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Salvilanguidulines, Four New Diterpenoids Isolated From *Salvia languidula* With An Unusual Epoxy Spiro γ-Lactone

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Key Word: Salvia languidula; Labiatae; new rearranged clerodane derivatives; diterpenoids; salvilanguidulines.

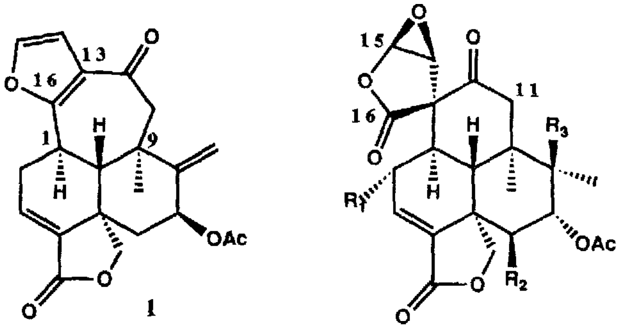
Abstract:. Four new diterpenoids with a rearranged clerodane skeleton were isolated from *Salvia languidula*. All of them contain an epoxy spiro γ-lactone function and a C_1-C_{13} bond. Their structures were established by spectroscopic methods and X-ray crystallographic analysis of one of them.

As a continuation of our systematic chemotaxonomic study of Mexican Salvias[1] we have analyzed several species classified[2] in section *Angulatae* (*Salvia*, Subgenus *Calosphace*). Diterpenoids with rearranged skeletons of clerodanic origin have been previously isolated from *S. tiliaefolia* [3] and *S. rhyacophila* [4].

In a previous communication[5] we described the structure of languiduline **1**, a diterpenoid isolated from *S. languidula*, (*Salvia*, Section *Angulatae*, subsection *Glumacea*) with a rearranged clerodane skeleton which we have named languidulane. In this communication we describe the isolation and structural elucidation of salvilanguidulines A-D.

Salvilanguiduline A, **2a** m.p. 250-251 °C , $[\alpha]_D = -180°$ (c. 0.2, $CHCl_3$), did not exhibit a molecular ion at m/z 416 for the expected molecular formula $C_{22}H_{24}O_8$, but in its mass spectrum showed a peak at m/z 386 (M^+ - 30) and the base peak at m/z 43 indicating an acetate group. The IR spectrum ($CHCl_3$) showed an α,β-unsaturated γ-lactone (1774 cm^{-1}), absorptions due to acetate and ketone groups at 1724 cm^{-1}, and double bond (1674 cm^{-1}).

The ^1H NMR spectrum of **2a** (Table 1) was very similar to the spectrum of the languidulane derivative isolated from *S. sousae* [6]. The AB system ascribed to the 14,15 double bond was replaced by an AB system observed at δ 3.76 and 5.66 (J=2 Hz), which could be explained if the molecule possesses a 14,15 epoxy butanolide moiety with a fully substituted C-13, i.e. an epoxy spirolactone group.[7] A doublet at δ 3.28 (J=12 Hz) was ascribed to H-11β. This assignment was confirmed by spin decoupling experiments which showed sharpening of this doublet on irradiation of the singlet signal due to Me-20. The long range coupling between Me-20 and H-11β is only possible if they are antiperiplanar. The chemical shift of H-11β suggested the deshielding effect produced by the C-16 carbonyl group, which must be therefore β oriented. In order to corroborate the structure 2a proposed for salvilanguiduline A and the relative stereochemistry of the epoxy spiro lactone group, the X-ray diffraction analysis of a single crystal of 2a was performed.



1

2a $R_1=R_2=R_3=H$
2b $R_2=R_3=H$ $R_1=OH$
2c $R_1=R_3=H$ $R_2=OH$
2d $R_1=R_2=H$ $R_3=OH$

Figure 1

The structure of salvilanguiduline A is shown in figure 2[8]. All ring junctions except that formed between rings A and D are trans. The cyclohexene ring A adopts a sofa conformation, while cyclohexane rings B and C possess a chair conformation. The γ-lactone ring D adopts an envelope conformation with C-5 as a flap. The epoxy spiro lactone at C-13 is essentially planar within experimental error. The equatorial methyl substituent at C-8 holds a syn-relationship with the acetoxy at C-7 and the methyl at C-9. The acetoxy group forms a dihedral angle of 74.8(4)° with the least-squares mean plane of cyclohexane ring B. The epoxy-spirolactone lies perpendicular to the cyclohexane ring C with the carbonyl oxygen on the β-side of the molecule and directed toward the center of this ring. A short contact between H-11 β and the C-16 carbonyl is a consequence of the orientation of the γ lactone ring which minimizes the interactions between the oxygen atoms of the epoxy moiety and the keto group at C-12.

Salvilanguiduline B, 2b mp 289-291 °C, $[\alpha]_D = -50°$ (c 0.12, MeOH), showed in the IR spectrum (nujol) a hydroxy group (3350 cm^{-1}), α, β unsaturated γ-lactone (1780 cm^{-1}), an acetate carbonyl (1735 cm^{-1}) and a ketone group (1712 cm^{-1}). The ^1H NMR spectrum (see Table 1) is similar to that described for 2a, but exhibited a doublet at δ 6.7 (J=2 Hz) which was assigned to H-3. The multiplicity and coupling constant of this signal indicated the presence of an α-oriented substituent at C-2, which must be a hydroxyl group whose geminal proton appeared as a multiplet at δ 4.55. The orientation of the hydroxy group was confirmed by the strong deshielding effect on H-14 (Δδ=0.67 ppm), which is only possible if the epoxy spirolactone holds a spacial relationship as show in Fig. 2.

Salvilanguiduline C, 2c mp 256-8 °C, showed in the IR spectrum (nujol) the presence of hydroxy group (3360 cm^{-1}), a γ-lactone (1785 cm^{-1}), an α,β-unsaturated γ-lactone (1775 cm^{-1}), an acetate carbonyl (1738 cm^{-1}) and a ketone group (1720 cm^{-1}). The ^{13}C NMR spectrum[10] led to a molecular formula $C_{22}H_{24}O_9$ and confirmed the presence of the functional groups indicated by the IR spectrum. The signal at δ 65.24 (s) was assigned to C-13 and the resonances at δ 105.27 and 68.16 to the ketalic C-15 and C-14 respectively. The ^{13}C NMR spectrum was assigned by comparison with the reported spectral data of clerodanic diterpenoids[11]. The ^1H NMR spectrum of 2c (see Table 1) was in agreement with the proposed structure. The AB system for the C-19 methylene did not show the long range coupling for the pro-S proton, suggesting the presence of a C-6β substituent[12]. This was confirmed by a doublet at δ 3.91 (J=2 Hz) assigned to a geminal proton of a hydroxy group, coupled to the double doublet of H-7. The β orientation of the hydroxy group at C-6 causes a paramagnetic deshielding of H-10 (δ 3.2, d, J=12 Hz). The coupling constant of H-10 indicated its trans-axial relationship with H-1. The bond between C-1 and C-13 must be equatorial. Spin decoupling experiments showed that Me-20 group is only long range coupled to H-11 β.

The minor constituent was Salvilanguiduline D, 2d mp 283-285 °C, $[\alpha]_D$= -50° (c 0.12, MeOH). The ^1H NMR spectrum (see Table 1) was very similar to that discussed for 2a, but exhibited some changes. The Me-17 was a singlet at δ 1.15 and H-7 was observed as a triplet, therefore the hydroxy group is attached to C-8. The relative stereochemistry of this group was assigned as β as a consequence of the deshielding effect produced on H-11 β (δ 3.98, J=12 Hz) when compared with 2a (Δδ=0.7 ppm) which is due to a 1-3 diaxial relationship between them. This is also true for H-10 which appeared as a doublet at δ 3.25 (J=12 Hz).

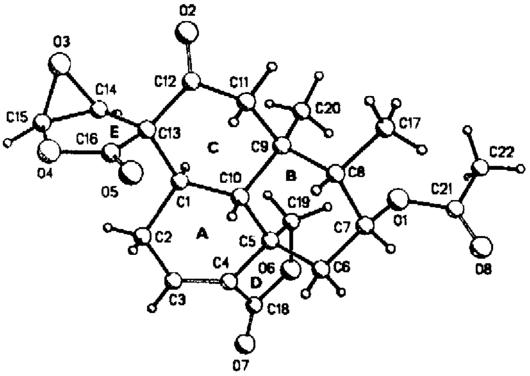
Table 1 ^1H NMR Data for 2a 2b 2c and 2d

	2a*	2b	2c	2d
H-2		4.55 m		
H-3	6.60 dd	6.70 d	6.60 dd	6.60 dd
	(7,3)	(2)	(7,3)	(7,3)
H-6α			3.91d	
			(2)	
H-7	5.35 td	5.37 td	5.12 dd	5.15 t
	(4,2)	(4,2)	(4,2)	(3)
H-10			3.20 d	3.25 d
			(12)	(12)
H-11β	3.28 d	3.20 d	3.30 d	3.98 d
	(12)	(12)	(12)	(12)
H-14	3.76 d	4.43 d	3.90 d	3.85 d
	(2)	(0.6)	(2)	(2)
H-15	5.66 d	5.72 d	5.75 d	5.70 d
	(2)	(0.6)	(2)	(2)
Me-17	0.90 d	0.92 d	0.88 d	1.15 s
	(7)	(7)	(7)	
H-19	4.89 d	4.85 d	4.80d	4.83 d
	(8)	(8)	(8)	(8)
H-19'	3.84 dd	3.95 dd	3.95 d	4.0 br d
	(8,2)	(8,2)	(8)	(8)
Me-20	1.00 s	1.00 s	0.99 s	1.05 s
OAc	2.14 s	2.16 s	2.15 s	2.14 s
OH		5.20	3.90	4.90

Run at 80 MHz using $CDCl_3$-DMSO-d_6 as solvent and TMS as internal standard. Coupling constants in Hz are in parenthesis. Chemical Shifts are in δ values. * Run as $CDCl_3$ solution.

Figure 2

Computer generated perspective drawing of Salvilanguiduline A



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8. Crystal Data: $C_{22}H_{24}O_8$, colourless, crystal dimensions 0.19x0.22x0.42 mm, monoclinic, a=6.589 (2), b=13.946 (4), c=10.614 (4) Å, β= 96.65(2)°, U=968.8(5) Å^3, space group $P2_1$, Z=2, $F_{(000)}$ =440. Using ω:2θ scans at variable scan rate 1271 unique reflections were collected in the range $3<2\theta<100°$, 1238 having $F_o>3\sigma(F_o)$ were used in the structure analysis. Data were collected at 298 K on a Nicolet P3F diffractometer using Ni-filtered CuK_α radiation (λ=1.54178 Å).The cell parameters were determined by least-squares refinement of 25 accurately centered reflections in the range $10.6<2\theta<30.2°$. The data were corrected by Lorentz and polarization effects but not for absorption. The structure was solved by direct methods using the program SHELXTL[9] which revealed the position of all the non-hydrogen atoms. Hydrogen atoms were inserted at calculated positions using a rigid model with a common thermal parameter. The non-hydrogen atoms were refined with anisotropic thermal parameters and refinement converged with R=0.028, wR=0.034. The function minimized was $\Sigma w(|F_o|-|F_c|)^2$ where $w=(\sigma^2(F_o)+0.001F_o^2)^{-1}$. The final difference map showed no features greater than ± 0.15eÅ^{-3}.
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