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5βH,6αH,7αH,10αCH_3-EUDESMAN-6,12-OLIDES: A NOVEL STEREOCHEMICAL GROUP OF NATURAL SESQUITERPENE LACTONES. STEREOSTRUCTURE OF ISOSILEROLIDE[1]

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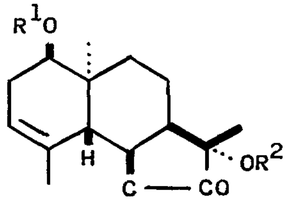
Abstract: A new stereochemical group of eudesmanolides - 5βH,6αH,7αH,10αCH_3-eudesman-6,12-olides - was identified mainly on the basis of proton NMR spectroscopy and checked by X-ray analysis

From the roots of Laserpitium siler L. (Umbelliferae family, tribe Laserpitieae) of Slovenian origin we isolated, in addition to a series of sesquiterpene lactones based on the guaianolide skeleton[2,3], isosilerolide (I), m.p. 141-143°C, $[\alpha]_D^{20}$ -138.9°, composition $C_{22}H_{30}O_6$. When saponified, it gave dihydroxy lactone II, m.p. 183-184°C, $[\alpha]_D^{20}$ -83.1^1 and the composition $C_{15}H_{22}O_4$. Partial hydrolysis of I gave crystalline hydroxy ester lactone III, m.p. 118-120°C, $[\alpha]_D^{20}$ -107.8° and the composition $C_{20}H_{28}O_5$, and also the non-crystalline hydroxy ester lactone IV, $[\alpha]_D^{20}$ -86.9°, of the composition $C_{17}H_{24}O_5$. Esterification of dihydroxy lactone II with benzoyl chloride gave non-crystalline monobenzoate V, $[\alpha]_D^{20}$ -162.0°, of the composition $C_{22}H_{26}O_5$. The fundamental structural features of the compounds mentioned follow from the elemental analysis, IR and mass spectra.



I : R^1= $COCH_3$; R^2= COC_4H_7
II : R^1= R^2= H
III : R^1= H; R^2= COC_4H_7
IV : R^1= $COCH_3$; R^2= H
V : R^1= COC_6H_5; R^2= H

The ^{1}H-NMR spectra of compounds I-V were measured on a 200 MHz instrument in $CDCl_3$ (data see Table 1). In the spectrum of isosilerolide (I) two ester groups were identified, one as acetate (δ 2.06 s, 3H) and the other as angelate (δ 1.89 p, 3H; 2.00 dq, 3H and 6.17 qq, 1H) further two sp^3-methyls (δ 0.88 s, 3H and 1.61 s, 3H) and sp^2-methyl (δ 1.91 m, 3H). In the downfield region of the spectrum an olefinic hydrogen was evident (δ 5.34 m, 1H) together with two CH-O hydrogens (δ 4.91 dd, 1H and 4.62 bd, 1H). The largest part of the structural information was provided by the spectrum of the lactone diol II (Table 1) in which the signals of all hydrogens of the molecule could be identified and assigned by decoupling experiments. This also enables us to propose the eudesmanolide skeleton, with the lactone ring closed at $C_{(6)}$ and the hydroxy groups located at $C_{(1)}$ and $C_{(11)}$, as the basis of compound II. A comparison of the spectra of partially hydrolysed derivatives III and IV permitted the localization in isosilerolide (I) of the acetyl group in the position $C_{(1)}$ and the angelyl group in the position $C_{(11)}$ on the basis of acylation shifts. From the

Table 1 ^{1}H-NMR Parameters of Isosilerolide (I) and its derivatives II-V

Protons	Chemical shifts in compounds				
	I	II[a]	III	IV	V[b]
$H_{(1)}$	4.62	3.38	3.40	4.62	4.86
$H_{(2)}$	2.42	2.46	2.49	2.39	2.49
$H_{(2')}$	2.10	2.03	1.7-2.1	2.07	2.22
$H_{(3)}$	5.34	5.35	5.37	5.34	5.37
$H_{(5)}$	2.44	2.38	2.41	2.45	2.6
$H_{(6)}$	4.91	4.79	4.90	4.78	4.84
$H_{(7)}$	3.25	2.69	3.26	2.70	2.72
$H_{(8)}$	1.62-	1.80	1.7-	1.6-	1.6-
$H_{(8')}$	-1.86	1.63	-2.1	-1.9	-1.9
$H_{(9)}$		2.09			
$H_{(9')}$	1.21	1.18	1.18	1.25	1.30
$H_{(13)}$	1.61	1.46	1.63	1.45	1.42
$H_{(14)}$	0.88	0.85	0.81	0.90	0.98
$H_{(15)}$	1.91	1.87	1.90	1.88	1.92
$H_{(18)}$	1.89	-	1.90	-	-
$H_{(19)}$	6.17	-	6.18	-	-
$H_{(20)}$	2.00	-	2.02	-	-
$H_{(22)}$	2.06	-	-	2.04	-

[a] Representative values of coupling constants of compound II in Hz: $J_{1,2}=3.9$; $J_{1,2'}=1.6$; $J_{2,2'}=18.7$; $J_{2,3}=3.9$; $J_{2',3}=3.3$; $J_{5,6}=10.4$; $J_{6,7}=7.3$; $J_{7,8}=8.6$; $J_{7,8'}=6.0$; $J_{8,8'}=14.2$; $J_{8,9}=7.0$; $J_{8,9'}=7.0$; $J_{8',9}=7.0$; $J_{8',9'}=7.0$; $J_{9,9'}=13.6$; $J_{1,3}=1.2$; $J_{2,5}=2.5$; $J_{2',5}=1.8$; $J_{3,5}=1.8$; $J_{2,15}=2.6$; $J_{2',15}=1.6$; $J_{3,15}=1.4$

[b] aromatic protons: 7.1-8.0

values of coupling constants $J_{5,6}$= 10.4 and $J_{6,7}$= 7.3 Hz and their comparison with the analogous ones in eudesmanolides with known configurations on $C_{(5)}$, $C_{(6)}$ and $C_{(7)}$[4], as well as from an analysis of models we inferred that the relative configuration of the hydrogens $H_{(5)}$ and $H_{(6)}$ is trans, while the hydrogens $H_{(6)}$ and $H_{(7)}$ are probably cis-oriented. The distinct downfield shift of the hydrogen $H_{(7)}$ after acylation of the $C_{(11)}$-OH group (about 0.55 ppm) indicates their cis-orientation. The assumption of the usual 3-orientation of the substituent on $C_{(7)}$ in eudesmanolides leads to the 5βH,6αH,7αH-configuration. When irradiating $C_{(10)}$-CH_3 in derivative II a NOE enhancement was observed on hydrogens $H_{(6)}$ (6%), $H_{(1)}$ (6%), $H_{(7)}$ (9%) and $H_{(2)}$ (7%), so that a cis-orientation of the methyl at $C_{(10)}$ could be assumed with respect to $H_{(6)}$ and $H_{(1)}$, i.e. the configuration 10αCH_3,1βOH. On the basis of the mentioned conclusions the structure of isosilerolide may be represented by formula I.

The proposed structure I for isosilerolide was further checked by X-ray analysis of a crystal of the native lactone. Isosilerolide (I) crystallizes from di-isopropyl ether in an orthorhombic system with 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 the intensity data collected on a diffractometer, and refined by the full matrix least-squares method to a final R index of 0.056 (1 407 reflections). A stereoview of the molecule of isosilerolide is shown in Fig. 1.

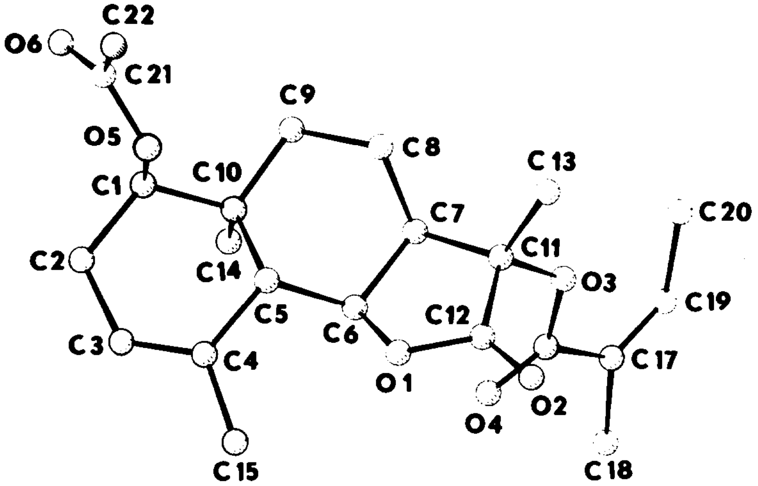


Fig. 1 Stereoview of the molecule of isosilerolide

The ring junctions of eudesmanolide skeleton are trans at $C_{(5)}$-$C_{(10)}$ and cis at $C_{(6)}$-$C_{(7)}$. The cyclohexene ring has a sofa conformation, with $C_{(10)}$ constituing the out-of-plane atom, while the cyclohexane ring adopts a conformation intermediate between the $C_{(5)}\beta$,$C_{(8)}\beta$-boat and the $C_{(5)}\beta$,$C_{(10)}\alpha$-twist conformation. The γ-lactone ring exhibits a flattened half-chair conformation with $C_{(6)}$ and $O_{(1)}$, displaced with respect to the α and the β sides of the plane through the atoms $C_{(7)}$, $C_{(11)}$ and $C_{(12)}$.

We derived the absolute configuration of isosilerolide (I) by determining the absolute configuration of the chirality centres both on $C_{(1)}$, on the basis of the benzoate rule[5-8], and on $C_{(11)}$ by means of the sector rule[9,10]. The difference of the molecular rotations of monobenzoate V ($[M]_D$ -600) and dihydroxy lactone II ($[M]_D$ -221.3) indicated the R-configuration on $C_{(1)}$. The maxima in the CD spectra of dihydroxy lactone II (225 nm, $\Delta\varepsilon$+2.2) and the ester lactone IV (223 nm, $\Delta\varepsilon$+2.0) are in agreement with the S-configuration at $C_{(11)}$. The determination of the absolute configuration on both mentioned chirality centres shows that isosilerolide has the structure, including absolute configuration, represented by formula I[11].

Isosilerolide (I) is the first representative of a new, so far undescribed stereostructural group of native eudesmanolides, which may be characterized as 5βH,6αH,7αH,10αCH_3-eudesman-6,12-olides.

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