3 Hz. [d] $J(13,13')$ = 0.8 Hz. [e] The value could not be determined.

TABLE X

Proton NMR parameters of 4α,15-dihydroxy- and 4α-hydroxy-15-acetoxyguaianolide derivatives *XX*, *XXI*, *XXIII*, and *XXXII* in $CDCl_3$

Protons	Chemical shifts, ppm/Signal multiplicities			
	XX	*XXI*	*XXIII*	*XXXII*
H-1	3.51 ddd	3.50 ddd	3.46 bq	3.36 ddd
H-2α	2.48 ddd	2.40 ddd	2.51 ddd	2.43 ddd
H-2β	1.64 ddd	1.65 m	1.62 ddd	1.70 ddd
H-3	3.81 um	3.82 um	4.16 um	4.19 dd
H-5	2.32 dd	2.33 dd	2.31 bt	2.35 dd
H-6	4.83 dd	4.81 dd	4.65 dd	4.56 dd
H-7	3.15 tt	3.14 tt	3.15 tt	3.16 tt
H-8	5.16 ddd	5.11 ddd	5.19 ddd	5.06 dt
H-9α	2.41 dd	2.40 dd	2.40 dd	2.30 dd
H-9β	2.73 dd	2.72 m	2.74 m	2.78 dd
H-13	6.21 d	6.20 d	6.24 d	6.23 d
H-13′	5.62 d	5.60 d	5.62 d	5.66 d
H-14	5.14 d	5.14 d	5.17 bd	5.18 b
H-14′	4.86 d	4.86 d	5.06 bt	4.97 b
H-15	5.02 d	5.00 d	4.01 b	4.01 b
H-15′	4.12 d	4.22 d	4.01 b	4.01 b
Ester protons				
CH_2O	4.39 bd	4.42 bt	–	–
CH_2Cl	–	–	3.87 d, 3.65 d	–
OAc	2.17 s	2.17 s	–	–
$=CH_2$	6.34 q, 5.95 q	–	–	6.19 p, 5.69 p
=CH	–	6.92 tq	–	–
CH_3	–	1.89 q	1.56 s	1.99 dd
Protons		Coupling constants, Hz		
1,2α	11.3	11.3	10.8	10.2
1,2β	7.5	7.5	8.5	8.6
1,5	9.0	9.0	10.0	9.8
2α,2β	14.7	14.6	14.5	14.4
2α,3	6.0	[a]	6.5	6.6
2β,3	2.3	2.6	3.4	4.9
5,6	11.3	11.3	10.4	11.4
6,7	9.1	9.2	9.2	9.0
7,8	9.8	9.8	9.7	9.9
7,13	3.5	3.5	3.4	3.4

TABLE X
(*Continued*)

Protons	Coupling constants, Hz			
	XX	*XXI*	*XXIII*	*XXXII*
7,13′	3.0	3.1	3.0	3.0
8,9α	2.6	2.6	3.2	4.5
8,9β	5.0	5.1	5.0	5.0
9α,9β	15.2	14.5	14.8	14.4
14, 14′	1.9	1.8	1.6	[a]
15, 15′	12.6	12.6	[a]	[a]

[a] The value of parameter could not be determined.

both compounds is supported by a good accord of their spectral data. In the remaining three compounds (*XXXIV – XXXVI*), the 1(10) double bond is preserved but instead of the second double bond they contain an epoxide grouping in position 4,5 (H-5 at δ 2.65 and C(4)–CH_3 at δ 1.3). The pair *XXXV* and *XXXVI* contains further oxygen functionalities in positions 8 and 9 and the compounds differ from each other only by esterification of the 8-hydroxyl group in compound *XXXVI*. The presence and position of the hydroxy groups were proved by TAI-acylation. The relative configurations in positions 5 to 9 follow from the coupling constants of protons in the given fragment and from model considerations. The last member of the germacranolide series – isospiciformin (*XXXIV*) – has the lactone ring closed at C(8) and contains free hydroxyl in position 6 (H-6: δ 3.44 dd, *J*(6,5) = 9.0 and *J*(6,7) = 9.6 Hz). The position of this hydroxyl was confirmed by TAI-acylation (acylation shifts, H-6: 1.43 ppm, the neighbouring H-5 and H-7: 0.16 and 0.27 ppm, respectively). A comparison with the ^{1}H NMR data described for the product of epoxidation of deacetyllaurenobiolide[44] confirms that both compounds are identical and have the structure *XXXIV*.

CD Spectra

The absolute configuration of our sesquiterpenic guaianolide lactones was mostly derived by combination of the Geissman rule[45] with the already solved relative configuration of the given lactone. Using this approach, we found that absolute configuration at C(7) in compounds *I – III*, *VIII – X*, *XV*, *XVIII – XXII*, *XXV* and *XXVII – XXXI* (Table I) is *R*. This assigned configuration was verified by comparison of their CD spectra in the

TABLE XI
Proton NMR parameters of germacranolide derivatives *XXVI*, *XXXIII* – *XXXVI* in $CDCl_3$

Protons	Chemical shifts, ppm/Signal multiplicities				
	XXVI[a,b]	*XXXIII*[b]	*XXXIV*	*XXXV*	*XXXVI*
H-1	4.95 ddp	5.17 ddd	5.37 bt	5.67 bdd	5.67 bdd
H-2	2.22 m	2.27 m	[c]	2.32 um	2.33 bm
H-2′	2.07 dq	2.21 dq	[c]	2.52 dq	2.52 dddd
H-3	2.53 ddd	2.63 ddd	[c]	2.18 ddd	2.20 ddd
H-3′	1.94 bdt	1.97 tdd	1.36 bdt	1.28 bdt	1.31 bdt
H-5	4.80 bd	4.71 dq	2.66 d	2.69 d	2.62 d
H-6	4.87 t	4.81 dd	3.44 dd	3.96 dd	4.35 dd
H-7	2.32 dt	2.65 m	3.00 m	3.61 m	3.83 m
H-8	4.01 dt	2.21 ddd	4.02 ddd	3.92 um	4.58 bd
H-9	2.67 dm	4.23 dd	2.80 bd	4.38 b	4.38 b
H-9′	2.36 dd	–	[c]	–	–
H-13	1.41 d	6.30 d	6.48 dd	6.51 dd	6.29 dd
H-13′	–	5.60 d	6.29 dd	6.07 dd	5.67 dd
H-14	1.31 bs	1.41 d	1.83 d	1.76 s	1.81 t
H-15	4.61 dd	4.31 dd	1.28 s	1.29 s	1.27 s
H-15′	4.56 d	4.11 bd			
Ester protons					
CH_2OH	–	–	–	–	4.16 um
OAc	2.09 s	–	–	–	–
=CH	–	–	–	–	6.03 q
CH_3	–	–	–	–	2.02 d
Protons			Coupling constants, Hz		
1,2	4.9	4.9	[d]	5.0	≈3.8
1,2′	11.8	11.7	[d]	12.0	≈12.4
1,14	1.4	1.5	1.2	<1	1.3
2,2′	12.3	13.0	[d]	13.0	13.7
2,3	2.4	2.7	[d]	2.4	1.6
2,3′	–	6.1	≈5.0	5.0	6.6
2′,3	4.5	4.9	[d]	5.0	5.8
2′,3′	12.2	12.2	≈12.0	13.0	12.8
3,3′	12.2	12.2	≈12.0	12.8	12.8
5,6	10.0	10.0	9.0	8.0	9.5
6,7	9.6	8.8	9.6	6.7	6.6
7,8	10.0	1.5	5.4	6.9	3.8

TABLE XI
(*Continued*)

Protons	Coupling constants, Hz				
	XXVI[a,b]	*XXXIII*[b]	*XXXIV*	*XXXV*	*XXXVI*
8,9	3.2	2.7	2.4	≤1	≤1
8,9′	10.7	–	10.8	–	–
9,9′	13.0	–	13.0	–	–
7,13	–	3.4	3.0	3.4	3.5
7,13′	–	3.2	2.6	3.0	3.2
13,13′	–	0	1.3	1.0	0.9
15,15′	13.0	13.8	–	–	–

[a] H-11: 2.91 p, J(11,7) = 7.1 and J(11,13) = 7.5 Hz. [b] H-8′: 1.90 ddd, J(7,8′) = 10.2, J(8′,8) = 14.6 and J(8′,9) = 10.8 Hz. [c] H-2, H-2′, H-3 and H-9′: 2.43 – 2.01 m. [d] Not determined.

region 256 – 275 nm with those of lactones *I*, *II* and *IX* (Table I) whose absolute configuration was determined by chemical correlation with α-santonine (*XIII*) as already mentioned above. The absolute configuration of lactones *XVI*, *XVII*, *XXIII* and *XXX*, which display no Cotton effect at about 265 nm, followed from comparison of the Δε values in the region 200 – 214 nm; this was positive in all cases for which the measurement was done. In our set of guaianolides (Table I), the only exception for which the absolute configuration, resulting from combination of the Geissman rule and the relative configuration on the one hand, and from the positive Δε value in the region 256 –275 nm on the other, was cebelin K (*XXIV*) (Δε +0.3 at 257 nm and +4.0 at 210 nm; see Table I). In this case, however, the dihedral angle C=C–C=O, which influences the Cotton effect in CD spectra of α-exomethylene-γ-lactones at about 260 nm ($n \rightarrow \pi^*$ transition), may range from about –10° to +10°, and therefore the Δε values may range from negative to positive values[46]. We thus assume that in cebelin K (*XXIV*) the arrangement of the exomethylene and carbonyl double bonds is "right-handed" (ref.[46]), with absolute configuration *R* at C(7). We can conclude that the formulae *I – III*, *VIII – X*, *XV – XXII*, *XXIV*, *XXVII* and *XXX* depict the absolute configuration of the lactones studied. We have also solved the absolute configuration of germacranolides[9,10] *XXXIII – XXXVI* which we isolated from a species of subtribe *Centaureinae*. In the CD spectrum, lactone *XXXIII* exhibits a Cotton effect at 218 nm (Δε +31.1; Table I) that is practically identical (in sense as well as magnitude) with those observed for a series of costunolide germacranolides of known absolute configuration. This Cotton effect corresponds to chirality of transannularly interacting double bonds in a ten-membered ring.

The absolute configuration in lactones *XXXV* and *XXXVI* was derived from comparison of the values and sense of Cotton effects with those observed for parthenolide[47] (*XXXVII*) and 9α-hydroxyparthenolide[48] (*XXXVIII*), compounds of known absolute configuration. The absolute configuration of isospiciformin (*XXXIV*) followed from its chemical correlation via deacetyllaurenobiolide (*XXXIX*) with laurenobiolide[44] (*XL*) whose absolute configuration was determined already earlier[49]. For all the lactones studied, we found *R*-configuration at C(7) and formulae *XXXIII – XXXVI* thus depict their absolute configuration.

Of sesquiterpenic lactones, which we mentioned as hitherto undescribed, the following two were described at the same time or subsequently: cebelin E (*XVIII*) as repensolide[31] and pterocaulin (*XXXII*) as repdiolide triol[32]. As concerns 15-deoxyrepin[6] (*XXXI*), the same formula has been ascribed to a sesquiterpenic lactone[33] from *Centaurea collina* L.; however, a comparison of our ^{1}H NMR data for 15-deoxyrepin (see *XXXI* in Table IX) with the published[32] ones shows differences in chemical shifts of the ester protons. The published[33] values for the lactone from *C. collina* (H-18: 3.57 d, H-18′: 3.78 d, H-19: 1.34 s) indicate that, instead of epoxymethacrylate, its molecule contains very probably a 2,3-dihydroxyisobutyrate moiety whose signals for H-18, H-18′ and H-19 (3.60 d, 3.87 d and 1.40 s; ref.[42]) are in good accord with the values found for the ester group in the lactone from *C. collina*. Very likely, the discussed lactone from *C. collina* is identical with lactones from *C. ornata* WILLD. (ref.[50]) and *C. kotschyi* BOISS (ref.[51]), assigned the 2,3-dihydroxyisobutyrate formula *XLI*.

The significance of the presence or absence of guaianolides and germacranolides in species of subtribe *Centaureineae* for its internal systematics will be published elsewhere.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Infrared spectra were recorded in chloroform on a Perkin–Elmer PE 580 spectrophotometer (wavenumbers in cm^{-1}). Mass spectra were measured on a ZAB-EQ (VG Analytical, Manchester, U.K.); electron impact, 70 eV. Optical rotations were determined on a Perkin–Elmer 141 polarimeter, CD spectra (in methanol) on a Jobin–Yvonne Mark V autodichrograph. Proton NMR spectra were measured on an FT NMR spectrometer Varian XL-200 and/or Varian UNITY 500 (at 200 and/or 500 MHz) in $CDCl_3$ with tetramethylsilane as internal reference. The structural assignment of proton signals was done using splitting pattern, decoupling experiments and (in some cases) 2D-COSY spectra. Difference 1D-NOE experiments were used for the stereochemical assignment of methylene protons in positions 2 and 9. Hydroxy derivatives were characterized by ^{1}H NMR spectra after in situ reaction with trichloroacetyl isocyanate (TAI-method[52,53]).

Isolation of Cebelin K (*XXIV*), Cebelin L (*XXV*), 17,18-Epoxy-19-deoxychlorojanerin (*XXX*) and Cebelin M (*XXVI*)

Aerial part of species *Centaurea bella* TRAUTV. (2.0 kg) was dried, ground and extracted with methanol. The solvent was distilled off under diminished pressure, the residue was dissolved in water (750 ml) and the mixture was extracted with chloroform and then with ethyl acetate. The chloroform

extract was dried, the solvent was evaporated and the residue (12.5 g) was chromatographed on a column of silica gel (400 g). Chloroform–acetone (19 : 1) eluted 810 mg of fraction A, containing mainly compound *XXV*, and 650 mg of fraction B (predominantly *XXIV*). Elution with chloroform–acetone (9 : 1) gave 930 mg of fraction C (compounds *XXVI* and *XXX*). Rechromatography of fraction A (810 mg) on silica gel (40 g) in hexane–ethyl acetate–chloroform (4 : 1 : 1) afforded fraction D (76 mg), enriched in compound *XXV*, fraction E (29 mg), enriched in compound *XXIV*, and noncrystalline cebelin K (*XXIV*; 7 mg). A further amount of cebelin K (*XXIV*; 16 mg) were obtained by rechromatography of the mentioned fraction E (29 mg) on silica gel (4 g) in chloroform–ethyl acetate (5 : 1). Cebelin K (*XXIV*); IR spectrum: 3 608 (hydroxyl); 1 762 (γ-lactone); 1 727 (ester); 1 653 (double bond); 1 150 (C–O). Mass spectrum, *m/z*: 346 (M), 244 (M – 102), 226 (M – 102 – 18), 85 (C_4H_9CO). For CD spectrum see Table I. For $C_{20}H_{26}O_5$ (346.4) calculated: 69.34% C, 7.57% H, 0.29% H act.; found: 69.28% C, 7.68% H, 0.37% H act. Fraction D was chromatographed on silica gel (8 g) in chloroform–ethyl acetate (5 : 1) to give noncrystalline cebelin L (*XXV*; 43 mg). IR spectrum: 3 586, 3 502 (hydroxyl); 1 763 (γ-lactone); 1 723 (ester); 1 679, 1 642, 1 604 (double bond); 1 185, 1 151 (C–O). Mass spectrum, *m/z*: 346 (M), 244 (M – 102), 85 (C_4H_9CO) and 57 (C_4H_9). For CD spectra see Table I. For $C_{20}H_{26}O_5$ (346.4) calculated: 69.34% C, 7.57% H, 0.29% H act.; found: 69.43% C, 7.71% H, 0.42% H act. Fraction C (930 mg, predominantly compounds *XXVI* and *XXX*) was rechromatographed on silica gel (100 g) in hexane–ethyl acetate–chloroform (2 : 1 : 1) to give noncrystalline 17,18-epoxy-19-deoxychlorojanerin[34] (*XXX*). IR spectrum: 3 615, 3 561 (hydroxyl); 1 767 (γ-lactone); 1 743 (ester); 1 662, 1 641 (double bond); 1 168, 1 139 (C–O). Mass spectrum, *m/z*: 398 (M), 296 (M – 102), 278 (M – 102 – 18), 260 (M – 102 – 18 – 36), 242 (M – 102 – 18 – 36 – 18), 69 (C_3H_5CO). For CD spectrum see Table I. For $C_{19}H_{23}ClO_7$ (398.8) calculated: 57.22% C, 5.81% H, 0.51% H act., 8.89% Cl; found: 56.98% C, 5.67% H, 0.63% H act., 8.63% Cl. Further chromatographic fractions afforded cebelin M (*XXVI*; 12 mg), m.p. 145 – 147 °C (acetone–chloroform–diisopropyl ether). IR spectrum: 3 610, 3 491 (hydroxyl); 1 767 (γ-lactone); 1 736, 1 234, 1 054 (C–O). Mass spectrum, *m/z*: 308 (M), 248 (M – 60), 230 (M – 60 – 18), 43 (CH_3CO). For CD spectrum see Table I. For $C_{17}H_{24}O_5$ (308.3) calculated: 66.22% C, 7.85% H, 0.33% H act.; found: 66.14% C, 7.97% H, 0.42% H act.

X-Ray Structure Determination of Linichlorin B (*XV*)

A colourless crystal of linichlorin B was found to be orthorhombic, space group $P2_12_12_1$, a = 11.535(3), b = 19.135(4), c = 8.398(4) Å, V = 1 835(2) Å^3, Z = 4, D_{calc} = 1.372 g cm^{-3}, D_{obs} = 1.38(2) g cm^{-3}. Cell constants were obtained on an Enraf–Nonius CAD4 diffractometer using MoKα radiation and a graphite monochromator. Intensity data were collected out to 2θ(Mo) = 50°. The data were corrected for Lorentz-polarization effects but not for absorption (μ = 2.4 cm^{-1}). 1 085 unique reflections with $I > \sigma(I)$ were used in the refinement.

The structure was solved by direct methods[54]. Hydrogen atoms attached to carbon atoms were placed in calculated positions and not refined, and those associated with hydroxyl group were not located and could not be included in the calculation; non-hydrogen atoms were refined anisotropically. The final values of the agreement factors $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $R_2 = [w(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{1/2}$, where the weights w assigned as $4F_o^2/\sigma^2(F_o^2)$ were 0.068 and 0.039, respectively. The final atomic positional parameters are listed* in Table II. The absolute con-

* Tables of hydrogen atom parameters, anisotropic thermal parameters, and observed and calculated structure amplitudes are available as supplementary material at the author (U. R.).

figuration of the molecule could not be determined unequivocally, a Bijvoet test being inconclusive; this is not at all surprising for these atoms with MoKα radiation. Since the configurations at C(1), C(5), C(6), C(7) have all been rigorously established[26], the absolute configuration chosen here corresponds to these known configurations.

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