LANGUIDULINE, A DITERPENOID WITH AN UNUSUAL STRUCTURE FROM SALVIA LANGUIDULA

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Abstract - The unusual structure of languiduline, a new diterpenoid isolated from Salvia languidula Epl (Labiatae), was deduced from the spectral data and confirmed by X-ray diffraction analysis.

Salvia genus has been shown to be a rich source of diterpenoids, mainly of the ent-clerodane[1] and abietane type.[2] It is represented in Mexico by over 275 species[3] mostly of the Salvia, subgenus Calosphace.[4]

As a result of our chemosystematic studies on Mexican Salvias, several ent-clerodane diterpenoids have been isolated.[1] Some of them presented a rearranged ent-clerodane skeleton, for example salvigenolide from Salvia fulgens[5] showed an 8(9→11) abeo ent-clerodane skeleton. Recently we have isolated from S. puberula[6] puberulin and iso-puberulin, two diterpenoids with novel benzonorcaradiene and benzocycloheptatriene skeletons of clerodanic origin.

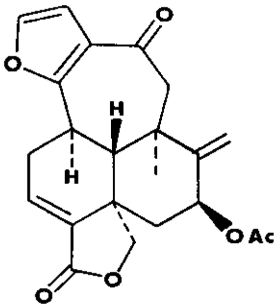
In continuation of our systematic study of Mexican Salvias we have analysed Salvia languidula Epl (Salvia, Section Angulatae, Subsection Glumaceae). From the acetonic extract of the aerial parts of the plant, a diterpenoid languiduline 1, was isolated after extensive chromatographic purification. Languiduline 1, showed mp 243-245°C, $[\alpha]_D^{20}$ =-193.43 (c 0.2, $CHCl_3$). Its mass spectrum was consistent with a molecular formula $C_{22}H_{22}O_6$ (M^+ 382), the base peak at m/z 339 (M^+-43) and a peak at 322 (M^+-60) indicated that it contained an acetate group. The ir spectrum of 1 showed the presence of an α,β-unsaturated γ-lactone function (1774 cm^{-1}) and acetate carbonyl at 1734 cm^{-1}. A strong band at 1654 cm^{-1} was attributed to an α,β-unsaturated ketone, the absorptions at 1565, 1528 and 880 cm^{-1} were assigned to a disubstituted furan ring. The uv spectrum of 1 [λmax 208, 220 and 265 nm (ε = 28000, 17000 and 5500)] indicated that the ketonic group is conjugated with the furan ring. These data suggested that the furan ring is fused to a tricyclic hydrocarbon skeleton which contains an α,β-unsaturated γ-lactone and an additional double bond.

The 300 MHz nmr spectrum of languiduline 1 and adequate double resonance experiments allowed for a complete assignment of all the protons in the molecule (Table 1). Thus it showed signals of an α,β-substituted furan ring and an α,β-unsaturated 18:19 olide. The C-19 methylene was observed as an

ABX system at δ 4.14 (H-19, pro-R, d, J=8.1 Hz) and 4.02 (H-19, pro-S, dd, J=8.1 and 2.4 Hz). The long-range coupling exhibited by H-19 pro-S suggested an α-axial orientation for C-19 and the absence of a β-substituent at C6.[7] The multiplicity of H-3 showed that it is bound to a methylene group. A singlet at δ 2.05 was ascribed to the acetate group; its geminal proton appeared as a doublet (J=8 Hz) at δ 5.72 and was shown to be coupled to H-6 (Table 1), therefore the acetate group must be bound to C7 and β-pseudo-axial. The ^{1}H nmr spectrum of 1 did not show the secondary methyl group doublet usually present in the protonic resonance spectra of clerodanic diterpenoids,[1,7] instead two vinylic singlets were observed at δ 5.43 and 5.36 and were assigned to the exocyclic C17 methylene double bond. This double bond must be spacially oriented in such a way as to exert a protective effect on the 19-pro-R proton (δ 4.14).[7]

Table 1. 300 MHz NMR SPECTRUM OF 1

H	δ	J in Hz
1	2.97 td	10, 3.1
2α	3.31 ddd	17, 7.9, 3.1
2β	2.41 ddd	17, 10, 2.4
3	6.88 dd	7.9, 2.4
6α	2.65 dd	15, 8
6β	1.68 dd	15, 2.4
7	5.72 d	8
10	2.94 d	10
11α	2.66 d	16.8
11β	3.35 dd	16.8, 0.74
14	6.77 d	2.1
15	7.35 d	2.1
17	5.43 s	- - -
17'	5.36 s	- - -
19 pro-R	4.14 d	8.1
19 pro-S	4.02 dd	8.1, 2.4
20	1.23 d	0.74
Ac	2.05 s	- - -



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H-1 and H-10 were localised at δ 2.97 (td, J=10 and 3.1 Hz) and 2.94 (d, J=10 Hz), respectively, which indicated a trans-axial relationship between them and the allylic nature of H-1, therefore C1 must be bound to C16 in languiduline 1. An ABX$_3$ system observed at δ 2.66 (d, J=16.8 Hz) and 3.35 (dd, J=16.8 and 0.74 Hz) was assigned to the C11 methylene which must be bound to the ketonic group and to a fully substituted carbon atom. The 11β proton showed a small long-range coupling with the C20 methyl which was observed at δ 1.23 (d, J=0.74 Hz).

The ^{13}C nmr spectrum of languiduline (Table 2) was consistent with the structure 1 proposed for it. A singlet at δ 192.96 was ascribed to the ketonic carbon atom. This carbon resonance is adequate for an α,β-unsaturated cycloheptenone.[8] It is noteworthy of mention the presence of only three non oxygen bearing sp^3 triplets assigned to C2, C6 and C11. The chemical shifts and multiplicity of C1 (δ 36.22, d) confirmed that it is bound to the α furan carbon 16.

Table 2. ^{13}C NMR SPECTRUM OF 1

C	δ	C	δ
1	36.22 d	12	192.96 s
2	32.37 t	13	123.28 s
3	132.69 d	14	110.14 d
4	136.20 s	15	142.06 d
5	45.11 s	16	158.72 s
6	40.97 t	17	118.18 t
7	73.98 d	18	168.04 s
8	151.14 s	19	72.17 t
9	39.33 s	20	21.40 q*
10	48.57 d	O<u>C</u>OCH$_3$	169.16 s
11	61.89 t	OCO<u>C</u>H$_3$	20.04 q*

Recorded at 20 MHz. TMS as internal standard SFORD multiplicity.

* These values may be interchanged.

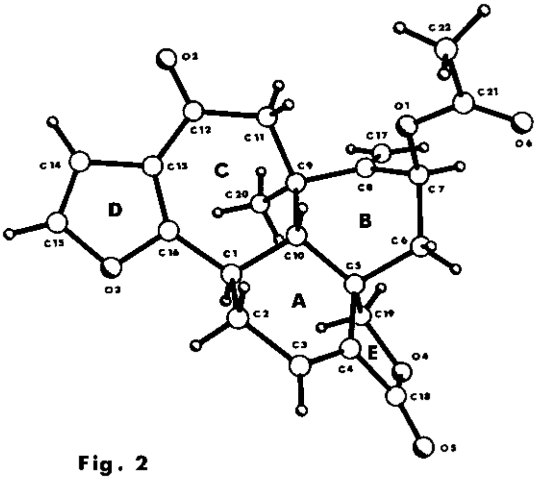

Fig. 2

The unusual structure of languiduline was confirmed by an X-ray analysis. Crystals of languiduline were obtained by slow crystallization from ethyl acetate. The crystal was orthorhombic in space group P2$_1$2$_1$2$_1$, with one molecule of composition C$_{22}$H$_{22}$O$_6$ per asymmetric unit (ρ_{calc}=1.29 g cm^{-3}), Z=4, a=11.229(4), b=11.394(5) and c=15.388(6) Å; V=1968.9(4) Å^3. Intensities of 1496 independent reflections were measured on a Nicolet R3m diffractometer using MoKα radiation (λ=0.7107Å) up to 2$\Theta\leq$45° of which 1247 were considered to be observed [I>2.5σ(I)]. The structure was solved by direct methods and refined anisotropically for the non-hydrogen atoms by least-squares. Hydrogen atoms were forced to ride on the corresponding carbon atoms with a fixed isotropic temperature factor U = 0.06 Å^2. Final R=0.047 (R$_\omega$=0.044) and no peaks greater than ± 0.19eÅ^{-3}. All calculations were performed using the program package SHELXTL[9] on a Nova 4S computer. A computer-generated drawing is given in Fig. 2 and reveals the relative stereochemistry of languiduline. The ring A has a <u>sofa</u>[10a] conformation: A/B and A/C rings are <u>trans</u>-fused with torsion[10b] angles of -33.2(5); 70.7(4)° and 60.9(5); -45.1(5)°, respectively. The junction A/E has torsion angles of 1.1(7); 36.8(4)°. The ring B has a twisted-boat conformation with the acetate group at C7 and the methyl group at C9 on axial and equatorial position, holding anticlinal [τ=121.5(5)°] and synperiplanar [τ=23.5(6)°] relation with the exocyclic C=C at C8. The B/C junction is <u>trans</u> [-35.2(5); 80.3(5)°]. The C ring has a sofa conformation. The carbonyl group C12-O2 is conjugated with the furan ring D. The γ-lactone ring E adopts an envelope conformation with flap at C5. The molecular packing is governed by van der Waals interactions.[11]

Languiduline 1 shows an unusual skeleton with a seven-membered ring as a result of the linkage of C1 to C16 in a clerodanic precursor. To our knowledge there are no precedents of this type of annulation in clerodanes of natural origin.

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    b) ibid., p. 192.

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