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FURANOEREMOPHILANES FROM *SENECIO CLIVICOLUS* WEDDELL

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ABSTRACT

A phytochemical investigation of the dried aerial parts of *Senecio clivicolus* Weddell led to the isolation of four furanoeremophilane sesquiterpenes. Their structures and relative configuration were established by NMR and HRMS-ESI analyses, and by comparison with data reported in the literature. Their presence in *S. clivicolus* is reported for the first time.

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INTRODUCCION

Senecio represent the largest genus of the family Asteraceae and has more than 1500 species [1]. Senecio species are used in traditional medicine for many purposes, such as a remedy for gastric-ulcer and stomach pain [2], chest pain, cough, fever and running nose [3, 4]. In the north region of Argentina *S. graveolens* is used to counteract mountain sickness, digestive and cough suppressant[5]. Of the 114 species of *Senecio* reported to grow in Bolivia [6], *Senecio clivicolus* is a perennial shrub growing in the mountainous regions. The leaves of *S. clivicolus* have been used to relieve the stomach pain [7] and as a anti-diarrhea remedy [8]. Moreover, the extract has been reported to be used to treat skin fungal infections[9].Only one phytochemical investigation of *S. clivicolus* has been reported so far [10], in which alpha-farnesene, germacrene D and 1-pentadecene were isolated and characterized. This study reports the isolation and chemical characterization of four furanoeremophilanes (Figure 1) from an ethanol extract of the dried aerial parts of *S. clivicolus*: decompostin (**1**), 6β-acetoxy-9-oxo-10α*H*-furanoeremophilane (**2**), 1α-hydroxy-6β-acetoxy-9-oxo-10α*H*-furanoeremophilane (**3**) and 1α-acetoxy-6β-acetoxy-9-oxo-10α*H*-furanoeremophilane (**4**).

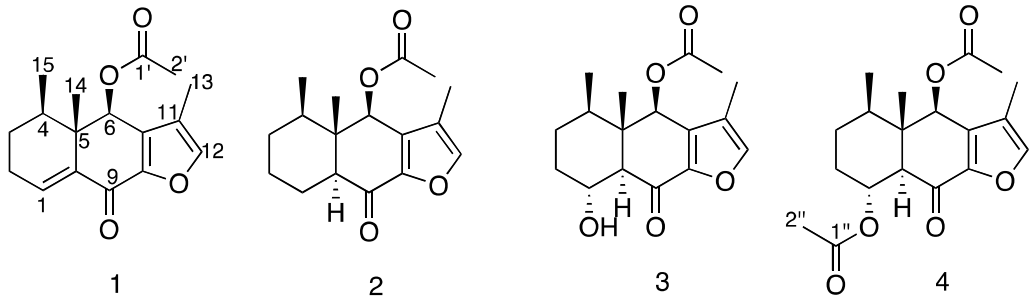

Figure 1. *Structures of compounds* ***1-4****.*

RESULTADOS Y DISCUSIÓN

The elemental composition of compound **1** was determined to be $C_{17}H_{20}O_4$, based on the 1D NMR spectra (^{1}H and ^{13}C NMR data for all four compounds are given in Table 1) as well as HRMS-ESI data. **1** consequently has eight degrees of unsaturation, and as the NMR data show the presence of three carbon-carbon double bonds and two carbonyl groups **1** is tricyclic. In the ^{1}H NMR spectrum a signal corresponding to a furan ring proton was observed at δ 7.41 (1H, q, *J*=1.0; 12-H), which in the COSY spectrum correlates with the methyl signal at δ 1.93 (3H, d, *J*=1.0; 13-H_3). In addition to this, and besides a methyl group obviously belonging to an acetyl group (δ 2.20, 3H, s), the proton spectrum indicated the presence of another two methyls by the signals at δ 1.09 (3H, s; 14-H_3) and δ0.99 (3H, d, *J*=6.8; 15-H_3). COSY and HMBC correlations from these as well as 1-H (δ 6.94, 1H, ddd, *J*=4.9, 3.2, 0.8) close

the left ring, and show that the acetoxy substituted C-6 is next to C-5 and that the carbonyl group C-9 is adjacent to C-10. HMBC correlations from 6-H, 12-H and 13-H_3 reveal all components of the furan ring, and the final bond between C-8 and C-9 is inevitable. The relative configuration of **1** was elucidated based on the NOESY correlations observed between H-6 and H-4 as well as between 14-H_3 and 15-H_3. The structure of compound **1** isolated here is identical to decompostin, previously reported from *Cacalia decomposita*[11] and *Psacalium beamanii*[12]. The HRMS-ESI of compound **2** indicated that its elemental composition is $C_{17}H_{22}O_4$, **2** consequently has one unsaturation less than **1**. Comparison of the spectroscopic data of **1** and **2** revealed that the C-1/C-10 double bond in **1** is a single bond in **2**, and COSY as well as HMBC correlations established the structure. The relative configuration of **2** was determined based on NOESY correlations between the three protons 4-H, 6-H and 10-H, and **2** was found to be identical to 6β-acetoxy-9-oxo-10α*H*-furanoeremophilane, previously reported from *S. chilensis and S. patagonicus*[13]. However, the ^{13}C NMR data reported [13] are significantly different from those recorded here, indicating that it is necessary to correct the chemical shifts for C-1, C-2, C-3, C-14 and C-15 in the literature. The NMR data of compound**3** ($C_{17}H_{22}O_5$ according to HRMS-ESI) and **4** ($C_{19}H_{24}O_6$ according to HRMS-ESI) are similar to those of compounds**1** and **2**, with the exception for the signals assigned to C-1 and C-10. In both **3** and **4** C-1 is oxygenated while C-10 is protonated, and extensive 2D NMR experiments show that, compared to **1**, the C-1/C-10 double bond had added water in **3** and acetic acid in **4**. NOESY correlations were observed between 1-H and 14-H_3, as well as between 4-H, 6-H and 10-H in both compounds, establishing their relative configuration. Based on these data the structures were established as 1α-hydroxy-6β-acetoxy-9-oxo-10α*H*-furanoeremophilane **3** and 1α-acetoxy-6β-acetoxy-9-oxo-10α*H*-furanoeremophilane **4**. Compounds **3** and **4** have previously been reported from *S. santelisis*[14].

Table 1: *^{13}C- and ^{1}H-NMR data of compounds 1-4.*

Position	1[a]		2[b]		3[b]		4[b]	
	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
1	138.3	6.94 ddd (4.9,3.2,0.8)	20.6	2.18 m* 1.41 m*	66.4	4.14 m	67.3	5.28 m
2	25.5	2.24 m* 2.24 m*	24.5	1.82 m* 1.29 m*	32.9	2.04 m 1.40 m*	31.3	2.11 m 1.40 m*
3	28.2	1.55 m* 1.45 m*	32.2	1.41 m* 1.29 m*	30.3	1.49 m* 1.40 m*	29.9	1.40 m* 1.40 m*
4	38.1	1.95 m*	42.1	1.82 m*	41.7	1.87 m*	41.5	1.86 m*
5	46.8		49.8		51.0		51.4	
6	74.9	6.29 s	75.7	6.33 s	75.2	6.34 s	75.3	6.36 s
7	136.0		134.6		136.2		133.8	
8	147.2		146.7		146.5		147.1	
9	176.5		186.7		189.3		184.7	
10	141.7		55.1	2.37 dd (12, 3.5)	60.8	2.37 d (9.5)	58.0	2.65 d (10.5)
11	121.5		120.7		121.2		120.7	
12	146.2	7.41 q (1.0)	145.1	7.33 br.	146.2	7.39 q (1.0)	145.1	7.32 q (1.0)
13	8.6	1.93 d (1.0)	8.5	1.91 br.	8.6	1.91 d (1.0)	8.67	1.88 d (1.0)
14	15.5	1.09 s	7.6	0.91 s	8.9	0.95 s	8.69	0.95 s
15	17.7	0.99 d (6.8)	17.7	0.89 d (6.6)	17.6	0.90 d (6.6)	17.5	0.91 d (6.6)
1'	171.0		170.3		170.9		171.0	
2'	21.6	2.20 s	21.6	2.18 s	21.6	2.17 m	21.6	2.16 s
1''							170.6	
2''							21.4	2.02 s
1-OH						4.52 d (1.7)		

Spectra recorded in: [a]Dichloromethane-d_2, [b]Chloroform-*d*. * Overlapping. Assignments were based on COSY, HMQC, HMBC, DEPT and NOESY experiments

EXPERIMENTAL

General experimental procedures

The optical rotations were measured with a Perkin-Elmer 341 polarimeter at 20°C. HRMS-ESI spectra were recorded with a Waters Q-TOF Micro system spectrometer, using H_3PO_4 for calibration and as internal standard. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were measured with a Bruker DRX400 spectrometer; the spectra were recorded in chloroform-*d* (solvent residual signals at δ_H 7.26 and δ_C 77.16) and dichloromethane-d_2 (solvent residual signals at δ_H 5.32 and δ_C 53.84). The chemical shifts (δ) are given in ppm, and coupling constants (*J*) in Hz. Vacuum liquid chromatography (VLC) and centrifugal preparative TLC (CTLC) separations were carried out using TLC

grade silica gel (Merck), while column chromatography were run on silica gel 60 (230-400 mesh, Merck). TLC analyses were carried out on silica gel GF_{254} pre-coated plates (Merck); chromatograms were visualized under a UV lamp (254 nm) and by spraying with vanillin (6%)-sulfuric acid (1.5%)-ethanol solution, followed by heating.

Plant material

The whole aerial parts of *Senecio clivicolus* Weddell were collected from south of Cochabamba-Bolivia at 2900 meters above sea level in April 2008. A voucher specimen (MZ-3741) was deposited at National Herbarium "Herbario Nacional Martin Cardenas" at Cochabamba-Bolivia.

Extraction and isolation

The air-dried powdered plant material (500 g) was extracted with 95% ethanol (3x1 L) for 3 days at room temperature. Removal of the solvent from the filtrate under reduces pressure provided an extract (70 g). Part of the extract was suspended in ethanol-water (80:20) and successively partitioned with hexane and chloroform. The chloroform fraction (15 g) was precipitated with ethyl acetate to yield a dark brown precipitate (550 mg) and a dark liquid, which was subjected to vacuum liquid chromatography on silica gel using heptane-ethyl acetate (80:20) as solvent. Ten main fractions were collected (1-10). Fraction 4 (570 mg) was precipitated with methanol to give a yellow precipitate that was purified by centrifugal preparative TLC with heptane-ethyl acetate (80:20) to yield compound **1** (15 mg). Fraction 3 (3.37 g) was precipitated with methanol to give compound **2** (20 mg). Furthermore, fraction 7 (350 mg) was washed with heptane and then subjected to column chromatography on silica gel eluted with toluene-diethyl ether (25:3.5) to give six fractions (A-F). Compound **3** (5 mg) was purified from fraction F by column chromatography using a mixture of heptane-ethyl acetate (70:30) as the eluent. Finally, fraction C contains compound **4** (60 mg).

Decompostin (**1**).

1 was obtained as a white amorphous solid. mp 195-198 °C. $[\alpha]_D^{20}$ -60° (*c* 0.60, $CHCl_3$). ^1H NMR (CD_2Cl_2 400 MHz) and ^{13}C NMR (CD_2Cl_2 100 MHz), see Table 1. HRMS-ESI calculated for $C_{17}H_{20}O_4$ $(M+H)^+$ 289.1440. Found: 289.1445.

6β-acetoxy-9-oxo-10αH-furanoeremophilane (**2**).

2 was obtained as a white amorphous solid. mp 147-150 °C. $[\alpha]_D^{20}$ -72° (*c* 0.70, $CHCl_3$) ^1H NMR ($CDCl_3$ 400 MHz) and ^{13}C NMR ($CDCl_3$ 100 MHz), see Table 1. HRMS-ESI calculated for $C_{17}H_{22}O_4$ $(M+H)^+$ 291.1596. Found: 291.1586.

1α-hydroxy-6β-acetoxy-9-oxo-10αH-furanoeremophilane **(3).**

3 was obtained as a yellowish oil. $[\alpha]_D^{20}$ -12° (*c* 0.20, $CHCl_3$) ^1H NMR ($CDCl_3$ 400 MHz) and ^{13}C NMR ($CDCl_3$ 100 MHz), see Table 1. HRMS-ESI calculated for $C_{17}H_{22}O_5$ $(M+H)^+$ 307.1545. Found: 307.1555.

1α-acetoxy-6β-acetoxy-9-oxo-10αH-furanoeremophilane **(4).**

4 was obtained as a white amorphous solid. mp 149-151 °C. $[\alpha]_D^{20}$ -84° (*c* 0.37, $CHCl_3$). ^1H NMR ($CDCl_3$ 400 MHz) and ^{13}C NMR ($CDCl_3$ 100 MHz), see Table 1. HRMS-ESI calculated for $C_{19}H_{24}O_6$ $(M+H)^+$ 349.1651. Found: 349.1654.

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