

STRUCTURE OF ISOSILEROLIDE, RELATIVE AND ABSOLUTE
CONFIGURATION OF SILEROLIDE AND LASOLIDE —
SESQUITERPENIC LACTONES OF NEW STEREOISOMERIC TYPE
OF EUDESMANOLIDES*

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On the basis of spectroscopic, particularly ¹H NMR data, isosilerolide was assigned structure *I*, including the absolute configuration. The structure was confirmed by X-ray diffraction. Isosilerolide represents a new stereoisomeric type of natural eudesmanolides, characterized as 5βH,6αH,7αH,10αCH₃-eudesman-6,12-olide. As shown by the chemical correlation of isosilerolide (*I*) with silerolide (*III*) and lasolide (*X*), the latter two natural lactones belong to this stereoisomeric group of eudesmanolides. Analysis of models and ¹H NMR data shows that structures of some eudesman-6,12-olides, published by other authors, should be corrected.

In our previous paper¹ we described isolation of a natural sesquiterpenic lactone *I* of composition C₂₂H₃₀O₆, m.p. 141–143°C, $[\alpha]_D^{20} -139^\circ$. The compound was obtained from the underground parts of the *Laserpitium siler* L. species (*Umbelliferae* family, *Laserpitieae* tribe) of Slovenian origin and was named isosilerolide. In a preliminary communication² we suggested its structure and now we publish our results in detail.

Infrared spectrum of isosilerolide (*I*) proved the presence of a γ-lactone grouping (1 780 cm⁻¹), an α,β-unsaturated ester (1 722 and 1 646 cm⁻¹) and an acetate group (1 722 and 1 250 cm⁻¹). Its mass spectrum exhibited no molecular peak but only characteristic fragments *m/z* 330 (*M*–60), 230 (*M*–60–100), 83 (C₄H₇CO⁺) and 55 (C₄H₇⁺), CD spectrum showed a maximum at 227 nm (Δε –4.1).

Saponification of isosilerolide (*I*) afforded a dihydroxy lactone *II*, C₁₅H₂₂O₄, m.p. 183–184°C, $[\alpha]_D^{20} -83^\circ$, identical (IR spectrum and mixture melting point) with the product arising by hydrolysis of silerolide (*III*)³. Silerolide, the natural sesquiterpenic lactone isolated by us from the roots of *L. siler* L. species of Bulgarian

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TABLE I
¹H NMR parameters of sesquiterpene lactones I–V, VII–X in deuteriochloroform

Proton	Chemical shifts (coupling constants)			
	I	II	III ^a	IV
H-1	4.62 dt (4.0; 1.6; 1.2)	3.38 dt (3.9; 1.6; 1.2)	4.62 bd (4.3; ±0)	3.38 bd (3.9; 1.6; ±0)
H-2	2.42 m	2.46 m (18.7; 3.9 (2×); 2.6 (3×); 2.5)	c	2.49 vbd
H-2'	2.10 m	2.03 m (18.7; 3.3; 1.2; 1.5 (3×); 1.7)	c	c
H-3	5.34 b (3.9; 3.3; 1.8 ± 0)	5.35 m (3.9; 3.3; 1.5 (4×))	5.34 b	5.35 um
H-5	2.44 bd (10.4; 1.8)	2.38 bd (10.4; 2.5; 1.7; 1.5)	c	2.41 bd
H-6	4.91 dd (10.4; 7.3)	4.79 dd (10.4; 7.3)	4.84 dd (11.0; 8.5)	4.88 dd (11.1; 8.6)
H-7	3.25 ddd (8.6; 7.3; 6.0)	2.69 ddd (8.6; 7.3; 6)	3.25 ddd (8.4; 7; 5.6)	3.24 dt (8.5; 6.4 (2×))
H-8	c	1.80 m (14.2; 7 (2×); 6)	c	c
H-8'	c	1.63 m (14.2; 8.6; 7 (2×))	c	c
H-9	c	2.09 m (13.6; 7.0 (2×))	c	c
H-9'	1.21 dt (13.6; 7.0 (2×))	1.18 dt (13.6; 7.0 (2×))	c	1.17 dt (12.8; 6.0 (2×))
H-13	1.61 s	1.46 s	1.57 s	1.62 s
H-14	0.88 s	0.85 s	0.87 s	0.80 s
H-15	1.91 b	1.87 m (2.6; 1.5 (2×))	1.91 b	1.90 b
—OAc	2.06 s	—	2.05 s	—
—OAng	6.17 qq (7.3 (3×); 1.5 (3×))	—	—	6.16 qq (7.3 (3×); 1.5 (3×))
	1.89 p (1.5 (4×))	—	—	1.89 p (1.5 (4×))
	2.00 dq (7.3; 1.5 (3×))	—	—	2.00 dq (7.3; 1.5 (3×))

^a Signals of —OSen: 5.69 m (1.4 (3×); 1.2 (3×)); 2.15 d (1.2); 1.91 d (1.4); ^b signals of —OBzl:

TABLE I
(Continued)

Chemical shifts (coupling constants)				
<i>V</i>	<i>VII</i> ^b	<i>VIII</i>	<i>IX</i>	<i>X</i>
4.62 bd (4.0; ±0)	4.88 bd (4.0; ±0)	—	3.44 bdd (11.0; 4.0; ±0)	3.49 dd (9.8; 6.4)
2.41 bd	2.49 bd	2.74 dt (14.8; 14.2; 6.6)	<i>c</i>	<i>c</i>
2.09 bd	2.22 bd	2.31 ddd (14.8; 4.9; 2.4)	<i>c</i>	<i>c</i>
5.34 um	5.39 um	<i>c</i>	2.40 ddd (13.7; 4.8; 2.4)	5.31 m
2.48 bd	2.60 bd	1.36 dd (10.8; 9.2)	<i>c</i>	<i>c</i>
4.78 dd (10.5; 7.2)	4.86 dd (10.3; 7.2)	4.75 dd (9.2; 6.9)	5.03 dd (11.0; 9.3)	4.74 dd (10.9; 8.5)
2.72 m	2.72 m	2.61 ddd (9.5; 6.9; 5.8)	3.34 dt (9.4; 4.7 (2×))	3.18 m
<i>c</i>	<i>c</i>	<i>c</i>	<i>c</i>	<i>c</i>
<i>c</i>	<i>c</i>	<i>c</i>	<i>c</i>	<i>c</i>
<i>c</i>	<i>c</i>	<i>c</i>	<i>c</i>	<i>c</i>
<i>c</i>	1.30 dt (13.0; 7.0 (2×))	<i>c</i>	<i>c</i>	<i>c</i>
1.46 s	1.44 s	1.41 s	1.61 s	1.51 s
0.92 s	1.01 s	1.21 s	0.75 s	0.76 s
1.88 b	1.93 b	1.15 d (6.5)	5.05 b	1.79 m
2.05 s	—	—	4.95 b	(2.5; 1.2 (2×))
—	—	—	—	—
—	—	—	6.17 qq (7.3 (3×); 1.5 (3×))	6.09 qq (7.3 (3×); 1.5 (3×))
—	—	—	1.89 p (1.5 (4×))	1.81 p (1.5 (4×))
—	—	—	2.00 dq (7.3; 1.5 (3×))	1.92 dq (7.3; 1.5 (3×))

7.97 m (2 H); 7.45 m (3 H); ^c parameters were not determined.

origin⁴, has been assigned constitution *IIIa* or *IIIb*. Partial saponification of isosilerolide (*I*) gave two products. One of them was hydroxy ester *IV*, m.p. 118–120°C, $[\alpha]_D^{20} - 108^\circ$, composition $C_{20}H_{28}O_5$, CD maximum at 226 nm ($\Delta\epsilon - 2.8$). Its IR spectrum proved a hydroxyl (3 620 and 3 530 cm^{-1}), a γ -lactone (1 769 cm^{-1}), an α,β -unsaturated ester (1 712 cm^{-1}) and a double bond (1 646 cm^{-1}), mass spectrum showed typical fragments m/z 248 ($M-100$), 230 ($M-100-18$), 83 ($C_4H_7CO^+$) and 55 ($C_4H_7^+$). The second saponification product was non-crystalline hydroxy ester lactone *V*, $[\alpha]_D^{20} - 87^\circ$, of composition $C_{17}H_{24}O_5$ whose IR spectrum exhibited bands due to hydroxy (3 580 and 3 440 cm^{-1}), γ -lactone (1 770 cm^{-1}) and acetate groups (1 729 and 1 252 cm^{-1}). No molecular peak was observed in the mass spectrum which contained peaks at m/z 248 ($M-60$), 159 ($M-60-71-18$) and 43 (CH_3CO^+). The compound had a CD maximum at 223 nm ($\Delta\epsilon + 2.0$). Detailed structural information was obtained from the ¹H NMR (Table I) and ¹³C NMR (Table II) spectra of the compounds *I*, *II*, *IV* and *V*. The spectrum of isosilerolide (*I*) revealed two ester groups, an acetate (δ 2.06 s, 3 H) and an angelate (δ 1.89 p, 3 H; 2.00 dq, 3 H; 6.17 qq, 1 H); further two sp^3 -methyl groups (δ 0.88 s and 1.61 s) and an sp^2 -methyl group (δ 1.91 bs). An olefinic proton signal (δ 5.34 m) and two CH—O proton signals (δ 4.91 dd and 4.62 bd) occur in the downfield region. In the spectrum of lactone diol *II* (Table I) we identified signals of all hydrogen atoms in the molecule by decoupling experiments. These data suggested that the compound *II* had an eudesmanolide skeleton with the lactone ring closed at $C_{(6)}$ and hydroxyl groups at $C_{(1)}$ and $C_{(11)}$. The acylation-induced changes in chemical shifts and comparison with the spectra of the partially hydrolyzed derivatives *IV* and *V* revealed that the acetate group in isosilerolide (*I*) is at $C_{(1)}$ whereas the angelate grouping at $C_{(11)}$. This assignment was proven independently by ¹H-nondecoupled ¹³C NMR spectrum of *I*. The carbonyl carbon of the acetoxy group is easily identified in the spectrum as a doublet of quartets at δ 170.44 ($J = 6.8$ ($3\times$) and 3.5 Hz): this, according to the acetate classification rule⁵ proves the secondary character of the carbon to which the acetoxy group is attached, i.e. $C_{(1)}$. Consequently, the angelate group, whose carbonyl carbon appears as a doublet of multiplets at δ 166.57 ($^3J(CO-C=C-H) = 14.0$ Hz), must be bonded to $C_{(11)}$.

The observed coupling constant $J_{5,6} = 10.4$ Hz for *I* agrees well with that for erivanin (*VI*) (11.0 Hz) which has been shown by X-ray diffraction⁶ to contain *trans*-arrangement of the hydrogen atoms at $C_{(5)}$, $C_{(6)}$ and $C_{(6)}$, $C_{(7)}$; however, the coupling constant $J_{6,7}$ is markedly smaller for *I* than *VI* (7.3 Hz vs 10.1 Hz). From this comparison, as well as from inspection of models, we can derive the relative configuration of the atoms $H_{(5)}$ and $H_{(6)}$ in *I* as *trans* whereas the relation of $H_{(6)}$ and $H_{(7)}$ as *cis*. The significant downfield shift of the $H_{(7)}$ signal on acylation of $C_{(11)}$ —OH (0.56 to 0.67 ppm) indicates a *cis*-relation of $H_{(7)}$ and $C_{(11)}$ —OH. If we assume the typical β -orientation of the substituent at $C_{(7)}$ in eudesmanolides, we arrive at configurations $5\beta H, 6\alpha H, 7\alpha H, 10\alpha CH_3$. Irradiation of the $C_{(10)}$ — CH_3 protons in the derivative *II*

enhanced the signals of $H_{(6)}$ (6%), $H_{(1)}$ (6%), $H_{(7)}$ (9%) and $H_{(2)}$ (7%); this Overhauser effect thus indicates a *cis*-orientation of the methyl group relative to $H_{(6)}$ and $H_{(1)}$, *i.e.* the $10\alpha\text{CH}_3, 1\beta\text{OH}$ configuration. These conclusions lead to the structure *I* for isosilerolide.

The structure *I* was confirmed by X-ray diffraction⁷. Crystallization of the natural isosilerolide from diisopropyl ether afforded orthorhombic crystals of parameters $a = 9.665(1)$, $b = 12.182(1)$, $c = 17.835(2)$ Å, space group $P2_12_12_1$, with four molecules in the unit cell. The structure was solved by direct methods from intensity data collected on a diffractometer and refined by full matrix least-squares methods to a final R index of 0.056 (1 407 reflections). A stereoview of the molecule of isosilerolide is shown in Fig. 1.

TABLE II
¹³C NMR chemical shifts of sesquiterpene lactones *I*, *II*, *IV*, *VII*, *IX* and *X*^a

Carbon	<i>I</i>	<i>II</i>	<i>IV</i>	<i>VII</i>	<i>IX</i>	<i>X</i>
C-1	75.25	72.23	72.96	75.42	75.12	74.84
C-2	29.47	31.37	31.95	28.72	33.96	32.04
C-3	120.59	119.05	119.27	119.55	32.53	121.79
C-4	133.87	133.25	133.79	133.13	142.57	133.01
C-5	42.62	44.20	41.11	43.97	49.31	47.38
C-6	78.56	78.87	78.76	79.02	77.92	78.30
C-7	39.87	40.21	39.52	41.56	37.60	38.86
C-8	19.17	18.78	19.02	19.81	18.04	18.48
C-9	31.09	29.79	30.34	30.28	31.18	31.29
C-10	36.86	36.57	37.22	35.98	40.04	37.34
C-11	80.71	74.76	80.17	75.30	79.54	79.94
C-12	174.44	178.13	174.80	179.24	174.92	174.70
C-13	20.64	20.59	20.39	21.24	20.65	19.84
C-14	17.92	19.72	18.25	18.92	11.15	11.52
C-15	23.19	22.25	23.07	22.51	110.04	22.41
Ester groups						
OAc: C=O	170.44	—	—	—	—	—
CH ₃	21.03	—	—	—	—	—
OCOR: C-1'	166.57	—	166.50	166.06	166.27	166.20
C-2'	128.03	—	127.01	133.00	126.82	126.78
C-3'	139.58	—	140.27	128.52(2)	140.33	140.21
C-4'	15.93	—	15.94	129.45(2)	15.87	15.79
C-5'	20.45	—	20.09	130.24	20.25	20.22

^a All spectra were run in deuteriochloroform except that of compound *I* (in d_6 -acetone) and *II* ($\text{CDCl}_3 + d_6$ -acetone 9 : 1).

The X-ray diffraction analysis of isosilerolide (*I*) shows that its molecule contains an eudesmanolide skeleton with *trans*-fused six-membered homocycles (configuration $5\beta\text{H}, 10\alpha\text{CH}_3$) and a *cis*-annulated γ -lactone ring, bonded to $\text{C}_{(6)}$ ($6\alpha\text{H}, 7\alpha\text{H}$), in accord with the NMR analysis. The conformation of the molecule in crystal is characterized by a sofa conformation of the cyclohexene ring with $\text{C}_{(10)}$ constituting the out-of-plane atom while the cyclohexane ring adopts a conformation intermediate between a boat ($B^{5,8}$) and a twist ($T^{5,8}$) form. The γ -lactone ring exists in a flattened half-chair conformation with $\text{C}_{(6)}$ and $\text{O}_{(1)}$ displaced respectively to the α and β sides of the plane determined by the atoms $\text{C}_{(7)}$, $\text{C}_{(11)}$ and $\text{C}_{(12)}$.

We tried to assign absolute configuration to isosilerolide (*I*) by determination of absolute configuration at $\text{C}_{(1)}$ using the benzoate rule⁸⁻¹¹, and at $\text{C}_{(11)}$ using the sector rule^{12,13}. The non-crystalline monobenzoate *VII*, $\text{C}_{22}\text{H}_{26}\text{O}_5$, $[\alpha]_D^{20} -162.0^\circ$, was prepared by esterification of dihydroxy lactone *II* with benzoyl chloride. Its IR spectrum exhibited bands due to a free hydroxy group ($3\ 575$ and $3\ 450\ \text{cm}^{-1}$), a γ -lactone group ($1\ 770\ \text{cm}^{-1}$) and an ester of aromatic acid ($1\ 711$, $1\ 602$, $1\ 586$, $1\ 495$ and $1\ 278\ \text{cm}^{-1}$). The mass spectrum displayed typical fragments of m/z 248 ($\text{M}-122$), 230 ($\text{M}-122-18$), 105 ($\text{C}_6\text{H}_5\text{CO}^+$) and 77 (C_6H_5^+). The structure was confirmed by ^1H and ^{13}C NMR spectra (Table I and II). The CD spectrum contained a maximum at 230 nm ($\Delta\epsilon -6.9$). The difference between molecular rota-

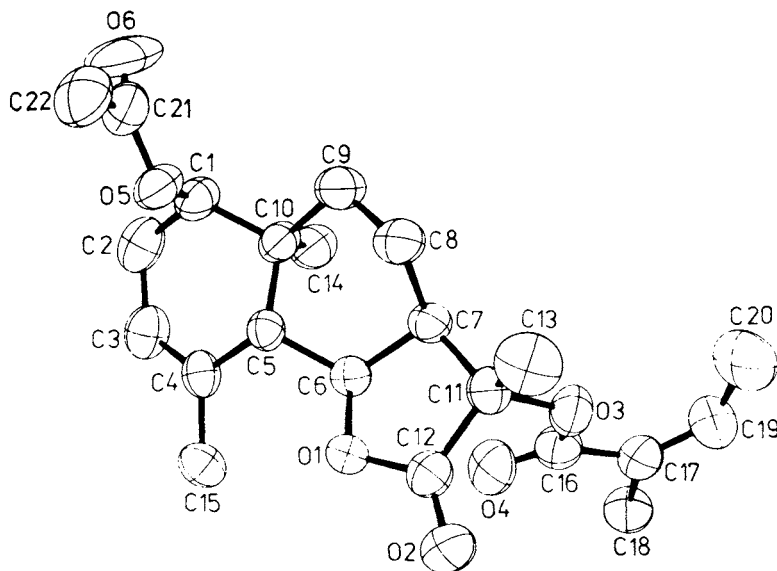


FIG. 1

Stereoview of the molecule of isosilerolide (*I*) (from X-ray diffraction analysis)

tion of the monobenzoate *VII* ($[\text{M}]_{\text{D}} - 600$) and the dihydroxy lactone *II* ($[\text{M}]_{\text{D}} - 221.3$) indicates the *R*-configuration at $\text{C}_{(1)}$. As concerns the chirality center $\text{C}_{(11)}$, the maxima in the CD spectra of the dihydroxy lactone *II* (225 nm, $\Delta\epsilon + 2.2$) and the ester lactone *V* (223 nm, $\Delta\epsilon + 2.0$) are in accord with the *S*-configuration. The derived absolute configurations at both chiral centers are compatible with the formula *I* for isosilerolide.

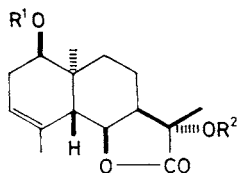
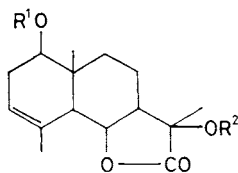
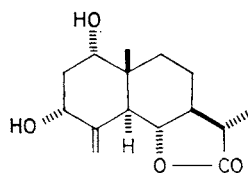
As already mentioned, we have correlated chemically isosilerolide (*I*) with silerolide (*III*) *via* the unsaturated dihydroxy lactone *II* and prepared *III* by esterification of *V* arising by partial saponification of isosilerolide. These transformations lead to the structure *III* for silerolide. The position of the ester groups is confirmed by identical chemical shifts ($\delta 4.62$) of the $\text{H}_{(1)}$ signals in the spectra of *I* and *III* (indicating the presence of the same ester) whereas the $\text{C}_{(11)}-\text{CH}_3$ shifts are somewhat different ($\delta 1.61$ and 1.57 , respectively) as the result of structurally different ester groups on $\text{C}_{(11)}$. Due to the very small amount of silerolide *III* we were not able to get ^{13}C NMR data required for proving the ester positions.

As already reported³, silerolide (*III*) has been chemically correlated *via* lactone *VIII* with natural lasolide (*IX*) (from underground parts of *L. trilobum* (L.) BORKH., *Umbelliferae* family, *Laserpitieae* tribe)¹⁴, whose constitution we have suggested¹⁵. As follows from the method of preparation of *VIII* from lasolide (*IX*) and silerolide (*III*), the chiral centers at $\text{C}_{(5)}$, $\text{C}_{(6)}$, $\text{C}_{(7)}$, $\text{C}_{(10)}$ and $\text{C}_{(11)}$ were not affected during the correlation. The original relative configuration at $\text{C}_{(1)}$ in lasolide can be determined from the coupling constants $J_{1,2} = 4$ and $J_{1,2'} = 11 \text{ Hz}$ ¹⁵ showing an equatorial orientation of the hydroxyl at $\text{C}_{(1)}$. Thus, the absolute configuration of other chiral centers in *I* and lasolide being the same, lasolide has *S*-configuration at $\text{C}_{(1)}$ and its structure is represented by formula *IX*.

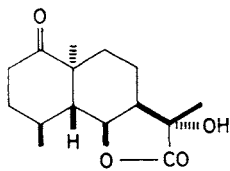
The discussed three natural sesquiterpenic eudesmanolide lactones *I*, *III* and *IX* are the first representatives of a new, hitherto undescribed stereoisomeric series of $5\beta\text{H}, 6\alpha\text{H}, 7\alpha\text{H}, 10\alpha\text{CH}_3$ -eudesman-6,12-olides (*XI*) with *7S*-configuration.

After our preliminary communication², a work appeared¹⁶ on natural lactones from *Pegolettia senegalensis* CASS. (*Compositae* family, *Inuleae* tribe) whose structures derived mainly using ^1H NMR spectroscopy were based also on *XI*. The paper reports that eudesmanolides from *Calostephane divaricata* BENTH. (*Compositae* family, *Inuleae* tribe)¹⁷ are *cis*-6,12-eudesmanolides and not *trans*-6,12-eudesmanolides¹⁶, and suggests a revision of absolute configuration at $\text{C}_{(10)}$ in critonilide (*XII*) and isocritonilide (*XIII*), obtained from *Inula crithmoides* L. (*Compositae* family, *Inuleae* tribe)¹⁸.

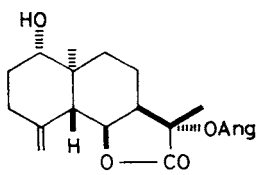
The eudesmanolides of the new stereoisomeric type *XI* were prepared by us also synthetically. On cyclization of laserolide (*XIV*)^{5,19} we obtained two isomeric diester-lactones *XV* and *XVI* which were hydrolyzed to the corresponding diol-lactones *XVII* and *XVIII*. The stereostructure of the cyclized derivatives *XV*–*XVIII* is described in our previous communication⁵.

I, R¹ = Ac ; R² = AngII, R¹ = R² = HIII, R¹ = Ac ; R² = SenIV, R¹ = H ; R² = AngV, R¹ = Ac ; R² = HVII, R¹ = Bzl ; R² = HIIIa, R¹ = Ac ; R² = SenIIIb, R¹ = Sen ; R² = Ac

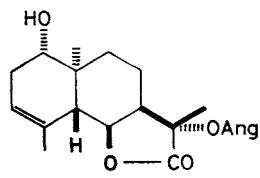
VI



VIII

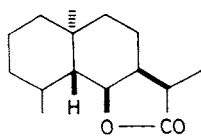


IX

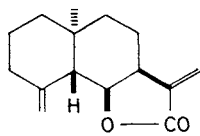


X

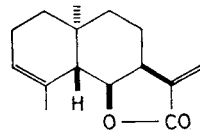
Having elucidated the structures of the eudesman-6,12-olides with *cis*-lactone grouping, we tried to characterize in more detail the two hitherto described eudesman-6,12-olide types: the large group of "*trans*-lactones" with *trans*-arrangement of C₍₁₀₎-CH₃, H₍₅₎, H₍₆₎ and H₍₇₎, and the group of "*cis*-lactones" with *trans*-relation of C₍₁₀₎-CH₃, H₍₅₎ and H₍₆₎ but *cis*-configuration of H₍₆₎ and H₍₇₎. The conforma-



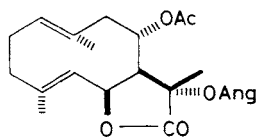
XI



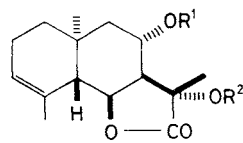
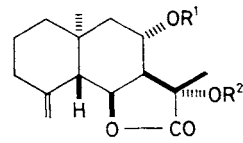
XII



XIII



XIV

XV, R¹ = Ac ; R² = AngXVII, R¹ = R² = HXVI, R¹ = Ac ; R² = AngXVIII, R¹ = R² = H

tional features of the ring B, together with the corresponding ^1H NMR spectral parameters, are summarized in Fig. 2. Both types contain a *trans*-decalin system with the angular $\text{C}_{(10)}$ -methyl and the $\text{H}_{(5)}$ atom in axial positions.

As seen on models, *trans*-lactones form a conformationally very rigid system with chair conformation of both the six-membered rings, of which the ring B must be of the $^5\text{C}^8$ type. The dihedral angles between the hydrogens, $\Phi_{5,6}$ and $\Phi_{6,7}$, should be close to 180° as confirmed by the high coupling constants $J_{5,6}$ and $J_{6,7}$ ($9.5 - 11.9$ Hz, see Table III). The relation of the hydrogen atoms in positions 7 and 8 should be expressed by $\Phi_{7,8\alpha} \approx 60^\circ$ and $\Phi_{7,8\beta} \approx 180^\circ$, again in agreement with the experimental

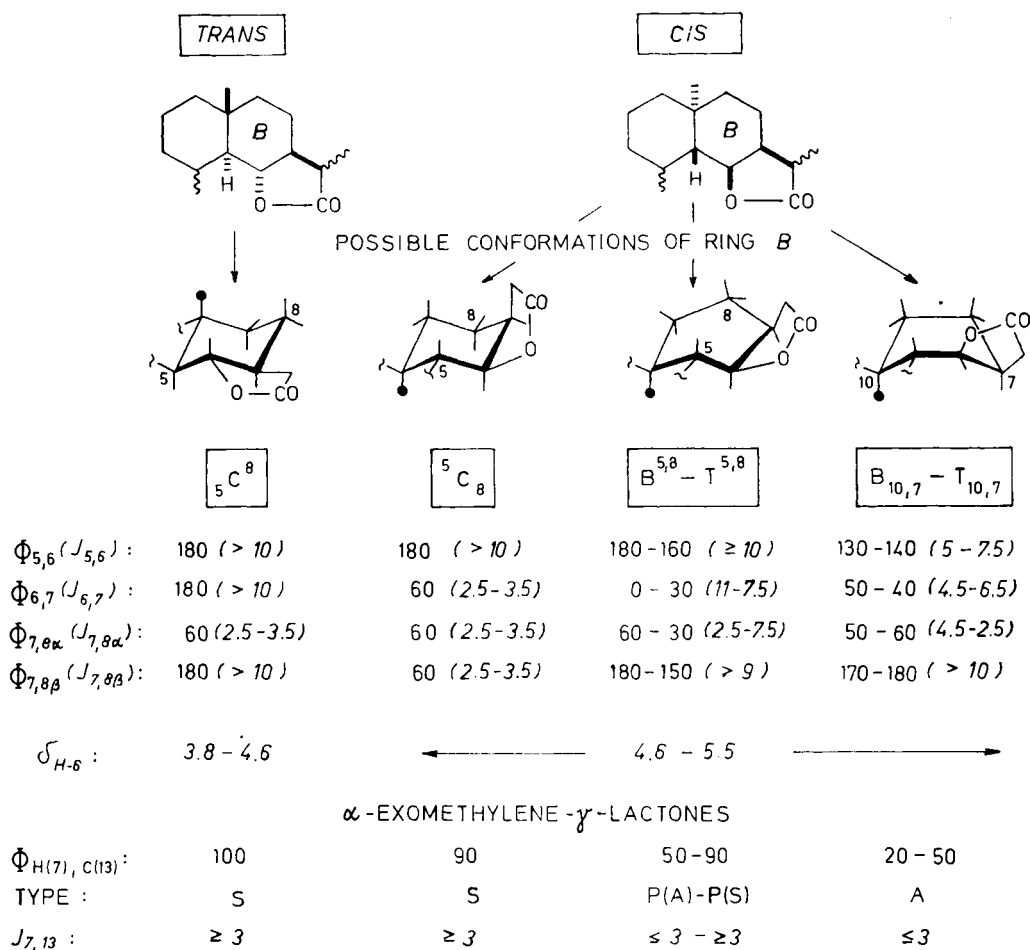


FIG. 2

Conformational and ^1H NMR characteristics of known types of eudesman-6,12-olides with *trans*- and *cis*-lactone grouping

TABLE III

Some ^1H NMR parameters of ring B protons of eudesman-*trans*-6,12-olides in deuteriochloroform

Compound	H(5)	$J_{5,6}$	H(6)	$J_{6,7}$	H(7)	$J_{7,8}$	$J_{7,13(13')}$	H(8)	Ref.
XIX	2.57	11	3.84	11	2.53	—	11	3.3 3	— 4.10 22
XXII	2.41	10	3.86	10	2.53	—	11	3.5 3	— 3.98 22
XXIII	^a	10	3.87	10	2.49	7	11	3 3	^a ^a 23
XXV	^a	10	3.88	11.5	2.46	—	^a	3 3	— ^a 24
XXIX	2.46	12	3.88	10.5	^a	^a	^a	3 3	^a ^a 25
XXXII	1.46	10	3.89	10	1.50	^a	^a	— —	^a ^a 23
XXXIV	2.57	11	3.91	11	2.10	3	11	— —	1.91 1.82 26
XX	2.60	11	3.92	11	2.76	—	11	3.3 3.0	— 5.22 22
XXIV	1.50	10	3.93	10	2.52	7	11	3 3	^a ^a 23
XXI	2.36	10	3.93	10	2.54	—	10	3 3	— 4.00 22
XXVI	2.71	12	3.93	11	2.53	3	11	3 3	2.05 1.65 27
XXXIII	1.44	10	3.94	10	1.70	^a	^a	— —	^a ^a 23
XXXV	^a	11.9	3.94	10.4	^a	—	^a	— —	— 3.95 28
XXXVI	1.59	11	3.94	10	1.59	^a	12	— —	1.70 1.44 29
XXXVIII	^a	10.5	3.95	10.5	2.6	^a	^a	3.2 3.0	^a ^a 24
XLI	2.77	11	3.96	11	3.09	3	11	3.5 3.0	2.16 1.85 26
XLIII	1.38	11	3.96	10	1.51	^a	^a	— —	1.91 ^a 29
XXX	2.44	12	3.97	10.5	^a	^a	^a	3 3	^a ^a 25
XLIV	1.96	11	3.98	10	1.63	^a	^a	— —	1.90 1.74 30
XXVII	^a	11.3	3.98	10.8	2.80	—	10.7	3.1 2.9	— 5.30 24
XLV	3.11	11	3.98	11	^a	^a	^a	3 3	^a ^a 25
XLVII	2.35	11.4	3.98	10.8	2.57	—	10.4	3.2 3.0	— 4.10 31
XLII	2.97	11	3.98	11	3.23	3.5	12.7	3.5 3.0	2.18 1.87 32
XLVIII	^a	9.5	3.99	9.5	^a	—	11.5	— —	— 4.01 33, 34
LI	2.04	11.5	3.99	10.5	1.69	—	^a	— —	— 3.99
LII	2.68	11	4.00	11	2.58	—	11	3 3	— 4.23 22
LIII	2.90	11.5	4.00	10.5	3.30	^a	^a	3.0 3.0	1.90 ^a 35
XXXI	2.42	11.2	4.00	11.3	2.77	—	11.3	3.0 2.8	— 5.20 36
XXXIX	2.84	10.5	4.01	10.5	2.56	3	12	3 3	2.00 1.70 27
IL	^a	10.6	4.02	10.6	^a	—	^a	— —	— 3.98 24
LIV	^a	11.8	4.02	10.8	2.51	^a	^a	3.2 3.2	^a ^a 24
LV	2.18	11	4.03	11	^a	^a	^a	3 3	^a ^a 37
LVI	2.68	11	4.03	10	2.54	3	10	3.3 2.8	2.03 1.62 38
XXVIII	^a	11	4.03	11	^a	—	^a	3.2 2.9	— 5.20 39
LVIII	2.92	12	4.05	11	3.04	^a	^a	3 3	2.08 2.08 26
LIX	1.81	11.5	4.05	11	2.58	3	11	3 3	^a ^a 40
VI	3.02	11.0	4.05	10.1	1.66	3.2	12.0	— —	^a ^a
XL	^a	10.9	4.07	10.9	2.86	—	10.7	3.1 2.9	— 5.23 24
L	^a	10.6	4.08	10.6	^a	—	10.6	— —	— 5.15 24
LXI	2.22	11.4	4.09	9.5	1.65	^a	^a	— —	^a ^a
XLVI	3.10	11	4.10	11	^a	^a	^a	3 3	^a ^a 25

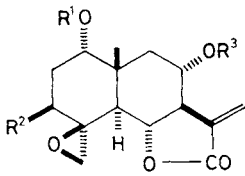
TABLE III
(Continued)

Compound	H(5)	$J_{5,6}$	H(6)	$J_{6,7}$	H(7)	$J_{7,8}$		$J_{7,13(13')}$		H(8)		Ref.
<i>LX</i>	1.82	11.5	4.11	10.8	2.59	<i>a</i>	<i>a</i>	3.2	3.1	<i>a</i>	<i>a</i>	
<i>LXII</i>	<i>a</i>	11	4.12	11	2.52	<i>a</i>	<i>a</i>	3	3	<i>a</i>	<i>a</i>	41
<i>LXIII</i>	2.53	11	4.13	11	<i>a</i>	<i>a</i>	<i>a</i>	3	3	<i>a</i>	<i>a</i>	25
<i>LXIV</i>	<i>a</i>	11	4.15	11	<i>a</i>	—	—	—	—	—	—	24
<i>LXV</i>	3.03	11	4.17	11	2.90	—	11	3.2	3.0	—	5.52	42
<i>XXXVII</i>	1.44	11	4.20	10	1.57	<i>a</i>	12	—	—	1.80	1.57	29
<i>LVII</i>	2.71	11	4.20	10	2.84	3	—	3.3	2.8	5.23	—	38
<i>LXVI</i>	2.30	11	4.40	11	2.81	3	—	3.5	3	5.78	—	43
<i>LXVIII</i>	<i>a</i>	10.8	4.42	10.8	<i>a</i>	<i>a</i>	—	—	—	5.30	—	24
<i>LXVII</i>	2.30	11	4.42	11	2.83	3	—	3.5	3	5.83	—	43
<i>LXX</i>	2.60	11	4.46	10.5	2.58	3	12	3.3	3	2.18	1.64	30
<i>LXXI</i>	2.25	11.5	4.47	11.5	2.83	3	—	3.5	3.5	5.76	—	44
<i>LXXII</i>	<i>a</i>	11.0	4.51	11.0	2.88	<i>a</i>	—	3.3	3.0	5.71	—	24
<i>LXIX</i>	<i>a</i>	10.8	4.51	10.8	<i>a</i>	<i>a</i>	—	—	—	4.28	—	24
<i>LXXV</i>	2.87	11.5	4.52	11.5	2.90	3	—	3.2	3.2	5.81	—	45
<i>LXXIII</i>	<i>a</i>	11	4.55	11	2.81	3	—	3.3	3.0	5.74	—	46
<i>LXXIV</i>	<i>a</i>	11.1	4.58	11.1	2.73	<i>a</i>	—	3.3	3.1	4.60	—	24

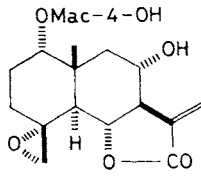
^a The parameter was not determined.

values of $J_{7,8\alpha}$ (3 Hz) and $J_{7,8\beta}$ (12 Hz), found *e.g.* for erivanin (VI)⁶. The H₍₆₎ proton signals in the spectra of *trans*-lactones appear in the range δ 3.8–4.6, depending on the chemical environment, as seen from Table III. The table contains ¹H NMR data for ring B proton signals for most of the so far described natural *trans*-lactones, arranged according to the increasing chemical shift of the H₍₆₎ proton. Of the several known compounds, differing only in the character of the ester group in the same position, we list only one representative.

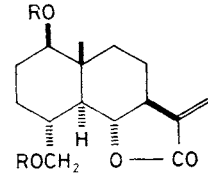
We cannot expect the *cis*-lactones to be as conformationally rigid as the *trans*-lactones. Models show that the chair form of the ring B (type ⁵C₈) can be destabilized by axial position of the C₍₁₁₎ atom and, moreover, in compounds with β -oriented methyl at C₍₁₁₎ (*e.g.* in *I*, *III* and *IX*), also by its steric interactions with the axial atoms H₍₅₎ and H₍₉₎. Further possible conformations of the ring B are represented by a boat form B^{5,8} (or twist-boat T^{5,8}) with C₍₅₎ and C₍₈₎ in the flagpole positions, or a boat B_{10,7} (or twist-boat T_{10,7}) with C₍₇₎ and C₍₁₀₎ in the flagpole positions (see Fig. 2). The existence of the type B^{5,8} or T^{5,8} has been proved in this work for the crystalline isosilerolide (*I*). In this conformation the above-mentioned steric interactions of the C₍₁₁₎-methyl are not present. The dihedral angles of the protons H₍₅₎, H₍₆₎ and H₍₇₎ for the individual conformational types of the *cis*-lactones are given in



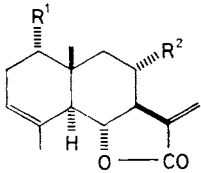
XIX, $R^1 = \text{Mac}-4\text{-OH}$; $R^2 = R^3 = \text{H}$
 XX, $R^1 = \text{Mac}-4\text{-OH}$; $R^2 = \text{H}$; $R^3 = \text{Mebu}$
 XXI, $R^1 = \text{Mac}$; $R^2 = \text{OH}$; $R^3 = \text{H}$



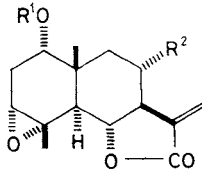
XXII



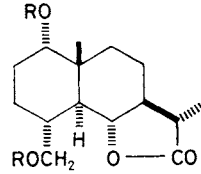
XXIII, $R = \text{Ac}$
 XXIV, $R = \text{H}$



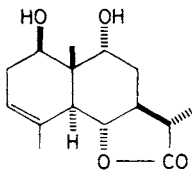
XXV, $R^1 = R^2 = \text{H}$
 XXVI, $R^1 = \text{OAc}$; $R^2 = \text{H}$
 XXVII, $R^1 = \text{H}$; $R^2 = \text{OAc}$
 XXVIII, $R^1 = \text{OH}$; $R^2 = \text{OAc}$



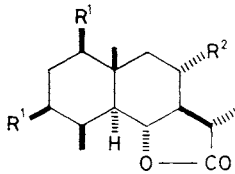
XXIX, $R^1 = \text{Ac}$; $R^2 = \text{H}$
 XXX, $R^1 = R^2 = \text{H}$
 XXXI, $R^1 = \text{H}$; $R^2 = \text{OAc}$



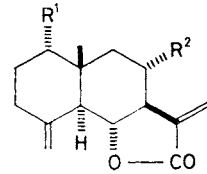
XXXII, $R = \text{Ac}$
 XXXIII, $R = \text{H}$



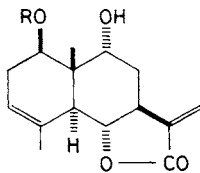
XXXIV



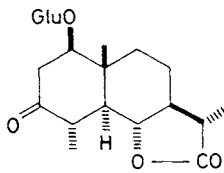
XXXV, $R^1 = \text{H}$; $R^2 = \text{OH}$
 XXXVI, $R^1 = \text{OAc}$; $R^2 = \text{H}$
 XXXVII, $R^1 = \text{OH}$; $R^2 = \text{H}$



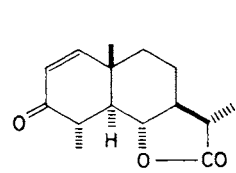
XXXVIII, $R^1 = R^2 = \text{H}$
 XXXIX, $R^1 = \text{OH}$; $R^2 = \text{H}$
 XL, $R^1 = \text{H}$; $R^2 = \text{OAc}$



XLI, $R = \text{H}$
 XLII, $R = \text{Ang}$

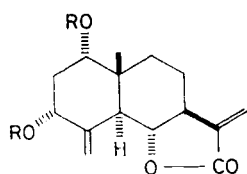


XLIII



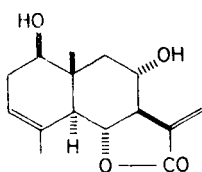
XLIV

Fig. 2. It follows that $J_{5,6}$ can be about the same as for the *trans*-lactones, except the $B_{10,7}$ conformation for which it is markedly lower. Lower values than for the *trans*-lactones should be generally found for the constant $J_{6,7}$; however, the experimental values depend strongly on the preferred conformation of the ring B (dihedral angle $\Phi_{6,7}$ is in the range $0^\circ - 60^\circ$). The preferred conformation of a *cis*-lactone should

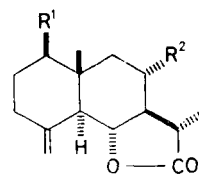
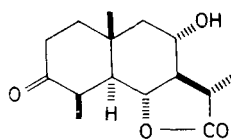


XLV, R = Ac

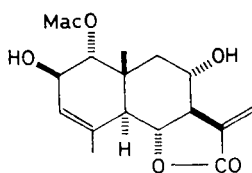
XLVI, R = H



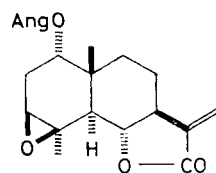
XLVII

XLVIII, R¹ = R² = OHIL, R¹ = H; R² = OHL, R¹ = H; R² = OAc

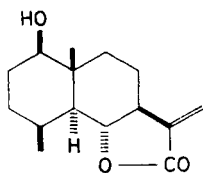
LI



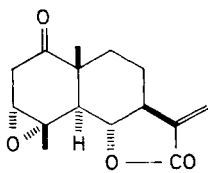
LII



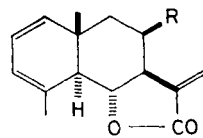
LIII



LIV

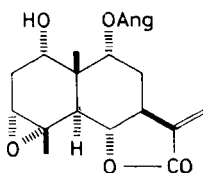


LV

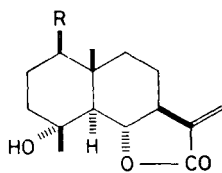


LVI, R = H

LVII, R = OiVal

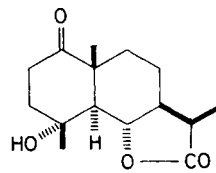


LVIII



LIX, R = H

LX, R = OH



LXI

TABLE IV
Some ^1H NMR parameters of ring B protons of eudesman-*cis*-6,12-olides

Compound	H(5)	$J_{5,6}$	H(6)	$J_{6,7}$	H(7)	$J_{7,8}$	$J_{7,13(13')}$	H(8)	Ref.	
LXXVI	2.65	9.5	4.59	7	3.73	4	—	2 1.7	5.11 —	17
LXXVII	2.58	9.5	4.59	7	3.72	4	—	2 1.7	5.16 —	17
LXXVIII	2.41	10.5	4.60	7	3.61	5	—	2.5 2.5	5.44 —	16
LXXX	2.95	9	4.60	6.3	2.96	3	11	—	1.83 1.65	16, 47
LXXXII	2.59	10	4.61	7	3.41	4.5	—	2.5 2.5	4.33 —	16
XIII	1.86	11	4.61	7.5	3.28	5.3	^a	3.5 3.5	2.03 ^a	18
LXXXIII	^a	12	4.62	10.2	3.10	^a	^a	—	^a ^a	48
LXXXIX	2.43	10.5	4.63	7	3.66	5	—	2.5 2.5	5.51 —	16
LXXXIV	2.58	9.5	4.63	7	3.74	4	—	2 1.7	5.17 —	17
LXXXVII ^b	2.42	10	4.63	6	^a	^a	^a	—	^a ^a	49, 50
LXXXV	2.63	9.5	4.64	7	3.73	4	—	2 1.7	5.24 —	17
LXXXVI	2.65	9.5	4.64	7	3.75	4	—	2 1.7	5.14 —	17
LXXXVIII ^b	^a	10	4.65	7	^a	^a	^a	—	^a ^a	49, 51
LXXXI	2.95	11	4.68	7	2.92	^a	^a	—	2.1 to 1.8	16, 47
XC	^a	11.5	4.69	8.5	2.70	—	3.0	—	— 4.00	16, 47, 19
XCII	2.40	10	4.71	7.5	^a	^a	^a	—	^a ^a	49, 52
X	^a	10.9	4.74	8.5	3.18	^a	^a	—	^a ^a	
VIII	1.36	10.8	4.75	6.9	2.61	5.8	9.5	—	^a ^a	
V	2.48	10.5	4.78	7.2	2.72	^a	^a	—	^a ^a	
II	2.38	10.4	4.79	7.3	2.69	6.0	8.6	—	1.80 1.63	
XVII	2.09	10.9	4.79	7.9	2.83	—	6.3	—	— 4.16	5
LXXXIX ^b	2.48	10	4.80	7.5	^a	^a	^a	—	^a ^a	49
XII	1.67	11	4.81	7.5	3.28	5.3	^a	3.5 3.5	2.03 ^a	16, 18
XCIV	1.94	10.5	4.83	7.5	3.73	5	—	3 3	5.45 —	16
III	^a	11.0	4.84	8.5	3.25	5.6	7.0	—	7.0 ^a ^a	
XCIII ^b	2.40	10	4.85	7.5	^a	^a	^a	—	^a ^a	49, 52
XCVI ^b	2.35	10	4.85	7.5	3.28	^a	^a	3.5 3.5	^a ^a	49, 52
XCV	1.95	10.5	4.86	7.5	3.80	5	—	3 3	5.56 —	16
VII	2.60	10.3	4.86	7.2	2.72	^a	^a	—	^a ^a	
XCVIII ^b	2.25	10	4.87	7.5	3.27	^a	^a	4 4	^a ^a	49, 53
XV	^a	11.6	4.88	9.2	3.45	—	3.8	—	— 5.24	5
IV	2.41	11.1	4.88	8.6	3.24	6.4	6.4	—	^a ^a	
IC ^b	^a	12	4.90	9.5	3.33	^a	^a	—	^a ^a	54
I	2.44	10.4	4.91	7.3	3.25	6.0	8.6	—	^a ^a	
XC I	^a	11.9	4.92	9.2	3.37	—	1.8	—	— 5.23	19
XCVII	2.35	10	4.92	7.5	3.28	^a	^a	3.5 3.5	^a ^a	49, 52
C	3.11	12	4.95	10.2	3.15	^a	^a	—	^a ^a	48
XVIII	1.94	11.2	5.00	9.0	2.91	—	3.0	—	— 4.32	5
CI	^a	12	5.02	10.2	3.30	^a	^a	—	^a ^a	48
IX	^a	11	5.03	9.3	3.34	4.7	4.7	—	^a ^a	
CII	^a	12	5.05	10.2	2.75	^a	^a	—	^a ^a	48

TABLE IV
(Continued)

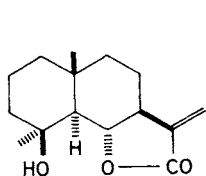
Compound	H(5)	$J_{5,6}$	H(6)	$J_{6,7}$	H(7)	$J_{7,8}$	$J_{7,13(13)}$	H(8)	Ref.	
<i>CIII</i> ^b	2.22	12	5.07	10.2	^a	^a	^a	^a	48	
<i>XVI</i>	^a	11.5	5.08	9.5	3.45	—	3.0	—	5.24	19
<i>CIV</i>	2.33	12	5.08	10.2	3.15	^a	^a	^a	^a	48
<i>CV</i>	2.35	12	5.10	10.2	3.05	^a	^a	^a	^a	48
<i>CVI</i>	^a	12	5.10	10.2	2.72	^a	^a	^a	^a	48
<i>CVII</i>	^a	12	5.10	10.2	2.70	^a	^a	^a	^a	48
<i>CIX</i>	2.60	12	5.17	10.2	3.25	^a	^a	^a	^a	48
<i>CVIII</i>	^a	12	5.20	10.2	3.24	^a	^a	^a	^a	48
<i>CX</i>	2.29	12	5.22	10.2	3.18	^a	^a	^a	^a	48
<i>CXI</i>	^a	12	5.30	10.2	^a	^a	^a	^a	^a	48
<i>CXII</i>	^a	12	5.37	10.2	3.25	^a	^a	^a	^a	48
<i>CXIII</i> ^b	^a	12	5.40	10.2	3.40	^a	^a	^a	^a	48
<i>CXIV</i>	2.17	12	5.42	10.2	3.35	^a	^a	^a	^a	48
<i>CXV</i>	2.33	12	5.42	10.2	3.30	^a	^a	^a	^a	48
<i>CXVI</i>	^a	12	5.46	10.2	3.35	^a	^a	^a	^a	48

^a The parameter was not determined; ^b the structure was corrected from "trans-" to "cis"-lactone in this paper (see text).

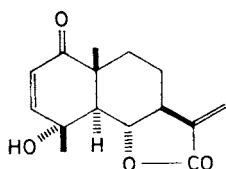
be sensitively reflected by the constants $J_{7,8\alpha}$ and $J_{7,8\beta}$ ($\Phi_{7,8\alpha} = \Phi_{7,8\beta} = 60^\circ$ for the chair vs $\Phi_{7,8\alpha} = 30-60^\circ$ and $\Phi_{7,8\beta} = 150-180^\circ$ for the boat). Common to the *cis*-lactones is a characteristic downfield shift of the $H_{(6)}$ signal, appearing in the region δ 4.6–5.5. The pertinent values are given in Table IV, listing 1H NMR data for the ring B protons in the hitherto described *cis*-lactones (including data for compounds whose structure has been corrected in this work in favour of the *cis*-configuration; *vide infra*).

The effect of the lactone ring on chemical shift of the $H_{(6)}$ proton signal can be demonstrated on lactones of *trans*- or *cis*-2-hydroxycyclohexaneacetic acid (*CXVII* and *CXVIII*, respectively) as simple models. It has been shown⁵⁵ that the CH—O proton in the *trans*-lactone *CXVII* resonates at δ 3.97 whereas that in the *cis*-isomer *CXVIII* at δ 4.60. The marked difference (0.63 ppm) between both stereoisomeric lactones may be caused by different contributions of anisotropy of the neighbouring bonds and by the Van der Waals effect^{56,57}. In the sesquiterpenic lactones the observed shifts of $H_{(6)}$ proton signals are influenced by further substituents in the molecule. The effect of the lactone ring configuration on this shift in the *trans*- and *cis*-lactones depicted in Fig. 2 can be therefore well estimated only by comparison of stereoisomeric pairs, as represented by *XXV* and *XIII* ($H_{(6)}$: δ 3.88 and 4.61) or

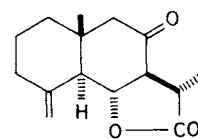
XXXVIII and XII ($H_{(6)}$: δ 3.95 and 4.81). These show downfield shift of 0.73 or 0.82 ppm for the *cis*-lactones. Analogous downfield shifts exist also for the $H_{(7)}$ proton signal in these pairs (0.82 and 0.68 ppm, respectively). However, the $H_{(7)}$ signal is generally less suitable for configurational determinations since its assignment in the spectrum is more difficult and the signal strongly depends on substituents in the neighbouring positions 8 and 11. On the other hand, the $H_{(6)}$ proton in all the compared groups of lactones has the same neighbouring substituents and structural differences occur thus only in the β or even more distant positions. Shielding contributions of the inductive substituent effects must be therefore relatively low (<0.3 ppm). For the *trans*-lactones with axial atom $H_{(6)}$ we can expect more marked deshielding effects of substituents R when $H_{(6)}$ and R are in a 1,3-diaxial relationship



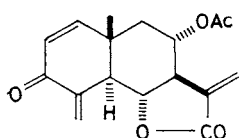
LXII



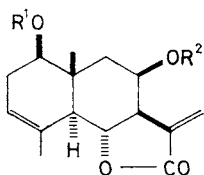
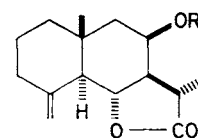
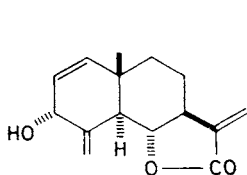
LXIII



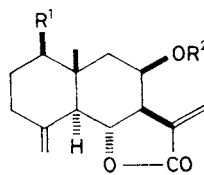
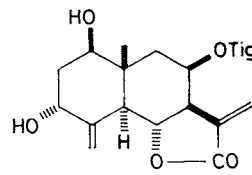
LXIV



LXV

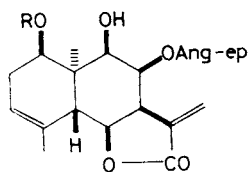
LXVI, $R^1 = \text{Ac}$; $R^2 = \text{Ang}$
LXVII, $R^1 = \text{H}$; $R^2 = \text{Ang}$ LXVIII, $R = \text{Ac}$
LXIX, $R = \text{H}$ 

LXX

LXXI, $R^1 = \text{OAc}$; $R^2 = \text{Ang-ep}$
LXXII, $R^1 = \text{H}$; $R^2 = \text{Ac}$
LXXIII, $R^1 = \text{OH}$; $R^2 = \text{Ac}$
LXXIV, $R^1 = R^2 = \text{H}$ 

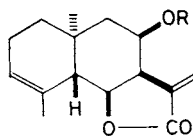
LXXV

(8β , 4β or 11β positions) as the result of the Van der Waals effect⁵⁶. Accordingly, the $H_{(6)}$ signal in the spectra of all *trans*-lactones with 8β -substituents is shifted downfield (δ 4.4–4.6) whereas for the 8α -OR derivatives this signal appears at δ 3.8–4.0 (see Table III). The effect of the 8β -OH (or 8β -OAc) can be determined from the pair XXXVIII and LXXIV (or XXXVIII and LXXII) to be 0.65 (or 0.58) ppm. Separation of the effects of the 4β - and 11β -substituents in the given set of compounds is difficult but they are evidently weaker. In the *cis*-lactones, the $H_{(6)}$ proton can assume a 1,3-diaxial arrangement with 8α and 4α substituents (strictly speaking only in the 5C_8 chair conformation of the ring B) or the 11α substituent (in boat conformations $B^{5,8}$ and $B_{10,7}$). The effect of the 8α substitution cannot be estimated because of lack of experimental data. The downfield effect of the 4α -substituent (4α -CH₃ or 4α -OH) is indicated by the fact that spectra of practically all thus-substituted derivatives display the $H_{(6)}$ signal downfield (δ 4.9–5.5) as compared with derivatives containing a $C_{(3)}=C_{(4)}$ or $C_{(4)}=C_{(15)}$ double bond (typically, δ 4.6–4.9). We can thus summarize that, in spite of variability introduced by substitution, the chemical shift of the $H_{(6)}$ signal can represent a significant criterion in configurational assignment to the lactone ring. Care must be taken in cases of borderline values of $\delta_{H(6)}$ (δ 4.5–4.7).



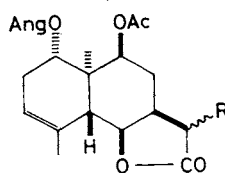
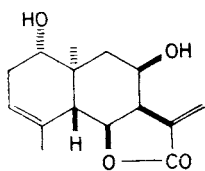
LXXVI, R = Ang

LXXVII, R = Ang-ep

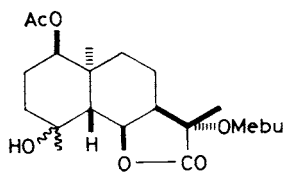


LXXVIII, R = Ang-4-OH

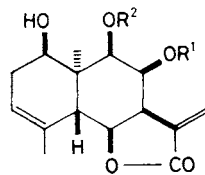
LXXIX, R = Fur

LXXX, R = β -CH₃LXXXI, R = α -CH₃

LXXXII

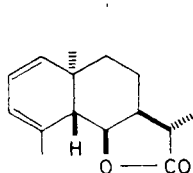


LXXXIII

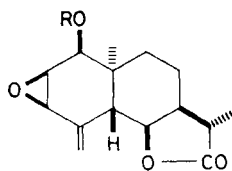
LXXXIV, R¹ = R² = Ang-epLXXXV, R¹ = Ang; R² = Ang-epLXXXVI, R¹ = Ang-ep; R² = Ang

For eudesmanolides with the $C_{(11)}=C_{(13)}$ double bond, the allylic coupling constants $J_{7,13}$ and $J_{7,13'}$ represent another parameter that can in principle be used for distinction between the *cis*- and *trans*-lactones. In accord with the generalized

lactone rule^{20,21}, *trans*-lactones (Fig. 2) belong to the *S*-type with the torsion angle $\Phi_{H(7),C(13)} \approx 90^\circ$ and the corresponding constants $J_{7,13}$ and $J_{7,13'} \geq 3$ Hz. The experimental data in Table III confirm the validity of these conclusions (only in rare cases the values of $J_{7,13'} = 2.8-2.9$ Hz can be distinguished in the spectra from $J_{7,13} \geq 3$ Hz). A more complex situation, however, exists with *cis*-lactones in which the type, angle Φ , and consequently also the constant J , depend on the ring B conformation. The conformation 5C_8 represents an *S*-type, with the same consequences as for the *trans*-lactones. In the forms $B^{5,8}$ or $T^{5,8}$ the lactone ring can be of the *P(S)* or *P(A)* type with the angle $\Phi_{H(7),C(13)}$ in the range $50-90^\circ$, and the $J_{7,13}$ and $J_{7,13'}$ values can be higher as well as lower than 3 Hz. Finally, conformation $B_{10,7}$ or $T_{10,7}$ of the ring B enforces an *A*-type of the lactone, with $\Phi_{H(7),C(13)}$ being $20-50^\circ$ and $J_{7,13}$ and $J_{7,13'} < 3$ Hz. In accord with this analysis, some values of $J_{7,13}$ and $J_{7,13'}$, listed in Table IV, are higher, whereas other are lower, than 3 Hz. Naturally, only values lower than 3 Hz indicate unequivocally a *cis*-lactone grouping whereas an interpretation of constants $J \geq 3$ Hz might be misleading and one has to take into account all available NMR data.

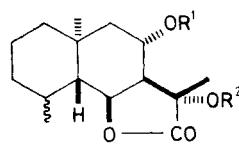
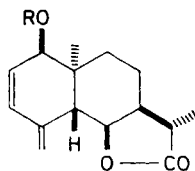


LXXXVII



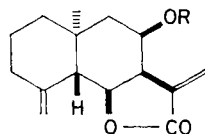
LXXXVIII, R = H

LXXXIX, R = Ang

XC, R¹ = R² = HXCI, R¹ = Ac; R² = Mebu

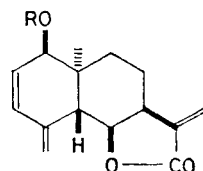
XCII, R = H

XCIII, R = Ang



XCIV, R = Ang-4-OH

XCV, R = Fur

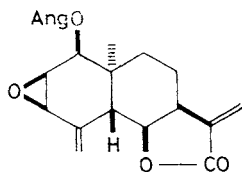


XCVI, R = Ang

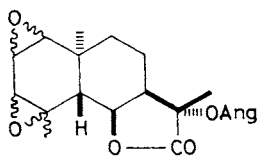
XCVII, R = H

On the basis of the above-discussed NMR criteria, we suggest that the hitherto published⁴⁹ structures for badkhisidin (CXIX), badkhisinin (CXX), dehydrooopodin (CXXI), feropodin (CXXII), oopodin (CXXIII) and oxylactone CXXIV should be corrected in favour of the *cis*-lactone structures LXXXIX, XCVIII, XCVI, LXXXVII, XCVI and LXXXVIII, respectively. The high values of $J_{7,13}$ and $J_{7,13'}$ (3.5–4 Hz) for badkhisinin (XCVIII) and dehydrooopodin (XCVI) correspond to a confor-

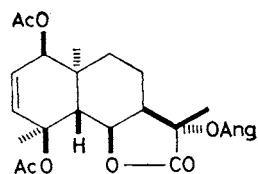
mation with $\Phi_{H(7),C(13)} \approx 90^\circ$ and $\Phi_{H(7),H(6)} \approx 20^\circ$ ($J_{6,7} = 8-9 \text{ Hz}$)²⁰, in fair agreement with the observed^{49,52,53} values $J_{6,7} = 7.5 \text{ Hz}$.



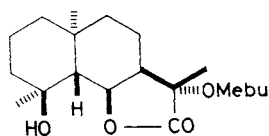
XCVIII



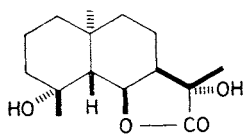
IC



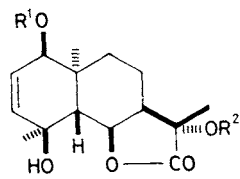
C



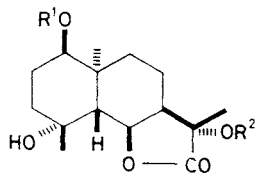
CI



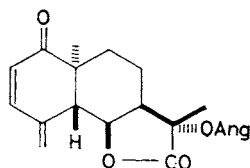
CII



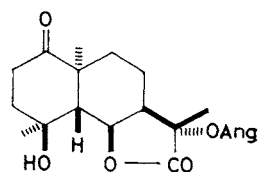
CIII, $R^1 = \text{H}$; $R^2 = \text{Ang}$
 CIV, $R^1 = \text{Ac}$; $R^2 = \text{Ang}$
 CV, $R^1 = \text{Ac}$; $R^2 = \text{H}$



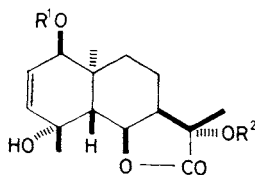
CVI, $R^1 = R^2 = \text{H}$
 CVII, $R^1 = \text{Ac}$; $R^2 = \text{H}$
 CVIII, $R^1 = \text{Ac}$; $R^2 = \text{Mebu}$



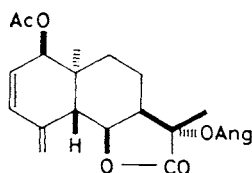
CIX



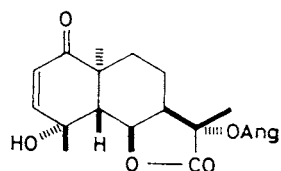
CX



CXI, $R^1 = \text{Ac}$; $R^2 = \text{H}$
 CXII, $R^1 = R^2 = \text{Ac}$
 CXIII, $R^1 = \text{H}$; $R^2 = \text{Ang}$
 CXIV, $R^1 = \text{Ac}$; $R^2 = \text{Ang}$
 CXXXII, $R^1 = R^2 = \text{H}$

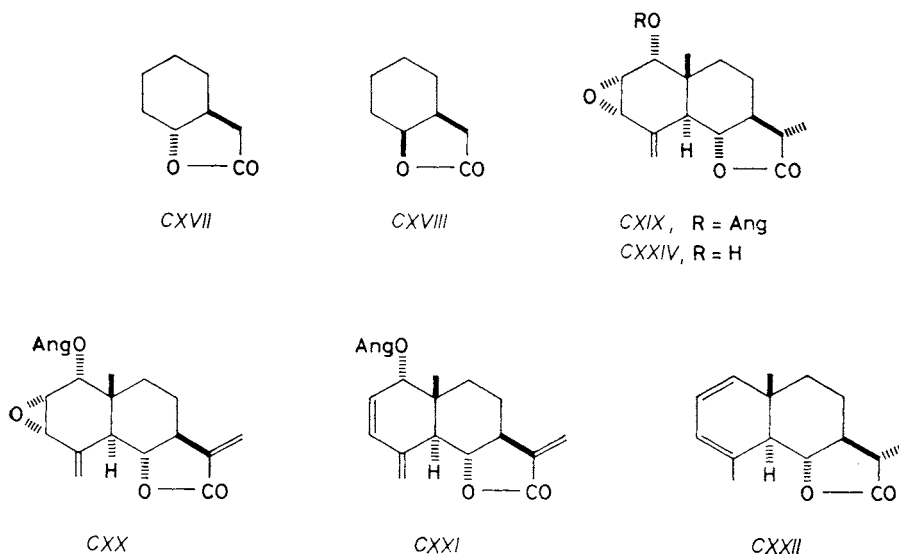


CXV

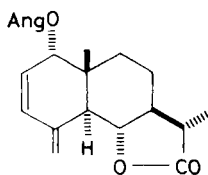


CXVI

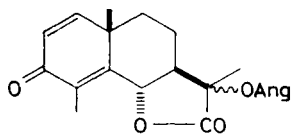
Decipienins A, B, D, E, F, G and H, isolated from *Melanoselinum decipiens* (SCHRADER, WENDL.) HOFFM. species (*Umbelliferae* family, *Laserpitieae* tribe)^{48,54,58}, are reported to have *trans*-annulation of the γ -lactone ring and *cis*-configuration of H₍₇₎ and C₍₁₀₎-CH₃, as depicted by the formulae CXXV–CXXXI. Since the spectra of all the mentioned decipienins and their derivatives exhibit the H₍₆₎ proton signals at δ 4.6–5.5 (except decipienin A, which contains a C₍₄₎=C₍₅₎ double bond and has the H₍₆₎ signal at δ 5.62), we can assume that also these eudesmanolides contain a *cis*-annulated γ -lactone ring. The high values of $J_{6,7}$ (≈ 10 Hz) are compatible with a *cis*-lactone grouping under assumption that the angle $\Phi_{6,7}$ is close to 0° (*i.e.* in the B^{5,8} boat conformation of the ring B, see Fig. 2). The H₍₇₎ proton signal in the spectrum of decipienins and their derivatives with esterified hydroxyl on C₍₁₁₎ appears at δ 3.05–3.40 whereas analogous compounds with a free hydroxyl at C₍₁₁₎ have δ 2.7⁴⁸. The magnitude of the acylation shift of the H₍₇₎ signal (about 0.5 ppm) indicates a *cis*-relation between the H₍₇₎ atom and the oxygen functionality at C₍₁₁₎. We are thus of the opinion that the existing structural assignment should be revised, the correct structures being IC for decipienin B, CXIII for decipienin D, CXXXII for decipienin E, CIII for decipienin F, CXXXIII for decipienin G, and CXXXIV for decipienin H.



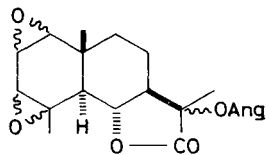
As concerns decipienin A, its suggested⁵⁴ structure CXXV corresponded to that of α -santonin (CXXXV) save the substitution at C₍₁₁₎. However, comparison of ¹H NMR parameters of both compounds reveals more substantial differences in the values of $\delta_{H(6)}$ (5.62 for decipienin A vs 4.81 for α -santonin) and of $J_{6,7}$ (9 Hz against



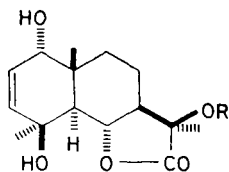
CXXIII



CXXV

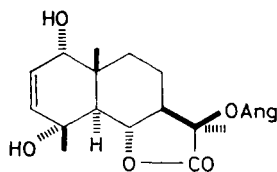


CXXVI

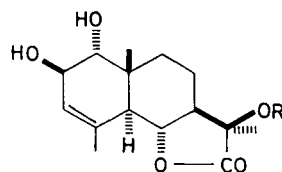


CXXVII, R = Ang

CXXVIII, R = H



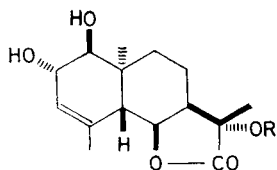
CXXIX



CXXX, R = Ang

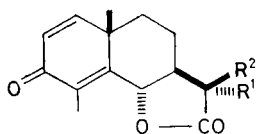
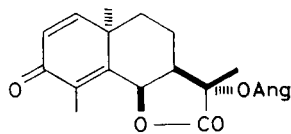
CXXXI, R = H

10.9 Hz). The presence of the $C_{(4)}=C_{(5)}$ double bond eliminates the parameters $\delta_{H(5)}$ and $J_{5,6}$ and undoubtedly influences the $\delta_{H(6)}$ values. The 1H NMR spectral parameters for the ring B protons in the so far described *trans*-lactones (CXXXV, CXXXIX – CXLIII, CXLV – CLVIII) and *cis*-lactones (CLIX – CLXVII), containing

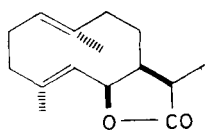


CXXXIII, R = Ang

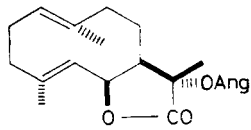
CXXXIV, R = H

CXXXV, R¹ = CH; R² = HCIL, R¹ = H; R² = CH

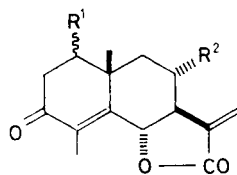
CXXXVI



CXXXVII



CXXXVIII

CXXXIX, R¹ = β -OH; R² = HCXL, R¹ = α -OH; R² = HCXL1, R¹ = β -OH; R² = OAc

the $C_{(4)}=C_{(5)}$ double bond, are summarized in Tables V and VI. Similarly to the above-discussed "saturated" lactones (Tables III and IV), *trans*-lactones show characteristic high values of $J_{6,7}$ (10–12.5 Hz) and $\delta_{H(6)}$ values in a wider range (δ 4.3–5.3; shifted downfield due to the $C_{(4)}=C_{(5)}$ double bond). For the conformationally more flexible "unsaturated" *cis*-lactones (Table VI) the $J_{6,7}$ values range from 4 to 10 Hz and the $H_{(6)}$ signals appear at δ 5.2–5.7. It is thus probable that decipenin A can be described by the structure CXXXVI.

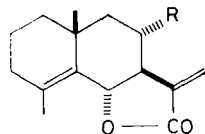
The above facts show that the natural 5 β H,6 α H,7 α H,10 α CH₃-eudesman-6,12-olides XI are obviously characteristic constituents of the *Laserpitieae* and *Peucedaneae* tribes and probably of the whole *Umbelliferae* family. We may assume that eudesmanolides of the type XI represent a further biogenetic step whose precursor is derived from 6 α H,7 α H-germacra-(E)1(10),(E)4-dien-6,12-olide (CXXXVII), as indicated *e.g.* by the simultaneous presence of 8-deacetylaserolide (CXXXVIII) and laserolide

TABLE V
Some ¹H NMR parameters of ring B protons of eudesm-4-en-*trans*-6,12-olides

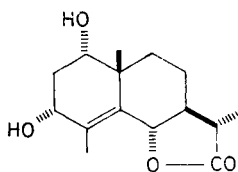
Compound	H(6)	$J_{6,7}$	H(7)	$J_{7,8}$	$J_{7,13(13')}$	H(8)	Ref.
CXXXIX	4.27	11	2.75	^a ^a	3.0 2.8	^a ^a	36
CXLII	4.52	11.5	2.53	3 11	3 3	^a ^a	40
CXLIV	4.55	11	^a	^a ^a	— —	^a ^a	59
CXLV	4.55	11.3	2.63	^a ^a	3 2.8	^a ^a	36
CXLIII	4.62	11.7	2.84	— 10.8	3.2 3.0	— 5.22	28
CXL	4.67	11.5	^a	^a ^a	3.0 3.0	^a ^a	25
CXLVII	4.69	11	^a	^a ^a	— —	^a ^a	59
CXLVIII	4.72	10	^a	^a ^a	— —	^a ^a	60
CXLI	4.80	11.3	3.05	— 11.3	3.0 3.0	— 5.25	36
CXXXV	4.81	10.9	1.89	^a ^a	— —	^a ^a	
CL	4.82	11.7	1.87	— ^a	— —	— 4.05	
CLI	5.00	11.6	^a	— ^a	— —	— 5.32	61
CIL	5.00	10.9	^a	^a ^a	— —	^a ^a	61
CLII	5.11	11	2.95	3 —	3.5 3.0	5.93 —	43
CLV	5.11	12	2.92	^a —	3.4 3.1	5.72 —	24
CLIII	5.12	11	2.95	3 —	3.5 3.0	5.85 —	43
CLIV	5.13	11	2.94	3 —	3.5 3.0	5.82 —	62
CLVI	5.13	11	2.90	^a —	3.3 3.0	5.76 —	46
CXLVI	5.15	12.5	3.02	3 —	3.5 3.2	5.81 —	45
CLVII	5.20	11.4	2.80	^a —	3.4 3.1	4.60 —	24
CLVIII	5.30	10.6	^a	^a ^a	— —	^a ^a	61

^a The parameter was not determined.

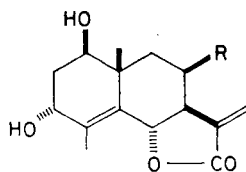
(XIV) beside lasolide (IX) in the *L. trilobum* (L.) BORKH. species (*Umbelliferae* family, *Laserpitieae* tribe)⁶⁵ and by the above-mentioned relatively facile cyclization of germacranolides of the type CXXXVII to eudesmanolides IX.



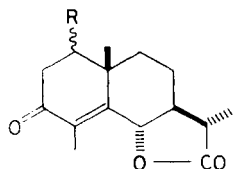
CXLII, R = H
CXLIII, R = OAc



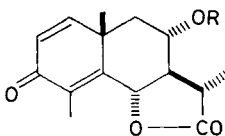
CXLIV



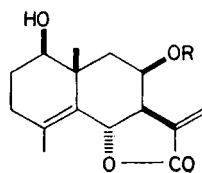
CXLV, R = H
CXLVI, R = OTig



CXLVII, R = α -OH
CXLVIII, R = β -OH



CL, R = H
CLI, R = Ac



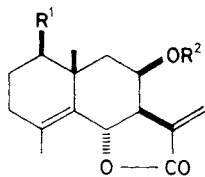
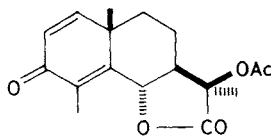
CLII, R = Ang-ep
CLIII, R = Ang
CLIV, R = Tig

TABLE VI

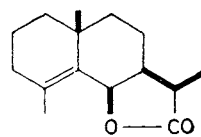
Some ¹H NMR parameters of ring B protons of eudesm-4-en-*cis*-6,12-olides

Compound	H(6)	$J_{6,7}$	H(7)	$J_{7,8}$	$J_{7,13(13')}$	H(8)	Ref.
CLIX	5.21	4	2.89	^a ^a	— —	^a ^a	63
CLX	5.28	6	2.98	^a ^a	2 2	^a ^a	63
CLXI	5.28	4	2.89	^a ^a	— —	^a ^a	63
CLXII	5.38	4.2	^a	^a ^a	— —	^a ^a	61
CLXIII	5.53	6	^a	— 8.5	— —	— 3.81	61
CLXIV	5.57	10	^a	^a ^a	— —	^a ^a	64
CLXV	5.59	4.6	^a	^a ^a	— —	^a ^a	61
CXXXVI ^b	5.62	9	3.22	^a ^a	— —	^a ^a	54
CLXVI	5.68	5.4	^a	— 11.3	— —	— 3.98	61
CLXVII	5.68	5.7	^a	— 10.5	— —	— 5.11	61

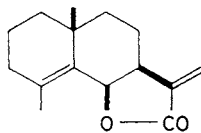
^a The parameter was not determined; ^b the structure of decipienin A was originally described with *trans*-lactone grouping and corrected in this paper (see text).

CLV, R¹ = H; R² = AcCLVI, R¹ = OH; R² = AcCLVII, R¹ = R² = H

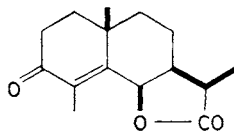
CLVIII



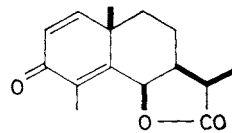
CLIX



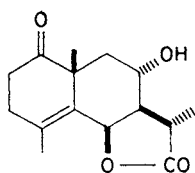
CLX



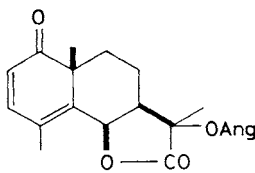
CLXI



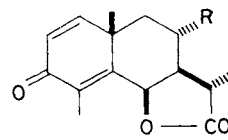
CLXII



CLXIII



CLXIV



CLXV, R = H

CLXVI, R = OH

CLXVII, R = OAc

The following abbreviations are used for the ester groups in the structural formulae:

Ac = acetate; Ang = angelate; Sen = senecioate; Bzl = benzoate; Mac-4-OH = 4-hydroxy-methacrylate; Mebu = 2-methylbutanoate; Mac = methacrylate; iVal = isovalerate; Ang-ep = epoxyangelate; Ang-4-OH = 4-hydroxyangelate; Fur = 3-furoate; Tig = tiglate; Glu = 2,3,4,6-O-tetraacetyl- β -D-glucoside.

EXPERIMENTAL

Melting points were determined on a Kofler block and are not corrected. Column chromatography was carried out on silica gel according to Pitra and Štěrba (30–60 μ , deactivated by addition of 11% of water), thin-layer chromatography on silica gel G Merck according to Stahl. Infrared spectra were taken in chloroform on a Perkin-Elmer PE 580 instrument, mass spectra on an AEI MS 902 spectrometer. NMR spectra were measured on a FT-NMR spectrometer Varian XL-200 (¹H on 200 MHz; ¹³C on 50.3 MHz) in deuteriochloroform with tetramethylsilane as internal standard. Optical rotations were determined in methanol with an objective Perkin-Elmer

141 polarimeter. Circular dichroism was measured on a Roussel-Jouan CD 185 dichrographe, in methanol.

Isosilerolide (*I*)¹

IR spectrum (cm^{-1}): 1 780 (γ -lactone), 1 722, 1 646 (α,β -unsaturated ester), 1 722, 1 250 (acetate). Mass spectrum (m/z): 330 ($M-60$), 230 ($M-60-100$), 83 ($\text{C}_4\text{H}_7\text{CO}^+$), 55 (C_4H_7^+). CD spectrum (nm, $\Delta\epsilon$): 227, -4.1 .

Dihydroxy Lactone *II*

A solution of isosilerolide (*I*; 230 mg) in methanol (5 ml) was mixed with 6.5% methanolic solution of potassium hydroxide (15 ml). After standing for 24 h at room temperature, water (50 ml) was added and most of the methanol was evaporated. The residue was acidified with 5% aqueous sulfuric acid and the mixture was worked up as usual, affording 105 mg of the title lactone *II*, m.p. 183–184°C (ethyl acetate), undepressed on admixture with the product of saponification of silerolide (*III*)³; $[\alpha]_{\text{D}}^{20} - 83^\circ$ (c 0.4). IR spectrum (cm^{-1}): 1 770 (γ -lactone), 3 625, 3 580, 3 460 (hydroxyl). Mass spectrum (m/z): 248 ($M-18$), 177 ($\text{C}_{12}\text{H}_{17}\text{O}$), 159 ($\text{C}_{12}\text{H}_{15}$). CD spectrum (nm, $\Delta\epsilon$): 225, $+2.2$. For $\text{C}_{15}\text{H}_{22}\text{O}_4$ (266.3) calculated: 67.65% C, 8.32% H, 0.76% H act.; found: 67.59% C, 8.04% H, 0.93% H act.

Ester-Lactones *IV* and *V*

A solution of isosilerolide (*I*; 560 mg) in methanol (150 ml) was stirred with 2% aqueous solution of sodium carbonate (100 ml) for 24 h at room temperature. The reaction was monitored by thin-layer chromatography. The mixture was acidified with 5% aqueous sulfuric acid (37 ml) and most of the solvent was evaporated *in vacuo*. The usual work-up procedure afforded 540 mg of material which was chromatographed on a column of silica gel (60 g) in toluene with increasing amount of ether. The lactone *IV* (150 mg) was obtained by elution with toluene-ether (19 : 1); m.p. 118–120°C (ethyl acetate); $[\alpha]_{\text{D}}^{20} - 108^\circ$ (c 0.4). IR spectrum (cm^{-1}): 3 620, 3 530 (hydroxyl), 1 769 (γ -lactone), 1 712 (α,β -unsaturated ester), 1 646 (double bond). Mass spectrum (m/z): 248 ($M-100$), 230 ($M-100-18$), 83 ($\text{C}_4\text{H}_7\text{CO}^+$), 55 (C_4H_7^+). CD spectrum (nm, $\Delta\epsilon$): 226, -2.8 . For $\text{C}_{20}\text{H}_{28}\text{O}_5$ (348.4) calculated: 68.94% C, 8.10% H, 0.38% H act.; found: 69.18% C, 7.89% H, 0.45% H act. Further elution with toluene-ether (9 : 1) gave the noncrystalline lactone *V* (54 mg); IR spectrum (cm^{-1}): 3 580, 3 440 (hydroxyl), 1 770 (γ -lactone), 1 729, 1 252 (acetate). Mass spectrum (m/z): 248 ($M-60$), 159 ($M-60-71-18$), 43 (CH_3CO^+). CD spectrum (nm, $\Delta\epsilon$): 223, $+2.0$. For $\text{C}_{17}\text{H}_{24}\text{O}_5$ (308.4) calculated: 66.21% C, 7.84% H, 0.38% H act.; found: 65.94% C, 7.65% H, 0.43% H act.

Benzoate *VII*

Benzoyl chloride (40 mg) was added to dihydroxy lactone *II* (60 mg) in pyridine (3 ml) and the mixture was stirred for 24 h at room temperature, the reaction course being followed by thin-layer chromatography. The mixture was diluted with water (30 ml), extracted with chloroform and the combined chloroform extracts were worked up in the usual manner. Chromatography of the residue (100 mg) on a silica gel column (10 g) in toluene-ether (9 : 1) afforded 65 mg of the noncrystalline benzoate *VII*, $[\alpha]_{\text{D}}^{20} - 162^\circ$ (c 0.2). IR spectrum (cm^{-1}): 3 450, 3 575 (hydroxyl), 1 770 (γ -lactone), 1 711, 1 602, 1 586, 1 278 (benzoate). Mass spectrum (m/z): 248 ($M-122$), 105 ($\text{C}_6\text{H}_5\text{CO}^+$), 77 (C_6H_5^+). CD spectrum (nm, $\Delta\epsilon$): 230, -6.9 . For $\text{C}_{22}\text{H}_{26}\text{O}_5$ (370.4) calculated: 71.33% C, 7.07% H, 0.38% H act.; found: 71.20% C, 7.11% H, 0.46% H act.

Silerolide (*III*) from Ester-Lactone *V*

Ester-lactone *V* (57 mg) in pyridine (3 ml) was heated with senecioid chloride (35 mg) in a sealed ampoule to 100°C for 24 h. Water (30 ml) was added, and the product was taken up in chloroform. The combined chloroform extracts were washed with 5% aqueous sulfuric acid, an aqueous solution of sodium hydrogen carbonate, water, dried over anhydrous sodium sulfate and taken down. The residue (49 mg) on preparative thin-layer chromatography in toluene — ether (7 : 3) gave silerolide (*III*; 2.3 mg), identical (IR and ¹H NMR spectra) with the authentic sample.

Elemental analyses were carried out in the Analytical Department of this Institute (Dr J. Horáček, Head) by Mrs E. Sýkorová, Mrs A. Froňková, Mr V. Štěrba and Dr V. Pechanec. The IR spectra were measured by Mrs K. Matoušková and Dr S. Vašíčková who interpreted them. Mass spectra were measured and interpreted by Dr L. Dolejš. Optical rotations were determined by Mrs Z. Ledvinová. We express our thanks to all of them.

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