Bioactive Furanoeremophilanes from *Senecio otites* Kunze ex DC.

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The furanoeremophilanes 6β-angeloyloxy-1,10-dehydrofuranoeremophilan-9-one (**1**), 6β-hydroxy-1,10-dehydrofuranoeremophilan-9-one (**2**) and 6β-propionyloxy-1,10-dehydrofuranoeremophilan-9-one (**3**) were isolated from *Senecio otites*, their structures elucidated by spectral analyses, and their insecticidal and phytotoxic properties evaluated. Compounds **1**–**3** proved to be effective aphid antifeedants against *Myzus persicae* and *Rhopalosiphum padi* and had postingestive negative effects on *Spodoptera littoralis* larvae. These compounds did not have any phytotoxic effects on *Lactuca sativa*.

Key words: Senecio otites, Furanoeremophilanes, Antifeedant and Insecticidal Effects

Introduction

The genus *Senecio* (Asteraceae) is widely distributed throughout the World, and is known to be a source of pyrrolizidine alkaloids, eremophilanolides, and furanoeremophilanes (Reina *et al*., 2001, 2006). These secondary metabolites have been shown to act on herbivorous insects eliciting food avoidance (Burgueño-Tapia *et al.*, 2007; Hägele and Rowell-Rahier, 2001; Reina *et al.*, 2001). Some of these compounds exhibit cytotoxic (Gao *et al*., 2003; Wu *et al*., 2005; Zhang *et al*., 2005), antihyperglycemic (Inman *et al*., 1999), antimicrobial (Garduño-Ramírez *et al*., 2001; Wang *et al*., 2007; Gu *et al*., 2004), anti-inflammatory (Jiménez-Estrada *et al*., 2006) or antioxidant activities (Doe *et al*., 2005; Shindo *et al*., 2004).

As part of our ongoing study on the plant-defensive properties of eremophilanolides and related compounds from *Senecio* species (Burgueño-Tapia *et al*., 2007; Reina *et al*., 2001, 2006), here we report on the structural elucidation of three furanoeremophilanes from *Senecio otites* Kunze ex DC., an endemic bush of southern Chile. Their structures are proposed on the basis of mono- and bi-dimensional high-resolution spectroscopic NMR data once comparing them to others previously published for similar compounds.

The biological activity of these compounds against several insect pests (*Myzus persicae*, *Rhopalosiphum padi* and *Spodoptera littoralis*) and insect (Sf9) and mammalian (CHO) cell lines will be evaluated along with their phytotoxic activity on *Lactuca sativa*.

Results and Discussion

Successive bioassay-guided chromatography of the plant extract on silica gel gave **1**–**3**. Compounds **1**, **2** and **3** were sesquiterpenes of the furanoeremophilane-type. The HREI mass spectrum of **1** showed a molecular ion peak at *m/z* 328.1686 corresponding to the molecular formula $C_{20}H_{24}O_4$. The ^{13}C NMR spectrum (DEPT experiment) showed 20 carbon atoms: five methyl, two methylene, five methine, and eight quaternary carbon atoms. Moreover, the ^1H and ^{13}C NMR spectra suggested the presence of an angeloyl group [δ_H 6.28 (1H, qq, H-3′), 2.10 (3H, dq, H-4′), 1.97 (3H, t, H-5′); δ_C 167.4 (s, C-1′), 142.0 (d, C-3′), 127.3 (s, C-2′), 20.9 (q, C-5′), 16.4 (q, C-4′)]. NMR spectroscopic data of **2** were similar to those obtained for **1**, except for the absence of an angelate group and a new signal at δ_H 4.23 (s) that can be attributed to a geminal proton of one hydroxy group. Its mass spectrum (EIMS experiment) showed a molecular ion peak at *m/z* 228 (100 %). Spectroscopic NMR data for **3**, $C_{18}H_{22}O_4$ (HREIMS), were similar to those obtained for **1**, with new signals at δ_H 2.5 (2H, q, $J = 7$ Hz), 0.9 (3H, t, $J = 7$ Hz),

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Table I. ^{1}H, ^{13}C and HSQC data of compounds **1**–**3**.

H	**1**		**2**		**3**	
	δ (J_{H-H} in Hz)	HSQC	δ (J_{H-H} in Hz)	HSQC	δ (J_{H-H} in Hz)	HSQC
1	7.0 t (3.7)	138.7 d	6.85 br s	138.4 d	6.93 t (3.7)	138.5 d
2	2.30 m	25.5 t	2.28 m	25.5 t	2.30 m	25.5 t
3	1.50 m	28.3 t	1.53 m	28.0 t	1.50 m	28.3 t
4α	1.97 m	38.2 d	1.92 m	37.8 d	1.90 m	38.1 s)
	C-5	47.0 s	C-5	46.8 s	C-5	46.9 s
6α	6.43 s	74.3 d	4.3 s	74.5 d	6.30 s	74.9 d
	C-7	136.6 s	C-7	136.4 s	C-7	114.3 s
	C-8	147.1 s	C-8	146.9 s	C-8	141.8 s
	C-9	177.1 s	C-9	176.7 s	C-9	177.0 s
	C-10	141.7 s	C-10	139.4 s	C-10	136.1 s
	C-11	121.6 s	C-11	121.3 s	C-11	121.4 s
12	7.39 q (1.1)	146.5 d	7.52 q (1.2)	146.1 d	7.30 q (1.0)	146.3 d
13	1.86 d (1.0)	8.7 q	1.91 d (1.0)	8.5 q	1.80 d (1.0)	8.9 q
14	1.13 s	16.2 q	1.14 s	15.7 q	1.13 s	17.9 q
15	0.98 d (6.8)	17.8 q	1.02 d (7.0)	17.7 q	0.98 d (6.8)	15.9 q
	C-1′	167.4 s			C-1′	174.4 s
	C-2′	127.3 s			2.50 q (7.0)	28.4 t
3′	6.28 qq (6.0, 1.4)	142.0 d			0.90 t (7.0)	9.12 q
4′	2.10 dq (5.8, 1.5)	16.4 q				
5′	1.97 t (1.5)	20.9 q				

Coupling constants (J) in Hz. ^{13}C NMR multiplicities were established by DEPT data.

δ_C 28.4 (t), 9.12 (q) from a propionyloxy group. 2D NMR experiments confirmed the positions of the substituents and the chemical shifts of the remaining protons (Table I).

The structures of these sesquiterpenes were confirmed as 6β-angeloyloxy-1,10-dehydrofuranoeremophilan-9-one (**1**), 6β-hydroxy-1,10-dehydrofuranoeremophilan-9-one (**2**), and 6β-propionyloxy-1,10-dehydrofuranoeremophilan-9-one (**3**) (Fig. 1), previously isolated from *Senecio lanceus* (Bohlmann *et al*., 1977) their NMR data were completed.

The antifeedant activity of the *S. otites* ethanolic extract and compounds **1**–**3** is shown in Table II. The extract was an effective antifeedant to both aphid species, *R. padi* being more sensitive than *M. persicae*. Compound **2** showed a moderate antifeedant effect against *S. littoralis*. Compounds **1**–**3** also acted as antifeedants to both aphid species, **3** being the most active against *M. persicae*, suggesting that the presence of a 6β-propionyloxy group may increase this selective effect.

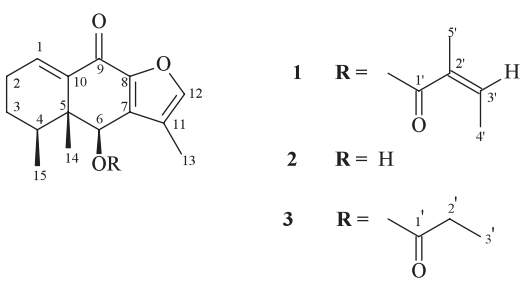

Fig. 1. Chemical structures of compounds **1**–**3**.

Cacalol has been shown to deter generalist insects (Hägele and Rowell-Rahier, 2001), and a furanoeremophilane isolated from *Ligularia macrophylla* significantly reduced the consumption by termites, *Coptotermes formosanus* (Cantrell *et al.*, 2007). Furthermore, eremophilanolides with a γ-butyrolactone group have been reported as strong *M. persicae* antifeedants (Reina *et al*., 2001). Additionally the acetylation of the hydroxy group at C6 increased the antifeedant activity of structurally related eremophilanolides on *M. persicae* (Burgueño-Tapia *et al.*, 2007).

Table III shows the nutritional effects of **1**–**3** on *S. littoralis* larvae. Compound **1** affected biomass gain (ΔB) and consumption (ΔI), while **2** and **3** had a negative effect on ΔB but not on ΔI. Treatment effects on ΔB did not disappear with covariance adjustment for **1** and **2** (pANCOVA2 < 0.05), indicating that these compounds are moderate postingestive antifeedants (**1**) or postingestive growth inhibitors (**2** and **3**), with (**1**, **2**) or without (**3**) additional toxic effects. Compounds **1** and **2** were cytotoxic to mammalian CHO cells

Table II. Antifeedant effects of the ethanolic extract (100 μg/cm^2) and compounds **1**–**3** (50 μg/cm^2) from *S. otites* against *S. littoralis* L6 larvae, *M. persicae* and *R. padi* adults. Mean values ± SE are presented.

Compound	*S. littoralis*	*M. persicae*		*R. padi*	
	% FI[a]	% C[b]	% T[b]	% C[b]	% T[b]
Extract	43 ± 2.8	70 ± 3.8	30 ± 3.8*	87 ± 2.9	13 ± 2.9*
1	32 ± 1.8	75 ± 3.9	25 ± 3.9*	73 ± 4.0	27 ± 4.0*
2	62 ± 2.3*	77 ± 3.6	23 ± 3.6*	73 ± 3.1	27 ± 3.1*
3	45 ± 2.8	80 ± 4.1	20 ± 4.1*	70 ± 3.8	30 ± 3.8*
Ryanodine[c]	100 ± 0	–	–	–	–
Polygodial[d]	–	98 ± 6	2 ± 2*	98 ± 8	2 ± 1*

* $p < 0.05$, Wilcoxon signed rank paired test.
[a] % FI = [1 – (T/C)] · 100, where T and C are the consumption of treated and control leaf disks, respectively.
[b] % C and % T represent the percentages of aphids settled on control and treated leaf disks, respectively.
[c] From González-Coloma *et al.* (1999).
[d] From Moreno-Osorio *et al.* (2008).

Table III. Consumption (ΔI) and biomass gain (ΔB) of orally injected *S. littoralis* L6 larvae, expressed as percentage of the control (mean values ± SE are presented), and cytotoxic effects on *S. frugiperda* Sf9 and mammalian CHO cells.

Compound	*S. littoralis*			CHO	Sf9
	ΔB[a]	ΔI[b]	pANCOVA2	ED_{50} [μg/ml][c]	
1	64 ± 8*	79 ± 4*	0.042	31.9 (27.3, 37.4)	71.8 (65.4, 78.8)
2	72 ± 7*	84 ± 6	0.033	5.8 (2.6, 13.0)	35.7 (27.5, 46.3)
3	76 ± 8*	84 ± 7	0.156	≈100	> 100
Rotenone[d]	56*	62*	< 0.05	38.14 (14.36, 101.16)	0.23 (0.15, 0.30)

[a] ΔB, change in insect body weight (mg dry weight).
[b] ΔI, mass of food consumed (mg dry weight).
[c] Effective dose (ED_{50}) and 95 % confidence limits (lower, upper).
[d] From González-Coloma *et al.* (2002).
* Significantly different from the control, $p < 0.05$, LSD test.

with a moderate effect on insect Sf9 cells, and **3** was not cytotoxic. Therefore the postingestive toxicity of these compounds on *S. littoralis* larvae cannot be attributed to cytotoxic effects. Similarly, eremophilanes from *Ligularia* spp. and *S. tsoongianus* showed only weak cytotoxic activity against human tumoural cells (Fei *et al.*, 2007; Wang *et al.*, 2007; Zhang *et al.*, 2005, 2007).

Similarly, structurally related eremophilanolides showed similar postingestive effects on *S. littoralis* larvae. Specifically cacalol methyl ether, cacalol acetate, and toluccanolide A acetate were postingestive growth inhibitors, while 13-hydroxy-14-oxocacalohastine, 13-acetyloxy-14-oxocacalohastine, 6-acetyloxyeuryopsin and 1(10)-epoxy-6-hydroxyeuryopsin were postingestive antifeedants (Burgueño-Tapia *et al.*, 2007). Furthermore, cacalol has been shown to reduce the growth of the generalist *Cylindrotoma distinctissima* due to postingestive physiological effects and consumption reduction (Hägele and Rowell-Rahier, 2001). Cacalol and its methyl ether and acetate derivatives inhibited ATP synthesis at the electron-transport level (Lotina-Hennsen *et al.*, 1991), and related cacalolides inhibited lipid peroxidation at the mitochondrial and microsomal level (Doe *et al.*, 2005). These metabolic effects could explain the insect toxicity and cytotoxic effects observed here.

Several cacalolides and eremophilanolides showed phytotoxic activity against *L. sativa* (radicle growth inhibition) (Burgueño-Tapia *et al.*, 2007). This phytotoxic action has been attributed to their inhibition of Hill's reaction in spinach chloroplasts during photosynthesis (Aguilar-Martínez *et al.*, 1996). However, compounds **1**–**3** had no phytotoxic effects on *L. sativa* (germination or radicle growth). Previous studies have shown that furanoeremophilanes isolated from *Ligularia ma-*

crophylla had selective phyotoxicity against the monocot *Agrostis stolonifera* while being infective to the dicot *L. sativa* (Cantrell *et al.*, 2007).

Experimental

General experimental procedures

Optical rotations were measured at room temperature on a Perkin-Elmer 343 Plus polarimeter. IR spectra were taken on a Perkin-Elmer 1600 FT spectrometer. NMR spectra were measured on a Bruker AMX 500 MHz spectrometer with pulsed field gradient, using the solvent as internal standard ($CDCl_3$ at δ_H 7.26 and δ_C 77.0). Exact mass measurements and EI mass spectra were recorded on an Autospec instrument at 70 eV. Silica gel (Merck Art. 15111, 7741, 5554) was used for column chromatography and TLC. Sesquiterpenes were visualized on TLC plates with a 25 % H_2SO_4 solution.

Plant material, extraction and isolation of compounds

Senecio otites Kunze ex DC. was collected during the flowering season in December 2005 at Chinquihue Alto in the south of Chile (Region X) and identified by Dr. Melica Muñoz from the Museo de Historia Natural in Santiago de Chile. A voucher specimen has been deposited in the Herbarium of this museum (number SGO 160095).

Air-dried aerial plant parts (1.5 kg) were ground and extracted with EtOH at room temperature. The extract was filtered and concentrated under vacuum producing a dry extract (69.5 g, 4.6 %). This crude extract was chromatographed on a silica gel (150 g) vacuum column. The elution was carried out with *n*-hexane/EtOAc (A) and EtOAc/MeOH (B) gradients to obtain six fractions: Fr-0 (*n*-hexane) (0.5 g), Fr-1 (A, 90:10) (5.7 g), Fr-2 (A, 80:20) (5.6 g), Fr-3 (A, 50:50) (4.7 g), Fr-4 (EtOAc) (7.8 g) and Fr-5 (B, 50:50) (19.5 g). The bioactive fraction Fr-2 (2.0 g) was chromatographed on a silica gel column using *n*-hexane/EtOAc mixtures of increasing polarity to obtain 150 fractions, each of 10 ml. The fractions were monitored by TLC using *n*-hexane/EtOAc (97:3), and similar fractions were combined to give a fraction of the sesquiterpenes (404 mg). Further purification of this fraction under the same chromatographic conditions afforded three **1** (50 mg), **2** (70 mg) and **3** (15 mg).

6β-Angeloyloxy-1,10-dehydrofuranoeremophilan-9-one (**1**): Colourless resin; $[\alpha]_D$ −40° (c $1.18 \cdot 10^{-1}$, $CHCl_3$). – EIMS: *m/z* = 328 $[M]^+$ (1 %), 246 (3 %), 245 (6 %), 228 (37 %), 213 (6 %), 200 (2 %), 177 (1 %), 153 (2 %), 115 (3 %), 109 (1 %), 83 (100 %), 55 (36 %). – HREIMS: *m/z* = 328.1686 $[M]^+$; calcd. for $C_{20}H_{24}O_4$ 328.1675. – ^1H and ^{13}C NMR: see Table I.

6β-Hydroxy-1,10-dehydrofuranoeremophilan-9-one (**2**): Resin; $[\alpha]_D$ −48.3° (c $0.62 \cdot 10^{-1}$, $CHCl_3$). – EIMS: *m/z* = 246 $[M]^+$ (19 %), 245 (6 %), 229 (21 %), 228 (100 %), 227 (6 %), 213 (35 %), 205 (10 %), 200 (7 %), 181 (49 %), 177 (10 %), 153 (4 %), 137 (17 %), 121 (9 %), 115 (7 %), 111 (16 %), 109 (15 %), 93 (18 %), 91 (22 %), 85 (26 %), 83 (72 %), 57 (46 %), 55 (36 %). – ^1H and ^{13}C NMR: see Table I.

6β-Propionyloxy-1,10-dehydrofuranoeremophilan-9-one (**3**): Amorphous powder; $[\alpha]_D$ −5.3° (c $0.3 \cdot 10^{-1}$, $CHCl_3$). – EIMS: *m/z* = 302 $[M]^+$ (1 %), 260 (4 %), 246 (23 %), 231 (7 %), 228 (100 %), 217 (11 %), 213 (36 %), 200 (8 %), 177 (12 %), 137 (19 %), 109 (15 %), 91 (18 %), 77 (16 %), 57 (91 %). – HREIMS: *m/z* = 302.1503 $[M]^+$; calcd. for $C_{18}H_{22}O_4$ 302.1518. – ^1H and ^{13}C NMR: see Table I.

Insect bioassays

S. littoralis and the aphid colonies (*M. persicae* and *R. padi*) were reared on artificial diet and their respective host plants (*Capsicum annuum* and *Hordeum vulgare*) and maintained at (22 ± 1) °C, > 70 % relative humidity, and a photoperiod of 16 h:8 h light:dark in a growth chamber.

Choice feeding assays

These experiments were conducted with sixth instar *S. littoralis* larvae and adults of *M. persicae* and *R. padi* (apterous). The upper surface of *Capsicum anuum* or *Hordeum vulgare* leaf disks/fragments (1.0 cm^2) were treated with 10 µl of the test substance. Three *S. littoralis* aphids were placed on five Petri dishes in twenty boxes and were allowed to feed in a growth chamber (environmental conditions as described above). Each experiment was repeated three times and terminated after the consumption of 50–75 % of the control disks (*S. littoralis*) or after 24 h (*M. persicae*). Feeding or settling inhibition (% FI or % SI) was calculated as % FI = $[1 - (T/C)] \cdot 100$, where T and C are the

consumption of treated and control leaf disks, respectively, and % SI = 1 – (% T7% C), where % C and % T represent the percentage of aphids settled on control and treated leaf disks, respectively (Gutiérrez *et al.*, 1997; Reina *et al.*, 2001). Ryanodine and polygodial were included as positive controls for *S. littoralis* and the aphids, respectively (González-Coloma *et al.*, 1999; Moreno-Osorio *et al*., 2008).

Oral cannulation

This experiment was performed with preweighed newly moulted *S. littoralis* L6 larvae. Each experiment consisted of 20 larvae orally injected with 40 μg of the test compound in 4 μl of DMSO (treatment) or solvent (control) as described in Reina *et al*. (2001). At the end of the experiments (72 h), larval consumption and growth were calculated on a dry weight basis. A covariance analysis (ANCOVA1) of food consumption (ΔI) and biomass gains (ΔB) with the initial larval weight (BI) as covariate (covariate $p > 0.05$) was performed to test for significant effects of the test compounds on these variables. An additional ANOVA analysis and covariate adjustment on ΔB with ΔI as covariate (ANCOVA2) was performed on those compounds significantly reducing ΔB to understand their postingestive mode of action (antifeedant and/or toxic) (Reina *et al.*, 2001). Rotenone was included as a positive control (González-Coloma *et al.*, 2002).

Phytotoxic evaluation

These experiments were conducted with *Lactuca sativa* var. Carrascoy seeds as described by Moiteiro *et al*. (2006). The germination was monitored daily and the radicle length measured at the end of the experiment (20 digitalized radicles randomly selected for each experiment) with the application Image J Version 1.37r, 2006 (http://rsb.info.nih.gov./ij/). An analysis of variance (ANOVA) was performed on germination and radicle length data. Juglone was included as a positive control (Burgueño-Tapia *et al.*, 2007).

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