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LABDANE DERIVATIVES AND A HIMACHALANOLIDE FROM *ACRITOPAPPUS LONGIFOLIUS**

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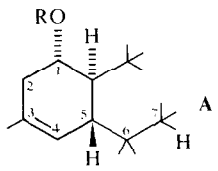
Key Word Index—*Acritopappus longifolius*; Compositae; Eupatorieae; new labdanes; sesquiterpene lactone; himachalanolide.

Abstract—The investigation of *Acritopappus longifolius* afforded, in addition to known compounds, further labdane derivatives and a new type of himachalanolide sesquiterpene lactone. The results support the chemotaxonomy of the genus and its relationship to *Radlkoferotoma* placed in the same group.

In addition to four species investigated previously [1] we have studied the constituents of *Acritopappus longifolius* (Gardner) K. et. R. (Compositae, tribe Eupatorieae). The roots contain bicyclogermacrene, γ-humulene, γ- and δ-cadinene, stigmasterol, the obliquin derivative **1** [2], the dehydro nerolidol angelate **2** [3] and a lactone, molecular formula $C_{20}H_{28}O_4$. The spectral data of the latter led to the structure **10**, a derivative of himachalane. The ^1H NMR data showed (Table 1) that three methyls were present, two tertiary and one olefinic. Spin decoupling after addition of Eu(fod)$_3$ led to the partial structure **A**:



The protons at C-5 and C-7 showed a clear *W*-coupling. The observed Eu(fod)$_3$-induced shifts showed that the tertiary methyls were located at the lactone ring, which must be β-orientated as follows from the observed shift of 5-H.

The ^{13}C NMR (Table 1) further indicated that a tricyclic compound must be present. The only possible structure therefore seemed to be **10**. This assumption was supported by the result of the reduction with diisobutyl aluminium hydride, which led to the formation of the diol **11**, clearly indicating that the secondary oxygen function was that of the angelate. Acetylation afforded the diacetate **13** as well as the monoacetate **12**. The mass spectra were also in good agreement with these structures. The formation of the toluene fragment supported the arrangement of the rings (elimination of angelic acid and splitting of the 5,6- and the 10,11-bonds). Compound **10** seems to be the first lactone with a himachalane skeleton. We therefore have named **10** 1α-angeloyloxy himachalanolide.

The aerial parts contained germacrene D, bicyclogermacrene, α- and γ-humulene, nerolidol, and the diol **5a** [4, 5]. Furthermore, the corresponding aldehydes **6** and **7** were present and their structures followed from the ^1H NMR spectral data (Table 2). The stereochemistry of the 13, 14-double followed from the chemical shifts of 16-H. Boranate reduction of **7** afforded the diol **5b**, the *Z*-isomer of **5a**, while MnO_2 oxidation of **5a** afforded **6**. Two lactones were isolated in minute amounts, the *ent*-labdane derivatives **8** and **9**, their structures followed from the ^1H NMR spectral data (Table 2). Most of the signals were very similar to those of similar compounds [1]. The position of the additional double bond in **9** was deduced from the chemical shifts and the observed couplings.

The polar fractions contained a mixture of the two epimeric lactones **3a** and **4a**, which could not be separated as well as the corresponding acetates. The structures followed from the ^1H NMR spectral data (Table 2), which were very similar to diterpenes isolated previously [1]. The assignment of which one was **3a** and which one was **4a** was not possible. In the mass spectrum of the acetates a fragment at *m/e* 191 was characteristic and was most probably formed after loss of acetoxyl by a retro Diels–Alder fragmentation. Compounds **3a** and **4a** have been named acritolongifolide A and B, respectively. Though the absolute configurations of the diterpenes were not determined they were most probably of the *ent*-labdane series, which are widespread in the tribe Eupatorieae [1].

The constituents of *A. longifolius* again support the chemotaxonomic situation of this genus. The isolation of **2** further indicates the relationship to *Radlkoferotoma*, where similar dehydronerolidol derivatives are present [6].

* Part 302 in the series "Naturally Occurring Terpene Derivatives". For Part 301 see Bohlmann, F., Fritz, U., King, R. M. and Robinson, H. (1981) *Phytochemistry* **20**, (in press).

Table 1. NMR spectral data of compounds **10**, **12** and **13** (270 MHz, TMS as internal standard, $CDCl_3$)

	10	Δ*	**12**	**13**	^{13}C	**10**		
1-H	5.13 *ddd*	0.99	4.92 *ddd*	4.92 *ddd*	C-1	69.9 *d*	C-1′	167.3 *s*
2α-H	2.07 *dd* (*br*)	0.55	2.04 *m*	2.3 *m*	C-2	35.0 *t*	C-2′	127.7 *s*
2β-H	2.38 *dd*	0.53	2.28 *dd*		C-3	133.3 *s*	C-3′	138.7 *d*
4-H	5.43 *ddq*	0.94	5.52 *s*(*br*)	5.52 *s* (*br*)	C-4	119.9 *d*	C-4′	15.7 *q*
5-H	2.60 *d* (*br*)	1.80	2.78 *d* (*br*)	2.75 *d* (*br*)	C-5	40.5 *d*	C-5′	20.49
7-H	1.75 *m*	~1.25	1.7 *m*	1.7 *m*	C-6	44.2 *s*		
11-H	2.49 *dd*	1.30	2.58 *dd*	2.48 *dd*	C-7	31.7 *t*		
12-H	—	—	4.87 *s*	5.84 *s*	C-8	20.4 *t*		
13-H	1.28 *s*	2.20	1.08 *s*	1.00 *s*	C-9	34.4 *t*		
14-H	1.43 *s*	0.57	1.22 *s*	1.20 *s*	C-10	83.2 *s*		
15-H	1.77 *dd* (*br*)	0.37	1.77 *dd* (*br*)	1.77 *s* (*br*)	C-11	45.6 *d*		
OCOR	6.08 *qq*	0.12	—	–	C-12	177.3 *s*		
	1.97 *dq*	0.19	—	–	C-13	30.9 *q*		
	1.85 *dq*	0.20	—	–	C-14	24.7 *q*		
OAc	—	–	2.04 *s*	2.05 *s*	C-15	23.5 *q*		
	—	—	–	2.08 *s*				

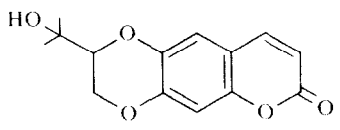
J (Hz): 1, 2α = 9; 1, 2β = 5; 1, 11 = 9; 2β, 15 = 1; 2β, 4 = 2β, 5 = 4, 5 = 1.7; 4, 15 = 1; 5, 7β = 2.5; 5, 11 = 11.

* Δ-Values after addition of $Eu(fod)_3$.

Table 2. ^{1}H NMR spectral data of compounds **3**–**9** (270 MHz, TMS as internal standard, $CDCl_3$)

	3a		**4a**	**3b**		**4b**	**5b**	**6**	**7**	**8**	**9**
5-H		2.42 *m*			2.40 *m*						1.95 *s(br)*
6-H		2.28 *m*			2.25 *m*					2.30 *m*	5.76 *d(br)*
7-H										5.46 *s(br)*	6.17 *dd*
9-H		2.02 *m*			2.0 *m*					1.95 *m*	1.9 *m*
12-H		3.00 *m*			3.0 *m*		2.08	2.25 *m*	2.53 *ddd*	2.58 *m*	2.58 *m*
12′-H		2.92 *m*							2.43 *ddd*	2.38 *m*	2.38 *m*
14-H	6.92 *s(br)*		6.91 *s(br)*	6.87 *s(br)*		6.86 *s(br)*	5.38 *t(br)*	5.91 *dd*	5.86 *d(br)*	5.86 *s(br)*	5.89 *s(br)*
15-H	—		—	—		—	4.13 *d(br)*	9.99 *d*	9.96 *d*	—	—
16-H	6.05 *s*		6.02 *s*		6.89 *s*		1.78 *s(br)*	2.20 *d*	2.04 *s(br)*	4.75 *s(br)*	4.74 *s(br)*
17-H	9.34 *s*		9.33 *s*	9.38 *s*		9.36 *s*	1.18 *s*	1.16 *s*	1.21 *s*	1.68 *s(br)*	4.95 *s(br)*
17′-H											4.74 *s(br)*
18-H		0.95 *s*			0.95 *s*		0.94 *s*	0.97 *s*	0.97 *s*	0.88 *s*	0.96 *s*
19-H		0.92 *s*			0.91 *s*		0.87 *s*	0.87 *s*	0.89 *s*	0.86 *s*	0.84 *s*
20-H		0.82 *s*		0.82 *s*		0.81 *s*	0.83 *s*	0.83 *s*	0.85 *s*	0.78 *s*	0.70 *s*

J (Hz): **5b**: 14,15 = 7; **6**: 14,15 = 8; 14,16 = 1.5; **7**: 11,12 = 12.5; 11′,12 = 5; 11,12′ = 5; 11′,12′ = 12.5; 12,12′ = 12.5; 14,15 = 8; **9**: 5, 7 = 2.5; 6, 7 = 10.



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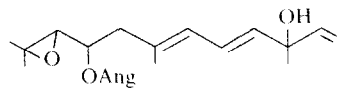

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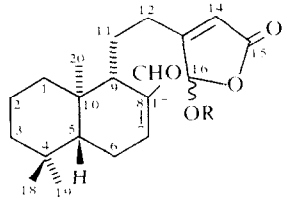
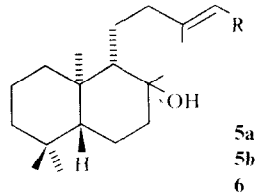
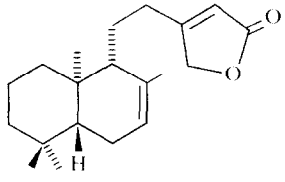


3a R = H (16α)
3b R = Ac
4a R = H (16β)
4b R = Ac



5a R = CH_2OH (13, 14 *E*)
5b R = CH_2OH (13, 14 *Z*)
6 R = CHO
7 R = CHO (13, 14 *Z*)



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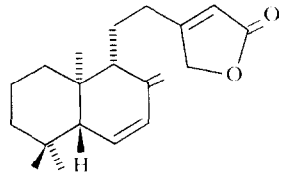

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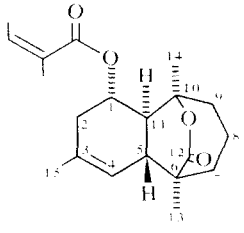

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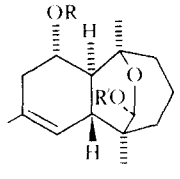


11 R = R' = H
12 R = Ac, R' = H
13 R = R' = Ac

EXPERIMENTAL

^{1}H NMR: 270 MHz, TMS as int. standard; MS: 70 eV, direct inlet; optical rotation, $CHCl_3$. The air-dried plant material (voucher RMK 8356, collected in northeastern Brazil) was extracted with Et_2O–petrol (1:2). The resulting extracts were first separated by CC (Si gel, act-grade II) and further by TLC (Si gel, GF 254). Known compounds were identified by comparing the IR- and ^{1}H NMR spectra with those of authentic compounds. The roots (160 g) afforded 20 mg bicyclogermacrene, 20 mg γ-humulene, 5 mg γ- and 5 mg δ-cadinene, 20 mg **1**, 10 mg stigmasterol, 5 mg **2** and 50 mg **10** (Et_2O–petrol, 1:3), while the aerial parts (450 g) gave 100 mg germacrene D, 5 mg bicyclogermacrene, 5 mg α- and 20 mg γ-humulene, 20 mg nerolidol, 5 mg **3** and **4** (1:1), 3 mg **5**, 30 mg **6** (Et_2O–petrol, 1:1); 20 mg **7** (Et_2O–petrol, 1:1), 2 mg **8** and 2 mg **9** (CH_2Cl_2–C_6H_6–Et_2O, 5:5:1).

1α-*Angeloyloxy-himachalanolide* (**10**). Colourless oil, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740 (δ-lactone), 1715, 1650 (C=CCO_2R); MS *m/e* (rel. int.): 332.200 (M^+, 0.1) ($C_{20}H_{28}O_4$); 232 (8) (M − Ang OH), 204 (11) (232 − CO), 119 (44), 112 (100), 92 (33) (Ph Me); 83 (49) ($C_4H_7CO^+$); CI (isobutane) 333 (14) (M + 1), 233 (100) (M + 1 − Ang OH).

$$[\alpha]_{24}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{+20.4 \quad +21.4 \quad +24.5 \quad +38.1} \quad (c = 1.5).$$

To 10 mg **10** in 2 ml Et_2O 20 mg DIBAH in 0.1 ml toluene at −78° were added. After addition of diluted H_2SO_4 the reaction product was extracted with Et_2O affording 6 mg **11**, which was heated for 1 hr with 0.1 ml Ac_2O. TLC (Et_2O–petrol, 1:1) gave 3 mg **12** and 3 mg **13**, **12**: MS *m/e* (rel. int.): 234 (6) (M − HOAc); 216 (25) (234 − H_2O); 201 (10) (216 − Me); 92 (100) (Ph Me).

8-*Hydroxy*-ent-*labd*-13(14)E-*en*-15-*al* (**6**). Colourless oil, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620 (OH); 2750, 1680, 1630 (C=CCHO); MS *m/e* (rel. int.) 306.256 (M^+, 7) ($C_{20}H_{34}O_2$), 291 (2) (306 − Me), 273 (2) (291 − H_2O), 205 (68) (M − H_2O, CH_2C(Me)=CHCHO), 84 (200) (Me_2C=CHCHO).

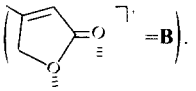
$$[\alpha]_{24}^{\lambda} = \frac{589 \quad 578 \quad 546 \quad 436\,\text{nm}}{-29.1 \quad -30.6 \quad -35.0 \quad -60.1} \quad (c = 1.4).$$

MnO_2 oxidation of **5a** afforded an aldehyde identical with **6**.

8-*Hydroxy*-ent-*labd*-13(14)Z-*en*-15-*al* (**7**). Colourless oil, IR: $\nu_{max}^{CCl_4}$ cm^{-1}: 3620 (OH), 2750, 1680 (C=CCHO); MS *m/e* (rel. int.): 306.256 (M^+, 3) ($C_{20}H_{34}O_2$), 291 (2) (M − Me), 205 (16) (M − Me, CH_2C(Me)=CHCHO), 84 (61) (Me_2C=CHCHO), 55 (100) ($C_4H_7^+$). 10 mg **7** in 1 ml MeOH were reduced with 10 mg $NaBH_4$. TLC (Et_2O–petrol, 3:1) afforded 7 mg **5b** (13(14)Z), ^{1}H NMR see Table 2, MS *m/e* (rel. int.): 291 (8) (M − OH), 273 (8) (291 − H_2O), 258 (6) (273 − Me), 55 (100) ($C_4H_7^+$).

Acritolongifolide A and B (**3a** and **4a**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3360 (OH), 1760 (γ-lactone), 2730, 1690, 1635

(C=CCHO); 5 mg **3a** and **4a** were heated with 0.5 ml Ac_2O for 1 hr at 70°: after evaporation and TLC (Et_2O–petrol, 3:1) 3 mg **3b** and **4b** were obtained, colourless gum, MS *m/e* (rel. int.): 314.188 (9) ($C_{20}H_{26}O_3$), 285 (10) (314 − ·CHO), 191.071 (22) ($C_{11}H_{11}O_3$, − ·OAc, RDA), 109 (100).

16-*Hydroxy*-ent-*labda*-7,13-*diene*-15-*oic lactone* (**8**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1785 (γ-lactone), 1650 (C=C); MS *m/e* (rel. int.): 302.225 (M^+, 4) ($C_{20}H_{30}O_2$), 287 (8) (M − ·Me), 98 (100) ( =**B**).

16-*Hydroxy*-ent-*labda*-6,8(17),13-*triene*-15-*oic lactone* (**9**). Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1785 (γ-lactone), 1650 (C=C); MS *m/e* (rel. int.): 300.209 (M^+, 2) ($C_{20}H_{28}O_2$), 285 (3) (M − ·Me), 257 (1) (285 − CO), 109 (100), 98 (44) (**B**).

$$[\alpha]_{24}^{\zeta} = \frac{589 \quad 578 \quad 546 \quad 436\,nm}{+8 \quad +9 \quad +10 \quad +18} (c = 0.2).$$

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