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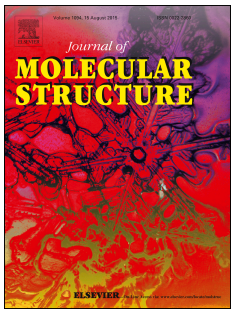

NMR analysis and crystal structure of hydroxyclerodanes from Mexican *Salvia* species

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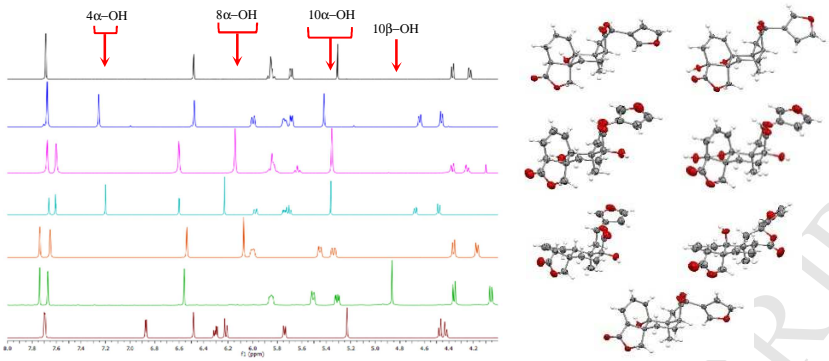
Graphical abstract



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NMR analysis and crystal structure of hydroxyclerodanes from Mexican *Salvia* species.

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Abstract

NMR and single crystal X-ray diffraction analysis of seven clerodanes from Mexican *Salvia* species was performed. We focused on clerodanes with tertiary hydroxyl group at C-4, C-8, and C-10, in which the establishment of absolute configuration around these chiral centers is nontrivial and the ^{13}C NMR signals can be misassigned. In addition, the analysis by ^{1}H NMR in aprotic solvent allowed us to establish a common pattern that correlates the chemical shift with the position of the hydroxyl groups, which constitute a good methodology for future structural elucidation of these kinds of compounds. The obtained data allowed us to establish the absolute configuration of five of these diterpenes and the structural revision of salvimicrophyllin D (**7**).

Keywords: Clerodane diterpenes, hydroxyclerodanes, *Salvia* species, NMR analysis, X-ray diffraction, crystal structure.

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1. Introduction

Clerodane diterpenes constitute a class of secondary metabolites with several biological properties of pharmaceutical interest, such as antiprotozoal, antiviral, and cytotoxic agents [1]; they have possible agrochemical applications due their antifeedant, insecticidal and phytotoxic effects [2]. In the last 25 years, about 1300 clerodanes has been isolated from various taxonomic groups such as fungi, bacteria, and principally plants. Of these, approximately 25% possess a decalin with *cis* fusion and 75% with a *trans* fusion [3]. In the particular case of clerodanes of plant origin, the genus *Salvia* from Lamiaceae family has been identified as a rich source of these compounds [4].

Clerodanes isolated from Mexican *Salvia* species commonly possess in their framework the follow functionalities: a 17,12 δ-lactone, a β-substituted furan ring bonded to C-12 and a 18,19 γ-lactone (**Fig. 1**)[5]. In recent years, the number of reports describing clerodane diterpenes containing tertiary hydroxyl groups in their structure in at least one of the follow positions: C-4, C-8 and C-10, has increased [6-10]. In addition, these compounds can present a decalin ring system, 18,19 γ-lactone, and a 17,12 δ-lactone with *cis* or *trans* fusions for each functionality, or a combination of both. In addition, the establishment of the stereochemistry by NMR at the carbons implied in these fusions can be limited when the spectra are acquired in routine protic solvents (*e. g.* $CDCl_3$ and mixtures $CDCl_3/CD_3OD$), even if 2D NMR experiments as NOESY and ROESY are employed [8,10]. The ^{13}C NMR signals for the implied carbons can be hidden by the signal of $CDCl_3$, however, leading to an erroneous assignment of signals. In this article, we described the results of the exhaustive analysis by NMR and single crystal X-ray diffraction of seven

hydroxyclerodanes isolated from Mexican *Salvia* species. This allowed the establishment of their absolute configuration, including the structure revision of salvimicrophyllin D (**7**), a complete assignment of NMR signals in DMSO-d_6 for these compounds, as well as the determination of their conformation in solid state.

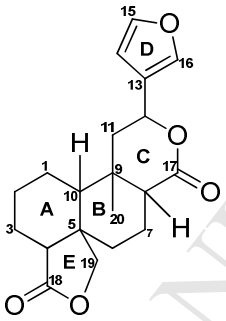

Figure 1. Structure of a conventional clerodane diterpene derived from Mexican *Salvia* species.

2. Experimental

*2.1 Isolation of compounds **1**-**5** and **7***

Sepulturins C (**3**) and D (**1**), infuscatin (**4**) and 8-hydroxysalviarin (**5**) were isolated from the leaves of *Salvia sahnnoni* Donnell Smith [8]. Amarissinin C (**2**) was isolated from the leaves and flowers of *S. amarissima* Ortega [10]. Salvimicrophyllin D (**7**) was obtained from the aerial parts of *S. microphylla* Kunth [9].

*2.2 Extraction and isolation of 7,8β-dihydrosalviacoccin (**6**)*

The leaves and flowers of *S. purepecha* Bedolla, Lara & Zamudio (1.3 kg) were collected at Tangancícuaro, Michoacán State, México, in October 2015 [11]. A voucher specimen was deposited at Herbario del Centro Regional del Bajío, Instituto de Ecología A.

C. (IEB-253452), which was determined by Dr. Brenda Y. Bedolla García. The dried and milled plant material was extracted by percolation with acetone (10 L) to obtain a dried extract (62 g). A solid crystallized from the acetone soluble extract, which was purified by several crystallizations with mixtures $CHCl_3$/MeOH and CH_2Cl_2/AcOEt to give 2.2 g of compound **6**.

2.3 NMR measurements

Each compound (10 mg) was dissolved in 1.0 mL of DMSO-d_6 and transferred to 5 mm NMR tubes using TMS as reference. The NMR spectra were acquired in a Varian Unity Plus 500 MHz spectrometer. Data processing was carried out using Mnova NMR software, version 6.0.

2.4 Single crystal X-ray diffraction (SXRD) analysis

SXRD experiments were carried out on a Bruker D8 Venture κ-geometry diffractometer with a Cu Kα radiation (λ = 1.54178 Å), or on a Bruker Smart Apex CCD diffractometer with monochromated Mo Kα radiation (λ = 0.71073 Å). The structures were solved by direct methods and refined full-matrix least on F^2, with anisotropic temperature factors for non-hydrogen atoms. Crystallographic data reported in this paper have been deposited in the Cambridge Crystallographic Data Centre. Copies of these data can be obtained free of charge via http: //www.ccdc.cam.ac.uk/conts/retrieving.html (or from Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk). Crystallographic Information Files were visualized using Mercury software, version 3.7.

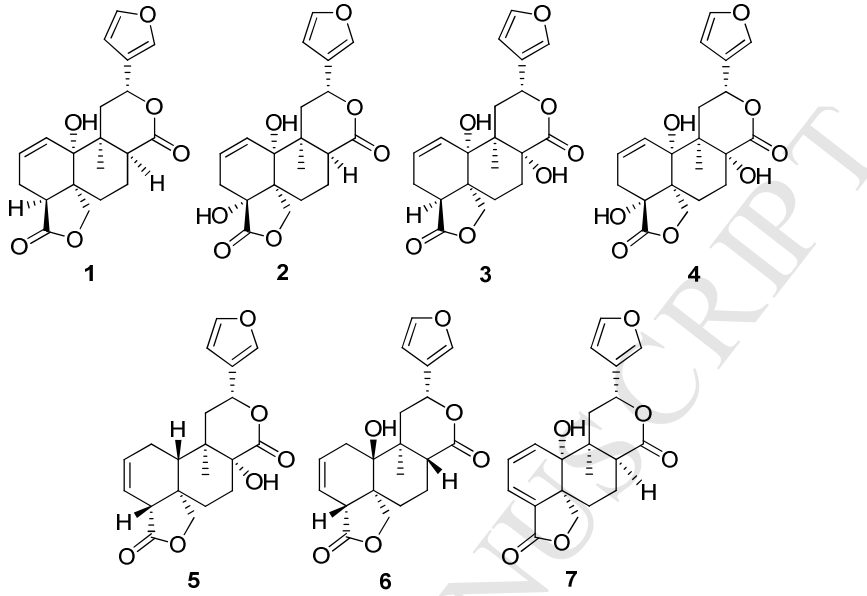

Figure 2. Hydroxyclerodanes studied from Mexican *Salvia* species: sepulturin D (**1**), amarissinin C (**2**), sepulturin C (**3**), infuscatin (**4**), 8-hydroxysalviarin (**5**), 7,8β-dihydrosalviacoccin (**6**) and salvimicrophyllin D (**7**).

3. Results and discussion

3.1 NMR analysis

The NMR analysis of seven clerodane diterpenes derived from Mexican *Salvia* species (**Fig. 2**) with a conventional framework (**Fig. 1**) and possessing tertiary hydroxyl groups at C-4, C-8 and C-10 in an aprotic solvent (DMSO-d_6) allowed a complete assignment of their ^{1}H and ^{13}C NMR signals (**Tables 1 and 2**). The pattern observed for the ^{1}H NMR chemical shifts of the hydroxyl groups showed a correlation with their position for each compound studied. Thereby, the OH groups at C-4 appeared in the range of δ_H 7.26-7.20; the OH groups at C-8 were displayed in the range of δ_H 6.23-6.07; and the chemical shift of OH groups at C-10 was dependent on the spatial disposition, OH groups

with α disposition were displayed in the range of δ_H 5.42-5.23, while the signal for the OH group with β-orientation in 7,8β-dihydrosalviacoccin (**6**) appeared at δ_H 4.86 (**Fig. 3**). The signals for the corresponding carbons attached to OH groups were displayed in the ^{13}C NMR spectra in the range δ_C 76.4-71.3 (**Table 2**). In the case of ^{13}C NMR signals, the chemicals shift differences did not allow a correct assignment, so they were assigned by their HSQC and HMBC correlations.

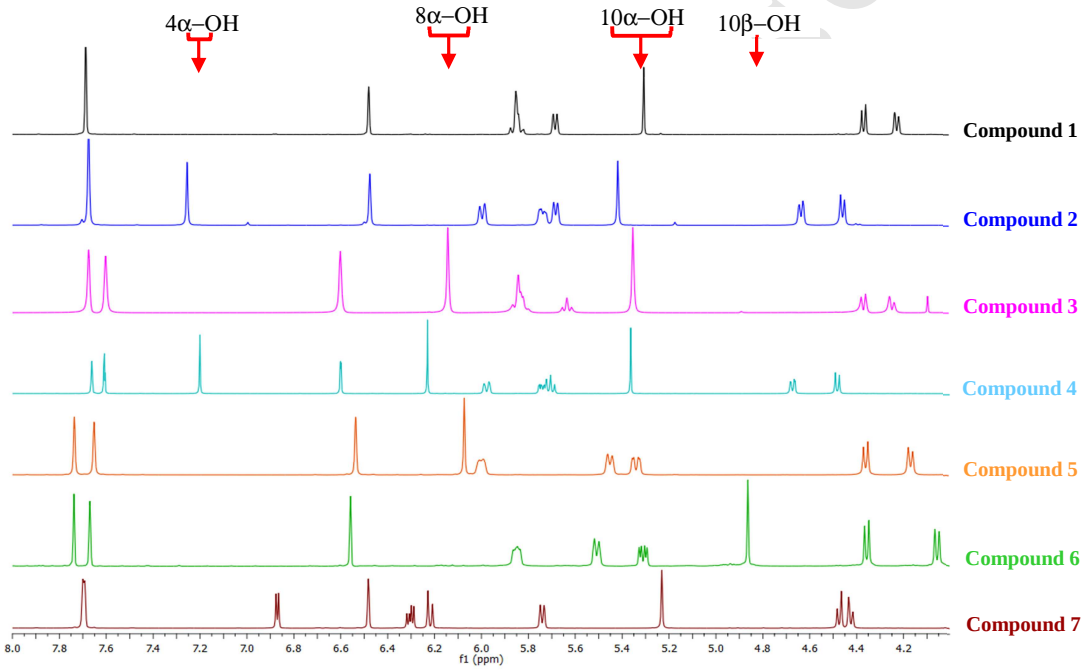

Figure 3. Expansions of the ^1H NMR spectra of compounds **1-7** performed in DMSO-d_6 at 500 MHz. Signals of the OH groups appear as singlet in the regions indicated by the red arrows.

The stereochemistry of compounds **1-7** was established considering the methylene at C-19 and the methyl group at C-20 with α-dispositions as is usual for *neo*-clerodane diterpenes from Mexican *Salvia* species [3, 7]. In addition, we focused on the fusion of the following structural fragments for stereochemistry establishment: the decalin ring system,

the 18,19 γ-lactone, the 17,12 δ-lactone, as well as the dispositions of the furan ring and the hydroxyl groups.

Compounds **1**-**4**, differ by the number and position of hydroxyl groups at C-4, C-8 and C-10 (**Fig. 2**). In the NOESY spectra of compounds **1**-**4**, correlations of OH-10 with H_2-19 and H_3-20 were observed, which determined the disposition of this OH group as α and also indicated *cis*-fused decalin rings (**Fig. 4**). The correlations of H-4 (compounds **1** and **3**) or OH-4 (compounds **2** and **4**) with H_2-19 and OH-10 suggested the presence of 18,19 γ-lactones with fusions *trans* [7]; cross peaks of H-8 (compounds **1** and **2**) or OH-8 (compounds **3** and **4**) with H_3-20 determined 17,12 δ-lactones with fusions *cis* and α-oriented. In compounds **2** and **4**, the observed NOE correlations between OH-4 and OH-10 suggested a 1,3-diaxial disposition. The spatial disposition of OH-8 in compounds **3** and **4** was determined as α by its correlation with H_3-20. The H-12 coupling constants values ($J_{11\alpha\text{-}12}$ = 8.0-9.0 Hz and $J_{11\beta\text{-}12}$ = 8.0-9.0 Hz) of these compounds indicated that the furan rings are α-oriented [10].

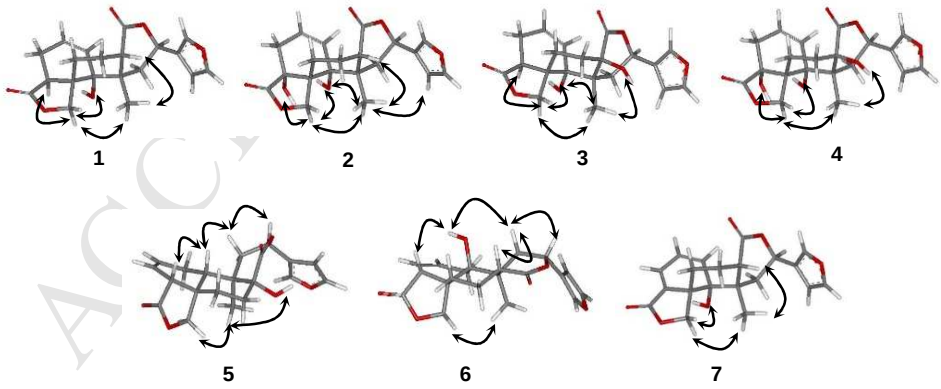

Figure 4. Key NOESY correlations for compounds **1**-**7**.

Compounds **5** and **6** possess the same molecular formula, differing by the position of the hydroxyl group. In compound **5** this group is attached at C-8, whereas compound **6** possesses this group at C-10. As in compounds **1**-**4**, the H-12 coupling constants ($J_{11\alpha\text{-}12}$ = 12.0-12.5 Hz and $J_{11\beta\text{-}12}$ = 4.0-5.5 Hz) of compounds **5** and **6**, also suggested a α-disposed furan ring with an equatorial orientation (**Fig. 4**). The NOESY spectra of both compounds showed cross peaks of H_2-19 with H_3-20, as well as H-10 (compound **5**) or OH-10 (compound **6**) with H-4 and H-11β, and from this last proton with H-12. The above information indicated that the decalin ring moiety and the 18,19 γ-lactone possess *trans*-fusions.

Compound **7** displayed in the NOESY spectrum, correlations of OH-10 with H_2-19 and H-11α, indicating a decalin ring with *cis*-fusion. The correlation of H-8 with H_3-20 indicated a 17,12 δ-lactone *cis*-fused. Additional cross peaks of H-14, H-15 and H-16 with H_3-20 determined a α-oriented furan ring. These data indicated that the disposition of the OH-10 must be changed to α, and the structure of compound **7** revised as depicted in **Fig. 2** [9].

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Table 1. [1]H NMR data (500 MHz) of compounds **1**-**7** in DMSO-d_6.

Position	**1**	**2**	**3**	**4**	**5**	**6**	**7**
1α	5.84 m[a]	6.00 d (10.5)	5.84 m[a]	5.98 d (10.5)	2.21 m[a]	2.47 dd (14.0, 2.0)	6.30 dd (9.5, 5.0)
1β					1.85 m[a]	2.07 dd (14.0, 5.5)	
2	5.84 m[a]	5.74 ddd (10.5, 5.0, 2.0)	5.84 m[a]	5.74 ddd (10.5, 5.5, 2.0)	6.00 dd (8.0, 3.0)	5.84 m	6.22 d (9.5)
3α	2.18 ddd (18.5, 5.5, 3.5)	2.34 dd (19.0, 4.5)	2.16 dt (18.5, 5.5) [a]	2.32 dd (18.5, 5.5)	5.45 dd (8.0, 2.0)	5.50 ddd (10.0, 3.0, 2.0)	6.87 d (5.5)
3β	1.93 m[a]	2.21 d (19.0)	1.92 dd (18.5, 12.0)	2.21 br d (18.5)			
4	3.04 dd (12.0, 6.0)		3.01 dd (12.0, 5.5)		2.84 br s	2.79 br s	
6α	1.53 dddd (12.5, 12.5, 4.0, 1.5)	1.07 br d (14.0)	1.22 ddd (14.0, 14.0, 3.5)	1.20 ddd (14.0, 14.0, 3.5)	1.72 ddd (14.0, 14.0, 3.5)	1.69 m	1.49 m[a]
6β	1.13 m[a]	1.38 ddd (14.0, 14.0, 5.0)	1.61 ddd (14.0, 14.0, 1.5)	1.28 ddd (14.0, 14.0, 2.0)	1.19 dd (14.0, 9.3)	1.48 m[a]	1.49 m[a]
7α	1.80 m[a]	1.87 br d (16.0)	1.74 ddd (14.0, 14.0, 4.0)	1.76 ddd (13.5, 13.5, 4.0)	1.84 m[a]	1.74 m[a]	1.74 m[a]
7β	1.76 m[a]	1.77 m[a]	2.12 ddd (14.0, 14.0, 4.0)	2.11 ddd (13.5, 13.5, 4.0)	2.23 m[a]	1.74 m[a]	1.74 m[a]
8	2.38 t (3.5)	2.39 br s				3.32 m[a]	2.47 t (3.5)
10					2.16 m[a]		
11α	2.85 dd (16.0, 8.0)	2.90 dd (18.0, 9.0)	1.84 dd (14.5, 8.5)	1.82 dd (14.5, 9.0)	1.79 dd (14.0, 3.5)	1.51 dd (14.0, 12.0)	2.83 dd (16.0, 8.5)
11β	1.90 dd (16.0, 1.5)	1.77 m[a]	2.52 dd (14.5, 8.5)	2.53 dd (14.5, 9.0)	2.16 m[a]	2.53 dd (14.0, 5.5)	1.93 dd (16.0, 1.0)
12	5.67 br d (8.0)	5.68 br d (8.5)	5.65 t (8.5)	5.71 t (9.0)	5.34 dd (12.5, 4.0)	5.30 dd (12.0, 5.5)	5.74 br d (8.5)
14	6.45 t (2.0)	6.48 br s	6.61 d (1.5)	6.60 d (2.0, 1.0)	6.54 d (1.5)	6.55 dd (1.5, 1.0)	6.48 dd (1.5, 1.0)
15	7.67 d (2.0)[a]	7.67 d (1.5)[a]	7.61 t (1.5)	7.61 t (2.0)	7.65 d (1.5)	7.67 t (1.5)	7.70 m[a]
16	7.67 d (2.0)[a]	7.68 br s[a]	7.68 br s	7.66 br s	7.74 br s	7.37 br d (1.0)	7.70 m[a]
19 *pro R*	4.36 d (8.5)	4.46 d (8.0)	4.38 d (8.5)	4.48 d (8.5)	4.36 d (9.0)	4.35 d (9.0)	4.47 d (9.0)
19 *pro S*	4.22 dd (8.5, 2.0)	4.64 dd (8.0, 1.5)	4.26 dd (8.5, 2.0)	4.67 dd (8.5, 2.0)	4.17 d (9.0)	4.05 br d (9.0)	4.42 dd (9.0)
20	1.12 s	1.14 s	0.93 s	0.96 s	0.84 s	0.80 s	1.11 s
4-OH		7.26 s		7.20 s			
8-OH			6.15 s	6.23 s	6.07		
10-OH	5.30 s	5.42 s	5.36 s	5.36 s		4.86 s	5.23 s

[a]Overlapped

Table 2. ^{13}C NMR data (125 MHz) of compounds **1**-**7** in DMSO-d_6.

Position	1	2	3	4	5	6	7
1	130.5, CH	130.5 CH	129.7 CH	130.7 CH	21.5 CH_2	29.1, CH_2	124.9, CH
2	129.5, CH	125.4 CH	130.8 CH	125.2 CH	129.8 CH	127.6, CH	134.6, CH
3	21.2, CH_2	28.8 CH_2	21.1 CH_2	28.4 CH_2	119.9 CH	120.5, CH	127.3, CH
4	40.8, C	76.4 C	40.0 CH	76.1 C	51.3 CH	51.1, CH	134.3, C
5	46.6, C	47.2 C	46.2 C	47.5 C	40.5 C	45.9, C	46.4, C
6	20.5, CH_2	24.1 CH_2	20.7 CH_2	24.4 CH_2	32.7 CH_2	28.8, CH_2	27.4, CH_2
7	15.9, CH_2	16.3 CH_2	25.3, CH_2	25.5 CH_2	26.5 CH_2	17.9, CH_2	15.9, CH_2
8	43.0, CH	42.6 CH	71.7 C[a]	71.3 C	74.7 C	41.2, CH	42.8, CH
9	39.4, C	40.8 C	47.6 C	47.0 C	39.2 C	41.1, C	39.2, C
10	73.7, C	75.5 C	74.0 C	75.8 C	37.3 CH	72.9, C	73.1, C
11	33.7, CH_2	33.2, CH_2	32.6 CH_2	32.0 CH_2	33.6 CH_2	38.3, CH_2	32.6, CH_2
12	70.6, CH	70.6 CH[a]	71.7 CH[a]	71.7 CH	69.8 CH	70.3, CH	70.9, CH
13	127.4, C	127.4 C	128.1 C	128.1 C	125.2 C	124.5, C	127.2, C
14	108.8, CH	108.8 CH	109.1 CH	109.1 CH	108.9 CH	109.3, CH	108.9, CH
15	144.5, CH	139.3, CH	143.7 CH	140.2 CH	143.8 CH	144.0, CH	144.6, CH
16	139.2, CH	144.5 CH	140.2 CH	143.8 CH	140.3 CH	140.4, CH	139.3, CH
17	176.1, C	172.0 C	170.3 C	170.2 C	171.6 C	175.3, C	172.5, C
18	172.2, C	174.3 C	175.9 C	174.3 C	175.5 C	175.8, C	168.2, C
19	71.3, CH_2	70.6 CH_2[a]	71.7 CH_2[a]	71.0 CH_2	70.2 CH_2	71.2, CH_2	70.2, CH_2
20	26.4, CH_3	26.8 CH_3	19.4 CH_3	19.8 CH_3	17.1 CH_3	21.2, CH_3	26.2, CH_3

[a] Overlapped

3.2 SXRD analysis

Hydroxyclerodanes **1**-**7** were crystallized employing mixtures of acetone/hexane, EtOAc/hexane, $CHCl_3$/MeOH and CH_2Cl_2/EtOAc. Six of these compounds (**1**, **2** and **4**-**7**) crystallized in the first space of group with an orthorhombic crystal system, compound **3** presented a group space $P\ 2_1$ and a monoclinic crystal system. The crystallographic parameters of these measurements are listed in **Table 3** and an ORTEP drawing view for each compound is described in **Fig. 5**. These analyses confirmed the structure and the stereochemistry proposed for compounds **1**-**7** based on the NMR data. In addition, each

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diterpene contains 5-6 chiral centers and the determination of the Flack parameter allowed the establishment of the absolute configuration of compounds **1** and **3-6** (**Table 3**).

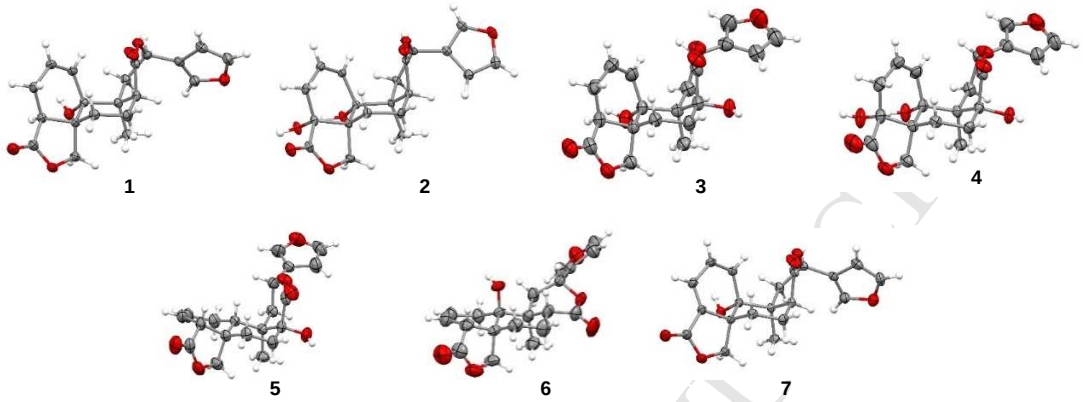

Figure 5. ORTEP drawing of compounds **1-7**.

The analysis of the conformation in solid state for compounds **1-7** was carried out following the classification based on the Cramer-Pople parameters [12]. These data are summarized in **Table 4**. In all the compounds, a chair conformation for ring B was preferred. In compounds **1-4** that contain a decalin ring system with *cis*-fusion and a 18,19 γ-lactone *trans*-fused conformations of half-chair, and intermediate between half-chair and envelope for ring A were observed. Apparently, the OH group at C-4 does not induce an effect to take any of these conformations. In the case of hydroxyclerodanes **5** and **6** which possess in their structure a *trans*-fused decalin moiety and a γ-lactone *cis*-fused, the conformations adopted by ring A is the same as observed for diterpenes **1-4**. In compound **7**, the presence of a 1,3-diene induces a sofa conformation in the ring A. In addition, compounds **1**, **2** and **5-7** contain a hydroxyl group at C-8 or C-10, but not both, presented a δ-lactone (ring C) with an intermediate conformation between envelope and half-chair; in

comparison with compounds **3** and **4** that possess two hydroxyl group at C-8 and C-10 that presented a ring C with half-chair conformation. With regard to ring E, compounds **1**-**6** adopted an envelope on C-5 conformation, independent of whether the fusion of the γ-lactone is *cis* or *trans*. Compound **7** showed a conformation twisted on C-18—C-5, due to the presence of the diene that confers rigidity to this ring.

4. Conclusions

The analysis by NMR in DMSO-d_6 of seven hydroxyclerodanes isolated from Mexican *Salvia* species allowed the complete assignment of their ^{1}H and ^{13}C signals, as well as their relative stereochemistry. The tendency that a was pattern exists that correlates the position of tertiary hydroxyl groups at C-4, C-8 or C-10 with their chemical shift, and constitutes a good starting point for the signal assignment of these kinds of groups in future works of structural elucidation was observed. In addition, the SXRD analysis confirmed the structure proposed for compounds **1**-**7**, the establishment of the absolute configuration of five of them through Flack parameter, and their conformation in solid state.

Supporting Information

^{1}H, ^{13}C and NOESY NMR spectra of compounds **1**-**7** associated with this article can be found in the online version.

Acknowledgments

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Table 3. Crystallographic data and refinement parameters for compounds **1-7**.

Crystal	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Empirical formula	C_{20} H_{22} O_6	$C_{20}H_{22}O_7$	$C_{20}H_{22}O_7$	$C_{20}H_{22}O_8$	$C_{20}H_{22}O_6$	$C_{20}H_{22}O_6$	$C_{20}H_{20}O_6$
Molecular weight	358.37	374.37	374.37	390.37	358.37	358.37	356.36
Crystal size (mm)	0.340 x 0.297 x 0.120	0.17 × 0.23 × 0.39	0.404 x 0.391 x 0.272	0.12 × 0.38 × 0.40	0.371 x 0.358 x 0.208	0.353 x 0.266 x 0.237	0.09 × 0.17 × 0.48
Temperature (K)	150(2)	150(2)	150(2)	298(2)	150(2)	298(2)	150(2)
Crystal system	Orthorhombic	Orthorhombic	Monoclinic	Orthorhombic	Orthorhombic	Orthorhombic	Orthorhombic
Space group	$P\,2_1\,2_1\,2_1$	$P\,2_1\,2_1\,2_1$	$P\,2_1$	$P\,2_1\,2_1\,2_1$	$P\,2_1\,2_1\,2_1$	$P\,2_1\,2_1\,2_1$	$P\,2_1\,2_1\,2_1$
a(Å)	7.2152(8)	7.4908(10)	9.6317(9)	7.0303(7)	7.2947(5)	10.5895(6)	7.2073(14)
b(Å)	10.6620(11)	10.0193(13)	7.3585(7)	9.6066(10)	14.9226(10)	12.1126(7)	10.878(2)
c(Å)	22.253(2)	22.647(3)	12.233(1)	26.044(3)	15.5967(10)	13.6155(8)	21.917(4)
α(°)	90	90	90	90	90	90	90
β(°)	90	90	96.790(2)	90	90	90	90
γ(°)	90	90	90	90	90	90	90
Z	4	4	2	4	4	4	4
Volume (Å^3)	1711.9(3)	1699.7(4)	860.93(14)	1758.9(3)	1697.8(2)	1746.41(17)	1718.2(6)
Calculated density (g/cm^3)	1.391	1.463	1.444	1.474	1.402	1.363	1.378
Absorption coeficient (mm^{-1})	0.85	0.111	0.915	0.965	0.857	0.833	0.102
Theta range for data collection (°)	3.973 to 79.629	2.223 to 28.281	3.639 to 74.460	4.907 to 78.972	4.100 to 72.037	4.887 to 79.449	2.638 to 28.282
Godness-of-fit on F^2	1.066	1.037	1.122	1.065	1.069	1.071	1.068
Rint	0.0458	0.0321	0.0605	0.0428	0.049	0.0399	0.0644
Final R,wR(F^2)values [I> 2F(I)]	0.0288, 0.0734	0.0310, 0.0775	0.0507, 0.1227	0.0277, 0.0704	0.0287, 0.0693	0.0360, 0.0981	0.0422, 0.0801
Final R,wR(F2)values (all)	0.0295, 0.0741	0.0321 0.0790	0.0524, 0.1249	0.0283, 0.0710	0.0301, 0.0704	0.0371, 0.0995	0.0547, 0.0873
Radiation source	CuKα Radiation	MoKα Radiation	CuKα Radiation	CuKα Radiation	CuKα Radiation	CuKα Radiation	MoKα Radiation
Flack parameter	0.08(4)	-------	0.11(8)	0.03(3)	0.01(6)	0.04(3)	-------
CCDC deposition number	1527123	1527124	1527125	1527126	1527127	1527128	1527129

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Table 4. Conformations in solid state for compounds **1-7**.

Compound	Ring A	Ring B	Ring C	Ring D	Ring E
1	Half-chair	Chair	Intermediate between envelope and half-chair	Planar	Envelope on C5
2	Half-chair	Chair	Intermediate between boat and screw-boat	Planar	Envelope on C5
3	Intermediate between half-chair and envelope	Chair	Half-chair	Planar	Envelope on C5
4	Intermediate between half-chair and envelope	Chair	Half-chair	Planar	Envelope on C5
5	Half-chair	Chair	Intermediate between envelope and half-chair	Planar	Envelope on C5
6	Intermediate between half-chair and envelope	Chair	Intermediate between boat and screw-boat	Planar	Envelope on C5
7	Sofa	Chair	Intermediate between boat and screw-boat	Planar	Twisted on C18 -- C5

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Highligths

- NMR analysis and crystal structure of seven clerodanes possessing OH groups at C-4, C-8 and C-10, isolated from Mexican *Salvia* species.
- Complete assignation of NMR signals in aprotic solvent (DMSO-d_6)
- Establishment of the absolute configuration of five clerodanes through X-ray crystallography.
- Revision of the structure of salvimicrophylline D (**7**).

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