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FURTHER SESQUITERPENE LACTONES FROM *INULA SALSOLOIDES*

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Key Word Index—*Inula salsoloides*; Compositae; sequiterpene lactones; germacranolides; eudesmanolides; melampolides.

Abstract—An extract of the aerial parts of *Inula salsoloides* afforded in addition to known compounds an eudesmanolide, two melampolides and two linear sesquiterpenes. The structures and spectroscopic data of two germacranolides are revised

INTRODUCTION

The taxonomy of the large genus *Inula*, which comprises *ca.* 100 species, is problematical [1]. Sesquiterpene lactones, present in a part of the genus, could be useful chemotaxonomic markers. As a part of our investigation of *Inula* species [2], we present our results with *I. salsoloides*. Previous investigations gave in addition to some common compounds [3] several sesquiterpene lactones of germacranolide type [4].

RESULTS AND DISCUSSION

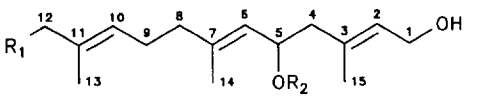
An extract of the aerial parts of *I. salsoloides* Türcz (Ostenf.) contained in addition to several widespread compounds (Experimental), the linear sesquiterpenes **1** and **2**, the 6,12-germacranolides 11β,13-dihydroeupatolide (**3**) [5], eupatolide (**4**) [6], budlein B (**5**) [7] (=desacetylovatifolin [8]), ovatifolin (**6**) [9] and **7**–**9**, the 8,12-germacranolide baylein [10, 11], the eudesmanolides **10** [12] and **11**, and the melampolides **12** [13], glabratolide **13** [14], **14** [15], **15** and **16**.

The structures of **1** and **2** followed from the ^{1}H NMR data (Table 1) and results of spin decoupling. The configurations of the double bonds followed from the chemical shifts of methyl groups and were confirmed by NOE experiments with compound **1**. By saturating the H-12 signal an increase in intensity of the H-10 signal (5%) was observed. Similarly the saturation of the H-14 resonance frequency caused a 10% increase of the intensity of the H-5 signal. Additionally the chemical shift of the aldehyde signal in the spectrum of **2** is indicative of an *E*-configuration.

The structures of **7**–**9** were easily deduced from the proton NMR data (Table 2) and by comparison with the spectra of the co-occurring precursors **4**–**6**. In each case H-5 was shifted upfield in the region typical of epoxide signals. Germacranolides with a free hydroxy group at C-8 having the same stereochemistry were not described previously. However, a recent paper by Cordell *et al.* on constituents from the title plant [4] described the isolation of the compounds **4**, **5**, and two epoxides, named inulasalsolin and inulasalsolide (**1** and **2** in Ref. 4). Their structures correspond to **7** and **8** with reversed stereochemistry at C-4 and C-5. In fact, this very confusing paper, full of errors, describes compounds identical with ours as indicated by almost identical spectral data, in particular the ^{13}C NMR data. The following discussion is related to the cited paper. The new trivial naming of these common compounds was not necessary. The numbering in the formulae is unusual. The NMR signals for compound **1** in Tables 3 and 4 are in part mixed up or missing. Several discussed NOEs are impossible (e.g. compound **1**: H-8/C-10 methyl; comp. **2**: H-8α/H-5, H-6/H-9α and H-6/H-9β). The NOE between C8-OH and C15-OH is an exchange phenomenon rather than a dipolar interaction. Germacranolides of that type usually adopt a conformation with both methyl groups above the plane of the ten membered ring (UU-conformation according to Watson and Kashyap [16]). This conformation forced the formation of a 4α,5β epoxide which posses the same conformation.

The ^{1}H NMR spectra of the eudesmanolides **10** and **11** showed similarities. In the spectrum of **11** a methyl doublet appeared instead of signals for the lactone exomethylenes indicating a dehydro derivative of **10**. The stereochemistry at C-11 was easily deduced from the coupling constant $J_{7,11} = 13$ Hz, typical of a *trans* orientation.

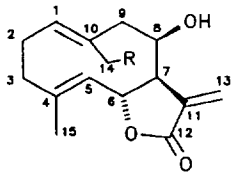
In the ^{1}H NMR spectra of the melampolides **13**–**16** identical sequences as in corresponding germacranolides were observed (Table 3). However, additional signals for



1 2

R_1 OH =O

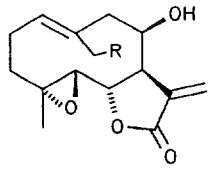
R_2 Ac H



3 4 5 6

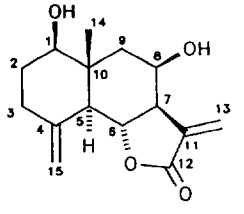
R H H OH OAc

11β,13H



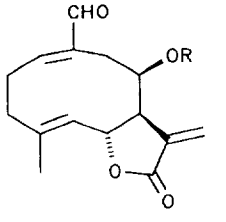
7 8 9

R H OH OAc



10 11

11β,13H



12 13 14 15 16

R H iBu iVal H iVal

11β,13H 4α,5β epoxide 4α,5β epoxide

Table 1. ^{1}H NMR data of **1** and **2** (400 MHz)

Proton	1	2
1	4.12 *d*	4.18 *d*
2	5.43 *brt*	5.47 *brt*
4	2.37 *brdd*	2.20 *m*
4′	2.19 *brdd*	2.20 *m*
5	5.62 *ddd*	4.51 *ddd*
6	5.12 *brd*	5.24 *brd*
8	2.21–2.04 *m*	2.20 *t*
8	2.21–2.04 *m*	2.49 *dt*
10	5.33 *brt*	6.46 *brt*
12	3.98 *brd*	9.39 *s*
13	1.65 *brs*	1.75 *brs*
14	1.70 *brs*	1.73 *brs*
15	1.70 *brs*	1.73 *brs*
OAc	2.01 *s*	

J(Hz): compounds **1** and **2**: 1,2 = 8,9 = 9,10 = 7; compound **1**: 4,4′ = 13.5, 4′,5 = 6.5; 5,6 = 9; compound **2**: 4,5 = 5; 5,6 = 8.

isobutyrate and isovalerate and the downfield shift of H-8 required corresponding ester groups at C-8. The chemical shift of the aldehyde proton indicated the *E*-configuration of the 1,10 double bond.

Table 2. ^{1}H NMR data of **7**, **8** and **9** (400 MHz)

Proton	7	8	9
1	5.16 *brdd*	5.43 *brdd*	5.56 *brdd*
2α	2.16 *m*	2.23 *brddd*	2.31 *m*
2β	2.43 *dddd*	2.49 *dddd*	2.55 *dddd*
3α	1.22 *ddd*	1.32 *ddd*	1.33 *m*
3β	2.11 *ddd*	2.16 *ddd*	2.21 *ddd*
5	2.77 *d*	2.81 *d*	2.78 *d*
6	4.57 *dd*	4.50 *dd*	4.54 *dd*
7	3.00 *dddd*	3.02 *dddd*	3.00 *dddd*
8α	4.60 *m*	4.47 *m*	4.60 *m*
9α	2.59 *dd*	2.77 *dd*	2.87 *dd*
9β	2.29 *dd*	2.52 *dd*	2.25 *dd*
13	6.34 *d*	6.40 *d*	6.42 *d*
13′	5.65 *d*	5.69 *d*	5.65 *d*
14	1.84 *brs*	4.47 *brd*	4.97 *brd*
14′		3.86 *brd*	4.80 *brd*
15	1.32 *s*	1.35 *s*	1.28 *s*
OAc			2.11 *s*

J(Hz): compounds **7**, **8** and **9**: 1,2β = 2α, 2β = 2β, 3α = 3α, 3β = 13; 2α,3β = 1.5, 2β,3β = 5.5; 5,6 = 6,7 = 8.5, 7,8 = 3, 7,13 = 3.5, 7,13′ = 3, 8,9α = 1, 8,9β = 5, 9α,9β = 14; compound **7**: 1,2α = 2, 2α,3α = 6; compounds **8** and **9**: 1,2α = 4, 2α,3α = 6.5, 14,14′ = 12.

Table 3. ^{1}H NMR data of **11**, **15** and **16** (400 MHz)

Proton	11	15	16*
1	3.46 *dd*	6.75 *ddd*	6.78 *ddd*
2	1.80 *m*	2.56 *m*	2.57 *m*
2′	1.58 *m*	2.56 *m*	2.57 *m*
3	2.32 *ddd*	2.37 *m*	2.37 *m*
3′	2.15 *m*	1.26 *m*	1.28 *m*
5	2.09 *brd*	2.69 *d*	2.71 *d*
6	4.56 *dd*	4.35 *dd*	4.25 *dd*
7	1.79 *ddd*	2.61 *m*	2.74 *m*
8	4.34 *m*	5.26 *ddd*	6.41 *ddd*
9	2.25 *dd*	2.87 *ddd*	2.98 *ddd*
9′	1.49 *dd*	2.35 *m*	2.29 *ddd*
11	2.73 *dq*		
13	1.24 *d*	6.39 *d*	6.31 *d*
13′		5.67 *d*	5.70 *d*
14	1.06 *s*	9.46 *d*	9.49 *d*
15	4.98 *brs*	1.62 *s*	1.60 *s*
15′	4.90 *brs*		

*iVal: H-2 = 2.17 (*m*), H-3 = 2.03 (*ddqq*), H-4 = 0.93 (*d*), H-5 = 0.92(*d*) *J*(Hz): compound **11**: 1,2 = 5, 1,2′ = 12, 2,3 = 2, 2′,3 = 6, 3,3′ = 14, 5,6 = 6,7 = 10, 7,8 = 2, 7,11 = 13, 8, 9 = 2.5, 8,9′ = 3, 9,9′ = 15, 11,13 = 6.5; compounds **15** and **16**: 1,2 = 8, 1,2′ = 10, 1,9 = 2, 5,6 = 6,7 = 10, 7,13 = 3.5, 7,13′ = 3, 7,8 = 1.5, 8,9 = 7, 8,9′ = 10, 9,9′ = 14, 9′, 14 = 1.5; OiVal: 2,3 = 3,4 = 3.5 = 7.

Table 4. ^{13}C NMR data of **7**, **8** and **9** (100 MHz)

Carbon	7	8	9
1	126.9 *d*	131.7 *d*	133.9 *d*
2	24.1 *t*	24.1 *t*	24.0 *t*
3	35.9 *t*	36.0 *t*	35.8 *t*
4	62.3 *s*	61.8 *s*	61.5 *s*
5	66.8 *d*	66.4 *d*	66.4 *d*
6	75.2 *d*	74.9 *d*	75.0 *d*
7	50.5 *d*	50.6 *d*	50.5 *d*
8	73.8 *d*	71.8 *d*	73.2 *d*
9	47.2 *t*	44.3 *t*	42.0 *t*
10	134.5 *s*	134.5 *s*	131.6 *s*
11	137.9 *s*	137.7 *s*	137.8 *s*
12	169.7 *s*	169.8 *s*	169.2 *s*
13	122.2 *t*	122.1 *t*	122.0 *t*
14	20.3 *q*	59.8 *t*	63.5 *t*
15	17.1 *q*	16.5 *q*	16.8 *q*
OAc			171.5 *s*
			21.0 *q*

EXPERIMENTAL

The ^{1}H NMR spectra were measured in $CDCl_3$ with residual $CHCl_3$ signal as internal standard, δ = 7.26 ppm. ^{13}C NMR spectra were measured in $CDCl_3$ with solvent peak as internal standard, δ = 77.0 ppm. The air-dried material (750 g, collected in July 1988; 32 km north-east of Gurvan-Tes, Mongolia) was extracted at room temp. with a mixture of petrol–Et_2O–MeOH (1 : 1 : 1). After defatting the extract was separated by CC using solvent mixture of petrol, MTB (methyl-*tert.*-butyl ether) and MeOH with increasing polarity. The less polar frs contained 15 mg of a mixture of fatty acid esters of lupeol, 150 mg lupeol, 40 mg taraxasteryl acetate, 200 mg taraxasterol, 100 mg stigmasterol, 30 mg squalene, 15 mg 2,5-dimethoxy-*p*-cymene, 130 mg 10-isobutyroyloxy-8,9-epoxy-thymol-isobutyrate. The polar frs were combined and separated by MPC (medium pressure chromatography) and further by HPLC and/or TLC (conditions of final purification are in parentheses) to give 25 mg naringenin, 15 mg 10-hydroxy-8,9-dihydrothymol, 1000 mg **7** (HPLC MeOH–H_2O, 7 : 3, R_t 5.3 min, always RP8, 8 × 250 mm), 300 mg ovatifolin **6**, 650 mg eupatolide (**4**), 100 mg glabratolide (**13**), 40 mg 11β, 13-dihydroeupatolide (**3**) and 650 mg **14**. HPLC (MeOH–H_2O, 3 : 2, R_t 6.4 min) afforded 30 mg **11**. TLC (CH_2Cl_2–toluene–MeOH, 9 : 9 : 2, R_t 0.3) yielded 200 mg **1**, 20 mg **2**, 600 mg baileyin, 90 mg **12**, 90 mg deacetylovatifolin (**5**), 70 mg **16**, and 50 mg **10**. 400 mg **9** was obtained by HPLC (MeOH–H_2O, 1 : 1, R_t 6.2 min), 100 mg **15** (HPLC, MeOH–H_2O, 2 : 3, R_t 7.5 min) and 1000 mg **8** (HPLC, MeOH–H_2O, 13 : 7, R_t 4.2 min). Known compounds were identified by comparing their spectral data with those of authentic material.

5-Acetoxy-12-hydroxyfarnesol (**1**). MS *m/z* (rel. int.): 236 $[M - AcOH]^+$ (4), 218 $[236 - H_2O]^+$ (6), 151 (75), 123 (95), 57 (100).

5-Hydroxy-12-oxofarnesol (**2**). MS *m/z* (rel. int.): 223.170 $[M - CHO]^+$ (3) (calcd for $C_{14}H_{23}O_2$: 223.170), 205 $[223 - H_2O]^+$ (3), 68 (100).

4α,5β-Epoxyeupatolide (**7**). MS *m/z* (rel. int.): 264.136 $[M]^+$ (1.3) (calcd for $C_{15}H_{20}O_4$: 264.136), 246 $[M - H_2O]^+$ (2.4), 161 (100).

4α,5β-Epoxydesacetylovatifolin (**8**). CI-MS *m/z* (rel. int.): 281 $[M + 1]^+$ (7), 263 $[(M + 1) - H_2O]^+$ (45), 245 $[(M + 1) - 2H_2O]$ (64), 217 (66), 163 (100).

4α,5β-Epoxyovatifolin (**9**). CI-MS *m/z* (rel. int.): 323 $[M + 1]^+$ (10), 305 $[(M + 1) - H_2O]^+$ (45), 263 $[(M + 1) - AcOH]^+$ (23).

8-epi-11β,13-Dihydrodentatin A (**11**). MS *m/z* (rel. int.): 266.152 $[M]^+$ (2) (calcd for $C_{15}H_{22}O_4$ 266.152), 248 $[M - H_2O]^+$ (38), 230 $[248 - H_2O]^+$ (55), 55 (100).

4α,5β-Epoxy-8β-hydroxy-14-oxoacanthospermolide (**15**). CI-MS *m/z* (rel. int.): 279 $[M + 1]^+$ (100), 223 (84), 151 (50), 102 (40), 79 (68).

4α,5β-Epoxy-8β-isovaleroyloxy-14-oxoacanthospermolide (**16**). MS *m/z* (rel. int.): 362.173 $[M]^+$ (1) (calcd for $C_{20}H_{26}O_6$: 362.173), 260 $[362 - RCOOH]^+$ (13), 161 (60), 85 $[RCO]^+$ (82), 57 $[C_4H_9]^+$ (100).

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