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THE FIRST SESQUITERPENE LACTONES ESTERIFIED WITH A SESQUITERPENIC ACID*

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Key Word Index—*Hypochoeris uniflora*; *H. glabra*; *Lactuca floridana*; Compositae; Lactuceae; sesquiterpene lactones; guaianolides; lactucin C_{15}-esters.

Abstract—From *Hypochoeris glabra* two guaianolides esterified with an unusual sesquiterpenic acid were isolated. Proton-catalysed rearrangement of the cyclopropane derivative led to a phenolic acid. The structures were elucidated by high-field ^{1}H NMR spectroscopy. Further guaianolides were isolated from *H. uniflora* and *Lactuca floridana*. These structures were elucidated by spectroscopic methods. The chemotaxonomic situation in the tribe is discussed briefly.

INTRODUCTION

So far not much is known about the chemistry of the tribe Lactuceae. In addition to widespread triterpenes and flavones [1] some more characteristic acetylenic compounds have been isolated from a few species [1] and also several sesquiterpene lactones are reported from eight genera [2–4], mostly guaianolides, but also germacranolides and eudesmanolides. We have now investigated two further *Hypochoeris* species and *Lactuca floridana*. Again all three species afforded guaianolides, two of them esterified with a new type of sesquiterpenic acid.

RESULTS AND DISCUSSION

The roots of *Hypochoeris uniflora* Vill. afforded in addition to lupeyl acetate and its Δ9,11 and Δ12,13 isomers small amounts of the sesquiterpene lactone **3** as could be deduced from the ^{1}H NMR data (Table 1). Spin decoupling allowed the assignment of all signals and the stereochemistry at C-5–C-8 followed from the couplings observed. Furthermore, the ^{1}H NMR signals were very similar to those of the aldehyde **2** obtained by oxidation of the corresponding acetate **1** (Table 1). The aerial parts only afforded a complex mixture of triterpenes and fatty acids, which have not been identified. The roots and the aerial parts of *Hypochoeris glabra* afforded a mixture of two sesquiterpene lactones, both esterified with a sesquiterpenic acid. Careful high-field ^{1}H NMR investigation led to the structures **6** and **12** (Table 2). Mild saponification of **6** gave lactucin (**5**), its structure being established by X-ray analysis [5], and the acid **13** in low yields. Consequently, in the ^{1}H NMR spectrum of **6** the signals of the lactone part could be assigned with certainty and most of the remaining ones by spin decoupling. The presence of the methylene group in conjugation with the ester group clearly followed from the corresponding typical down-field signals. Irradiation of the signal at 3.0 ppm showed that it has to be assigned to H-7′, which was coupled with a double doublet at 1.48 ppm. The latter was further coupled with a doublet at 2.04 ppm. These signals therefore must be those of H-5′ and H-6′. The proposed cyclopropane moiety was supported by the acid-catalysed rearrangement of **6** (see Scheme) to the phenol **7**, its structure following from the ^{1}H NMR spectrum of the corresponding diacetate **8** (Table 2). Inspection of models showed that the proposed stereochemistry agrees best with the couplings observed. Furthermore, the chemical shift of H-14′ required a proximity to the C-2 carbonyl; this would not be the case with an α-orientated 10-methyl group. The second lactone (**12**) differed from **6** only in the nature of the lactone moiety. The methylene protons at C-13 were replaced by a methyl doublet at 1.12 ppm and a doublet quartet at 1.90 ppm. The observed coupling $J_{11,13}$ indicated an α-orientated C-11 methyl. Most probably the lactone part is that of jacquinelin [6], where, however, the stereochemistry at C-11 was not assigned.

The acid **13** is an isomer of the precursor **14** of the lactucin-like lactones, its carbon skeleton being that of the known hydrocarbon α-cubebene. The acid **13** we have named hypoglabric acid. **6** and **12** are the first sesquiterpene lactones to be found esterified with a sesquiterpenic acid.

The aerial parts of *Lactuca floridana* Gärtn. afforded in addition to squalene, lupeol and its Δ12,13 isomer lactucin (**5**), lactucopicrin (**4**) two similar lactones, the acetates **1** and **10**, which, however, could only be separated after manganese dioxide oxidation. The ^{1}H NMR data of the aldehydes **2** and **11** (Table 1) clearly showed that these lactones again differed in the lactone moiety only, **2** being a methylene lactone and **11** the corresponding 11,13-dihydro compound. The α-orientation of the methyl group, however, was deduced only by analogy and from the chemical shift of H-13, while the couplings $J_{11,13}$ could not be estimated due to overlapping of signals. The roots only afforded the triterpenes lupeyl acetates and its Δ12,13-isomer.

The nature of the lactones isolated confirm that lactucin-like guaianolides are probably characteristic for parts of the Lactuceae, where, however, subtribe

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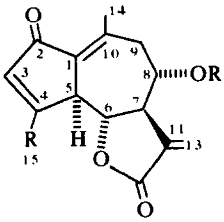
*Part 356 in the series "Naturally Occurring Terpene Derivatives". For Part 355 see Bohlmann, F. and Kassner, H. (1981) *Chem. Ber.* (in press).

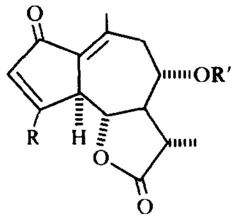
Table 1. ^{1}H NMR spectral data of compounds **1**–**3** and **11** (400 MHz, TMS as internal standard)

	1	**2**	**3**	**11**
H-3	6.46 *s* (*br*)	6.95 *d*	6.95 *d*	6.93 *d*
H-5	3.31 *m*	4.11 *d* (*br*)	4.12 *d* (*br*)	4.31 *d* (*br*)
H-6		2.65 *dd*	3.67 *ff*	3.65 *dd*
H-7	3.26 *dddd*	3.37 *dddd*	3.45 *dddd*	2.5 *m*
H-8	4.93 *ddd*	4.95 *ddd*	5.01 *ddd*	4.88 *ddd*
H-9α	2.50 *dd*	2.58 *dd*	2.62 *dd*	2.5 *d*
H-9β	2.74 *dd*	2.81 *dd*	2.87 *dd*	2.81 *dd*
H-11	—	—	—	2.5 *m*
H-13	6.24 *d*	6.24 *d*	6.21 *d*	1.36 *d*
H-13'	5.67 *d*	5.67 *d*	5.64 *d*	
H-14	2.47 *s* (*br*)	2.51 *s* (*br*)	2.51 *s* (*br*)	2.50 *s* (*br*)
	4.91 *d* (*br*)			
H-15	4.58 *d* (*br*)	10.18 *s*	10.18 *s*	10.15 *s*
OCOR	—	—	6.18 *s* (*br*) 5.72 *dq* 1.99 *s* (*br*)	—
OAc	2.17 *s*	2.18 *s*	—	2.13 *s*

J (Hz): compound **1**: 6,7 = 7,8 = 10.5; 7,13 = 3.5; 7,13' = 3; 8,9α = 10.5; 8,9β = 2.2; 9α,9β = 13.5; 15,15' = 18. Compounds **2** and **3**: 3,5 = 1.5; 5,6 = 7,8 = 10; 7,13 = 3.5; 7,13' = 3; 8β,9α = 10; 8β,9β = 2.5; 9α,9β = 13 (OMeacr: 3',4' = $4'_1 4'_2 \sim 1$); compound **11**: 3,15 = 1.2; 5,6 = 6,7 = 7,8 = 10; 8β,9α = 11; 8β,9β = 2; 9α,9β = 13.5; 11,13 = 6.5.



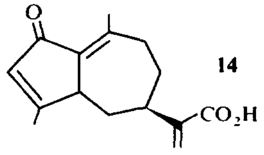
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
R	CH_2OH	CHO	CHO	CH_2OH	CH_2OH	CH_2OH	CH_2OH	CH_2OAc	CHO
R'	Ac	Ac	Meacr	A	H	B	C	D	B



	10	**11**	**12**
R	CH_2OH	CHO	CH_2OH
R'	Ac	Ac	B

B—OH

13



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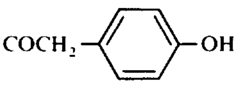

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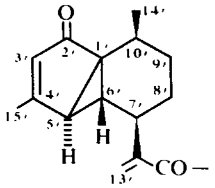

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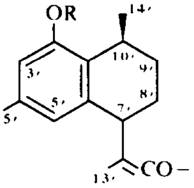

R = H

D = C, R = Ac

Table 2. ^{1}H NMR spectral data of compounds **6–9**, **12** and **13** (400 MHz, TMS as internal standard)

	6 (C_6D_6) 50°	**7** ($CDCl_3$)	**8** ($CDCl_3$)	**9** ($CDCl_3$)	**12** (C_6D_6)	**13**
H-3	6.45 *dt*	6.46 *s* (*br*)	6.41 *s* (*br*)	6.95 *d*	6.51 *dt*	
H-5	2.01 *d* (*br*)	3.67 *m*	3.67 *m*	4.13 *d* (*br*)	2.89 *d* (*br*)	
H-6	2.67 *dd*			3.67 *dd*	2.56 *dd*	
H-7	2.55 *dddd*	3.21 *dddd*	3.20 *ddd*		1.62 *m*	
H-8	4.70 *ddd*	4.99 *ddd*	4.99 *ddd*	5.05 *ddd*	4.56 *ddd*	
H-9α	2.23 *dd*	2.75 *dd*	2.76 *dd*	2.87 *dd*	2.17 *dd*	
H-9β	2.16 *dd*	2.45 *dd*	2.56 *dd*	2.58 *dd*	2.03 *dd*	
H-11	—	—	—	—	1.9 *dq*	
H-13$_1$	6.02 *d*	6.03 *d*	6.03 *d*	6.2 *d*	1.12 *d*	
H-13$_2$	5.27 *d*	5.25 *d*	5.26 *d*	5.59 *d*		
H-14	2.44 *s* (*br*)	2.46 *s* (*br*)	2.45 *s* (*br*)	2.52 *s* (*br*)	2.45 *s* (*br*)	
H-15	4.60 *d* (*br*) 4.17 *d* (*br*)	4.89 *d* (*br*) 4.57 *d* (*br*)	5.22 *d* (*br*) 5.02 *d* (*br*)	10.18 *s*	4.60 *d* (*br*) 4.14 *d* (*br*)	
H-3′	5.29 *dq*	6.42 *s* (*br*)	6.70 *s* (*br*)	5.33 *dq*	5.30 *s* (*br*)	5.31 *s* (*br*)
H-5′	1.60 *d* (*br*)	6.41 *s* (*br*)	6.43 *s* (*br*)	2.04 *d* (*br*)	1.55 *d* (*br*)	2.02 *d* (*br*)
H-6′	1.42 *dd*	—	—	1.48 *dd*	1.41 *dd*	1.51 *dd*
H-7′	2.93 *ddd* (*br*)	3.88 *dd* (*br*)	3.88 *dd* (*br*)	3.0 *m*	3.01 *ddd* (*br*)	2.95 *m*
H-8α′	1.2–1.4 *m*	1.86 *m*	1.87 *m*	1.2–1.4 *m*	1.2–1.4 *m*	1.3–1.5 *m*
H-8β′		2.08 *m*	2.07 *m*			
H-9α′		1.88 *m*	1.87 *m*			
H-9β′		1.73 *d* (*br*)	1.73 *d* (*br*)			
H-10′	2.15 *m*	3.13 *m*	3.12 *m*	2.3 *m*	2.12 *m*	2.28 *m*
H-13′$_1$	6.16 *s* (*br*)	6.40 *s* (*br*)	6.35 *s* (*br*)	6.34	6.10 *s* (*br*)	6.42 *s* (*br*)
H-13′$_2$	5.53 *s* (*br*)	5.70 *s* (*br*)	5.70 *s* (*br*)	5.82 *s* (*br*)	5.53 *s* (*br*)	5.77 *s* (*br*)
H-14′	1.70 *d*	2.19 *s* (*br*)	2.24 *s* (*br*)	2.12 *d*	1.74 *d*	2.11 *s* (*br*)
H-15′	1.67 *d*	1.27 *d*	1.27 *d*	1.48 *d*	1.62 *d*	1.46 *d*

J (Hz): compound **6**: 3,5 = 3,15 = 1.5; 5,6 = 6,7 = 7,8 = 10; $7,13_1 = 7,13_2 = 3$; 8,9α = 10; 8,9β = 3; 9α,9β = 13; $15_1,15_2 = 18$; 3′,5′ = <1; 3′,15′ = 1.2; 5′,6′ = 2.5; 6′,7′ = 3; 7′,8α′ = 6; 7′,8β′ = 8.5; 10′,14′ = 7; compounds **7** and **8**: 6,7 = 7,8 = 10.5; $7,13_1 = 7_1,13_2 = 3$; 8,9α = 10.5; 8,9β = 2; 9α,9β = 13.5; $15_1,15_2 = 18$; 7′,8α′ = 5.5; 7′,8β′ = 11.5; 9α′,9β′ = 14; 10′,14′ = 7; (OAc: 2.32 *s*, 2.13 *s*); compound **9**: 3,5 = 1.5; 5,6 = 6,7 = 7,8 = 10; $7,13_1 = 7,13_2 = 3$; 8,9α = 10; 8,9β = 2.5; 9α,9β = 13.5; 3′,5′ = 3′,15′ = 1; 5′,6′ = 6′,7′ = 3; 10′,14′ = 7; compound **12**: 3,5 = 3,15 = 1.5; 5,6 = 6,7 = 7,8 = 10; 7,11 = 12; 8,9α = 10; 8,9β = 2.5; 9α,9β = 13.5; 11,13 = 7; $15_1,15_2 = 18$; 3′,15′ = 1.2; 5′,6′ = 2.7; 6′,7′ = 3; 7′,8α′ = 6; 7′,8β′ = 8; 10′,14′ = 7; compound **13**: 5′,6′ = 2.5; 6′,7′ = 3; 10′,14′ = 7.

classification is still a problem. Following the proposal of Tomb [7] those genera, where lactones of this type have been reported, belong to the *Hypochoeris*, *Cichorium* and *Sonchus* group [1–4], though only a few genera have been investigated so far. All reports are concerning with species of the genera *Hypochoeris* [1, 4], *Lactuca* [1], *Crepis* [1], *Reichardia* (= *Picridium*) [1] and *Sonchus* [1]. Only from an *Urospermum* [1] and a *Taraxacum* [3] species unusual germacranolides have been isolated, while from *Sonchus* [1] and also from *Taraxacum* [3] species also eudesmanolides were reported. More detailed investigations are necessary, however, to get a clearer picture of the whole tribe. The proposed relationship between the Lactuceae and the Veronieae is supported by the occurrence of guaianolides and large amounts of triterpenes, mainly of the lupane type, in both tribes. However, these compounds are also present in other tribes, though not to the same extent.

EXPERIMENTAL

The fresh plant material, grown from seeds (except *Lactuca floridana*, air-dried) was extracted with Et_2O–petrol, 1:2 and the resulting extracts were separated first by CC (Si gel) and further by repeated TLC (Si gel). Known compounds were identified by comparing their IR and ^1H NMR spectra with those of authentic material.

Hypochoeris uniflora (*voucher* 80/1462). The roots (200 g) afforded 80 mg lupeyl acetate together with its Δ9,11 and Δ12,13 isomers, (*ca* 2:1:1) and 2 mg **3** (Et_2O–petrol, 3:1), while the aerial parts (1.5 kg) only gave a complex mixture of unidentified triterpenes (*ca* 1 g) and 300 mg of fatty acids.

Hypochoeris glabra (*voucher* 80/1385). The roots (200 g) gave 30 mg **6** and 5 mg **12** (separated by repeated TLC, Et_2O–CH_2Cl_2–C_6H_6, 1:1:1) and the aerial parts (2.5 kg) 20 mg **6** and 5 mg **12**.

Lactuca floridana (*voucher* LV 78/7). The roots (20 g) afforded 30 mg lupeylacetate and 20 mg of its Δ12,13 isomer, while the aerial parts (400 g) gave 20 mg squalene, 50 mg lupeol and its Δ12,13 isomer (*ca* 2:1), 1 mg **1** (Et_2O–petrol, 3:1), 5 mg **4**, 1 mg **5** and 1 mg **10** (Et_2O–petrol, 3:1). **1** and **10** could not be separated. Stirring with 30 mg MnO_2 in 2 ml Et_2O gave 1 mg **2** and 1 mg **11** (TLC: Et_2O–CH_2Cl_2–C_6D_6, 1:1:1).

Lactucin-8-O-*acetate* (**1**). Not separated from **10**, MnO_2 oxidation afforded **2**, colourless gum, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1785 (γ-lactone), 1750 (OAc), 1700 (C=CCO); MS *m/z* (rel. int.): 316.095 (M^+, 24) ($C_{17}H_{16}O_6$), 256 (M – AcOH, 35), 227 (256 – CHO, 12), 57 (100).

15-*Dehydrolactucin*-8-O-*methacrylate* (**3**). Colourless gum, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1780 (γ-lactone), 1725 ($C{=}CCO_2R$, CHO), 1700 (C=CC=O); MS *m/e* (rel. int.): 342, 110 (M^+, 5) ($C_{19}H_{18}O_6$), 256 ($M - RCO_2H$, 21), 69 ($C_3H_5CO^+$, 100).

Lactucin-8-O-*hypoglabrate* (**6**). Colourless crystals, mp 181° (Et_2O–C_6H_6); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610 (OH), 1775 (γ-lactone), 1710, 1645 ($C{=}CCO_2R$), 1690, 1620 (C=CC=O); MS *m/z* (rel. int.): 504.215 (M^+, 1) ($C_{30}H_{32}O_7$), 486 ($M - H_2O$, 1), 259 ($M - RCO_2$, 33), 246 (RCO_2H, 53), 228 ($246 - H_2O$, 100), 213 (228 – Me, 87), 199 (228 – CHO, 53); ^{13}C NMR ($CDCl_3$): (C-1–C-15): 133.1 *s*, 194.4 *s*, 124.7 *d*, 171.7 *s*, 53.3 *d*, 81.0 *d*, 55.0 *d*, 69.6 *d*, 44.4 *t*, 165.3 *s*, 133.1 *s*, 143.9 *s*, 168.0 *s*, 121.8 *t*, 18.6 *q*, 62.5 *t*; (C-1′–C-15′): 39.2 *s*, 207.3 *s*, 133.7 *d*, 145.7 *s*, 37.4 *d*, 28.3 *d*, 48.6 *d*, 23.5 *t*, 27.1 *t*, 37.4 *d*, 136.4 *s*, 176.3 *s*, 126.3 *t*, 21.5 *q*, 17.6 *q* (some signals may be interchangeable, assignment by comparison with similar compounds only).

$$[\alpha]^{\lambda}_{24^\circ} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{+118 \quad +125 \quad +148 \quad +250} \; (c = 1.35,\ CHCl_3).$$

20 mg **6** in MeOH were saponified with dil. KOH at room temp. The reaction was followed by TLC. After addition of acid TLC afforded 3 mg **5** and 2 mg **13**, colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3500–2700, 1695, 1620 ($C{=}CCO_2H$, C=CC=O); MS *m/z* (rel. int.): 246.131 (M^+, 24) ($C_{15}H_{18}O_3$), 228 ($M - H_2O$, 70), 213 (228 – Me, 100), 200 (228 – CO, 33), 199 (228 – CHO, 35).

10 mg **6** on standing in $CHCl_3$ containing a trace of HCl at RT for 12 hr afforded 2 mg **7**, colourless crystals, mp 135° (C_6H_6–petrol). 2 mg **7** on heating with 0.1 ml Ac_2O at 70° (1 hr) afforded 1 mg **8**, (^1H NMR spectrum see Table 2). 3 mg **6** on stirring with 50 mg MnO_2 in Et_2O afforded **9** (^1H NMR, see Table 2).

8α-*Acetoxyjaquinelin* (**10**). Only isolated as the aldehyde **11**, colourless gum IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1785 (γ-lactone), 1755 (OAc), 1710 (C=CCO); MS *m/z* (rel. int.): 318.110 (M^+, 11) ($C_{17}H_{18}O_6$), 258 (M – AcOH, 21), 57 (100).

8α-*Hypoglabroyloxyjaquinelin* (**12**). Colourless crystals, mp 190° (Et_2O–C_6H_6); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610 (OH), 1790 (γ-lactone), 1720, 1655 ($C{=}CCO_2R$), 1695, 1630 (C=CCO); MS *m/z* (rel. int.): 506.230 (M^+, 3) ($C_{30}H_{34}O_7$), 488 ($M - H_2O$, 1), 260 ($M - RCO_2H$, 10), 246 (RCO_2H^+, 60), 228 ($246 - H_2O$, 66), 213 (228 – Me, 70), 69 (100).

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