Oxygenated Bisabolane Fucosides from *Carthamus lanatus* L.

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The aerial parts of *Carthamus lanatus* (Asteraceae) afforded four new oxygenated bisabolane fucosides, 10-hydroperoxy-bisabola-2,11-diene 7-*O*-β-D-fucopyranoside, 11-hydroperoxy-bisabola-2,9-diene 7-*O*-β-D-fucopyranoside, 10-hydroxy-bisabola-2,11-diene 7-*O*-β-D-fucopyranoside and 11-hydroxy-bisabola-2,9-diene 7-*O*-β-D-fucopyranoside together with the known compounds α-bisabolol β-D-fucopyranoside, asperuloside, sitosterol 3-*O*-β-D-glucoside and stigmasterol 3-*O*-β-D-glucoside. Asperuloside appears to be the second representative of the iridoid monoterpene group found in the plant family Asteraceae, which until recently was considered to lack iridoids. The main constituent α-bisabolol fucoside exhibited noticeable antibacterial and cytotoxic activities.

Key words: Carthamus lanatus, Sesquiterpene Fucosides, Asperuloside

Introduction

Phytochemical studies of *Carthamus lanatus* L. (Asteraceae) showed the presence of flavonoids (El-Shaer *et al.*, 1998; Novruzov and Shamsizade, 1998), aromatic acids, serotonins (Lahloub *et al.*, 1993), lipids (Demir *et al.*, 1978), amino acids, carbohydrates (Yasuhuko *et al.*, 1979), etc. Until now, sesquiterpene fucosides from the bisabolane (Feliciano *et al.*, 1990a) and eudesmane (Feliciano *et al.*, 1990b) type were isolated. Sedative, antitumor and interferon-inducing activities were reported for *C. lanatus* (Benedi *et al.*, 1986; Yasuhuko *et al.*, 1979). In continuation of our studies on *C. lanatus* (Taskova *et al.*, 2002, 2003; Mitova *et al.*, 2003; Stefanov *et al.*, 2003) in the present paper we report data on its terpenoid composition. Antibacterial, antifungal and cytotoxic activity tests were performed on the main sesquiterpenoid constituent α-bisabolol β-D-fucopyranoside.

Experimental

Plant material

The aerial parts of *C. lanatus* were collected in July 2001 during the flowering season at the Losen village region, Sofia, Bulgaria. A voucher specimen (No 156639) was identified by Dr. Rilka Taskova and deposited in the Herbarium of the Institute of Botany, Bulgarian Academy of Sciences (SOM).

Extraction and isolation

The air-dried ground aerial parts (500 g) were extracted with methanol (5 l) at room temperature. The concentrated extract (78 g) was partitioned between upper and lower layer of hexane/methanol/water (19:19:2 v/v/v) and the lower layer (67 g) was extracted with diethyl ether (5.6 g; water part 59 g). The diethyl ether extract was chromatographed on a silica gel (Merck) column with mixtures of ethylacetate/methanol (20:1 to 1:1 v/v) to give pure **5** (fractions 35–40, 1.2 g). Fractions 41–44 (127 mg) were further separated by column chromatography on silica gel with ethylacetate as eluent and a mixture (54 mg, frs 11–15) of **1** and **2** as well as pure **6** (10 mg) were obtained. Fractions 56–58 (51 mg) were additionally purified by SEP-Pak C_{18} cartridges for rapid sample preparation (Waters, Milford, USA) with methanol and pure **3** (20 mg) was obtained. Fractions 68–70 (211 mg) were separated by silica gel column chromatography with chloroform/methanol/water (60:15:4 v/v/v) to give a mixture (26 mg) of stigmasterol 3-*O*-glucoside and sitosterol 3-*O*-glucoside (1:4) and pure **4** (20 mg).

Mixture of 10-hydroperoxy-bisabola-2,11-diene 7-O-β-D-fucopyranoside (**1**) *and 11-hydroperoxy-*

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bisabola-2,9-diene 7-O-β-D-fucopyranoside (**2**): ESIMS (positive mode): *m/z* (rel. int.) = 423 (69) $[M+Na]^+$, 439 (48) $[M+K]^+$, 407 (50) $[M+Na-16]^+$. – ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 5.84 (1H, dt, J = 16.0, 8.0 Hz, H-9 for **2**), 5.55 (1H, d, J = 16.0 Hz, H-10 for **2**), 5.34 (br s, H-2), 4.94 (br s, H_2-12 for **1/1′**), 4.40 (d, J = 7.1 Hz, H-1′), 4.15 (m, H-10 for **1/1′**), 2.43 (1H, dd, J = 14.5, 6.4 Hz, H-8a for **2**), 2.32 (1H, dd, J = 14.5, 7.0 Hz, H-8b for **2**), 1.72 and 1.74 (s, CH_3-13 for **1/1′**), 1.64 (s, CH_3-15), 1.28 (3H, s, CH_3-12 for **2**), 1.27 (3H, s, CH_3-13 for **2**), 1.27 and 1.26 (d, J = 6.4 Hz, CH_3-6′), 1.16 and 1.12 (s, CH_3-14). – ^{13}C-NMR (100.62 MHz, $CDCl_3$): see Table I.

10-Hydroxy-bisabola-2,11-diene 7-O-β-D-fucopyranoside (**3/3′**): ESIMS (positive mode): *m/z* (rel. int.) = 407 (63) $[M+Na]^+$, 423 (21) $[M+K]^+$, 385 $[M+H]^+$ (15). – ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 5.34 (br s, H-2), 4.85, 4.70 (br s, H_2-12), 4.07 (m, H-10), 1.67, 1.64 (s, CH_3-13), 1.66 (s, CH_3-15), 1.16 (s, CH_3-14), 1.28 (d, J = 6.8 Hz, CH_3-6′). – ^{13}C NMR (62.8 MHz, $CDCl_3$,): see Table I.

11-Hydroxy-bisabola-2,9-diene 7-O-β-D-fucopyranoside (**4**): ESIMS (positive mode): *m/z* (rel. int.) = 407 $[M+Na]^+$, 423 $[M+K]^+$. – ^{1}H NMR (250.13 MHz, $CDCl_3$): δ = 5.82 (1H, dt, J = 16.0, 7.0 Hz, H-9), 5.60 (1H, d, J = 16.0 Hz, H-10), 5.34 (1H, br s, H-2), 2.35–2.15 (2H, m, H_2-8), 1.66 (3H, s, CH_3-15), 1.30 (3H, s, CH_3-13), 1.28 (d, J = 6.8 Hz, CH_3-6′). – ^{13}C NMR (62.8 MHz, $CDCl_3$): see Table I.

Photooxidation of **5** *to* **1** *and* **2** *and further reduction to* **3** *and* **4**

5 (60 mg) was dissolved in 15 ml acetone and Bengal rose (1.5 mg) and pyridine (0.5 ml) were added. The reaction mixture was illuminated and air bubbled through it for 2 h. The reaction product was purified by PTLC on silica gel with ethylacetate/hexane (10:2 v/v) to afford a mixture of **1** and **2** (30 mg). NaI was added to the mixture (17 mg, 1:1 mol equiv.) and left for 48 h. The reaction was monitored by TLC and the product (47 mg) was elucidated as a mixture of **3** and **4**.

Antibacterial assay

Antimicrobial activity was studied by the modified disk diffusion method of Kujumgiev *et al.* (1993). The Gram-positive bacteria *Staphylococcus aureus*, the Gram-negative bacteria *Escherichia coli* and the fungus *Candida albicans* were used. **5** was tested at 1.36 μM/disk (500 μg/disk) using streptomycin as a positive control at 0.134 μM/disk (100 μg/disk) (inhibitory zone 28.0 ± 1.0 mm). The obtained results (Table II) were the mean of three replications. The absence of activity was evaluated by a diameter of the inhibitory zone less than 10 mm.

Cytotoxicity assay

The brine shrimp (*Artemia salina*) assay (Table II) was performed in triplicate with appropriate amounts of **5** dissolved in DMSO (1% final volume) using 10 freshly hatched larvae, suspended in 5 ml artificial sea water (Solis *et al.*, 1993). Concentrations of 2.7, 0.27, 0.027 and 0.0027 μM were used. For each dose tested deaths and survivors were counted after 24 h and data statistically analyzed, which affords LD_{50} values with 95% confidence intervals. Caffeic acid phenethyl ester (CAPE) was used as active reference substance.

Results and Discussion

The methanol extract of aerial parts of *C. lanatus* was partitioned between hexane/methanol/water (19:19:2 v/v/v) and the diethyl ether extract of the water/alcoholic part was separated by combination of chromatographic techniques. Four new oxygenated bisabolane fucosides (**1**–**4**; Fig. 1) in

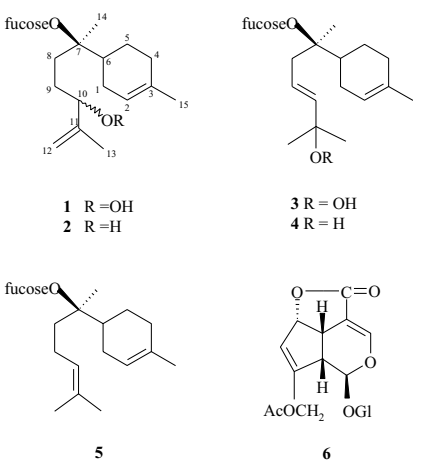


Fig. 1. 10-Hydroperoxy-bisabola-2,11 diene 7-*O*-β-D-fucopyranoside* (**1**); 11-hydroperoxy-bisabola-2,9diene 7-*O*-β-D-fucopyranoside* (**2**); 10-hydroxy-bisabola-2,11-diene 7-*O*-β-D-fucopyranoside* (**3**); 11-hydroxy-bisabola-2,9-diene 7-*O*β-D-fucopyranoside* (**4**); α-bisabolol β-D-fucopyranoside; (**5**); asperuloside (**6**).
* New compounds.

addition to four known compounds were afforded. By means of spectroscopic methods and comparison with literature data the latter compounds were identified as the known sesquiterpenoid fucoside α-bisabolol β-D-fucopyranoside (**5**) (Feliciano *et al.*, 1990a), the iridoid glucoside asperuloside (**6**) (El-Naggar and Beal, 1980) and two phytosterol glucosides, sitosterol 3-*O*-β-D-glucoside and stigmasterol 3-*O*-β-D-glucoside (Alam *et al.*, 1996). The phytosterol glucosides and asperuloside are reported for the first time for *C. lanatus.*

Compounds **1** and **2** were with comparable polarity and obtained as an inseparable mixture. The ESIMS (positive mode) showed molecular clusters at *m/z* 423 $[M+Na]^+$ and 439 $[M+K]^+$ indicating a molecular mass of 400 for both compounds. The peak at 407 $[M+Na-16]^+$ due to the elimination of oxygen from the cluster ion indicated the peroxide nature of **1** and **2**. The ^1H (experimental) and ^{13}C NMR (Table I) data of **1** and **2** showed that they were derivatives of the main sesquiterpenoid constituent in the plant α-bisabolol fucopyranoside (**5**) containing a bisabolane skeleton, a fucoside moiety and a different side chain. Moreover, **1** appeared to be an epimeric mixture at C-10. The structures of **1** and **2** were elucidated by 2D NMR COSY, HMQC and HMBC spectra. The characteristic signals for the side chain of **1** included unsaturation at C-11 (δ_c 143.7/143.8 s) and a pair of exomethylene protons at C-12 (δ_H 4.94) corresponding to two signals in the ^{13}C spectrum at δ 113.3/113.6 t, an allylic methyl group (δ_H 1.72/1.74, s; δ_C 17.5/17.7 q) and a signal for C-10 at δ_c 89.2 d, a value typical for a hydroperoxinated carbon. The differences in the ^1H and ^{13}C NMR spectra for both isomers were too small to make conclusions about their stereochemistry. The second peroxide **2** possessed in the side chain a two-substituted double bond (δ_H 5.84 dt, J = 16.0, 8.0 Hz and 5.55 d, J = 16.0 Hz; δ_c 126.5 δ and 136.7 d, respectively) and a deshielded carbon signal at δ 81.4 s, consistent with a hydroperoxide group at the position C-11. The coupling constants $^3J_{H9\text{-}H10}$ (16.0 Hz) in **2** indicated *trans* configuration at the double bond.

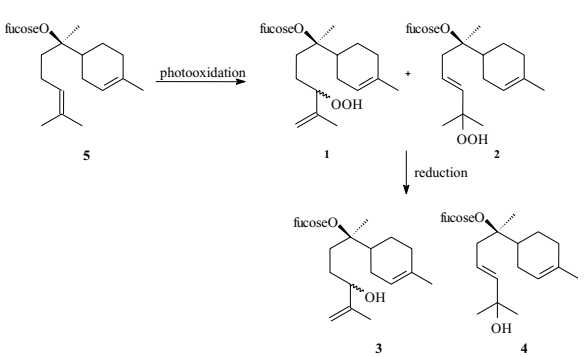
Table I. ^{13}C NMR spectral data for compounds **1–5** in $CDCl_3$.

C	**1/1′**[a]	**2**	**3/3′**[a]	**4**	**5**
1	27.1 t	27.1 t	28.0/28.5 t	26.9 t	26.8 t
2	120.3 d	120.3 d	120.3 d	120.2 d	120.5 d
3	134.4 s	134.4 s	134.5 s	134.1 s	134.3 s
4	31.9 t	31.9 t	30.9 t	30.6 t	30.9 t
5	23.5 t	23.5 t	23.5 t	22.4 t	23.4 t
6	41.4[b] d	41.6[b] d	41.0/41.1 d	41.4 d	40.9 d
7	82.1 s	82.1 s	82.2/82.0 s	81.7 s	81.8 s
8	32.4 t	40.3 t	33.7 t	39.8 t	37.7 t
9	23.5 t	126.5 d	27.2/27.0 t	122.2 d	21.6 t
10	89.2 d	136.7 d	75.6 d	140.3 d	124.8 d
11	143.7/143.8 s	81.4 s	147.5 s	70.4 s	131.0 s
12	113.3/113.6 t	24.4[d] q	110.4/110.8 t	29.4 q	17.7 q
13	17.5/17.7 q	24.7[d] q	17.9/18.1 q	29.4q	25.6 q
14	19.7[c] q	19.3[c] q	19.4/19.6 q	19.4 q	20.1 q
15	23.4 q	23.4 q	23.4 q	23.1 q	23.3 q
1′	97.3 d	97.3 d	96.9/ 97.0 d	97.0 d	97.0 d
2′	71.7 d	71.7 d	71.6 d	71.2 d	71.5 d
3′	71.7 d	71.7 d	71.8 d	71.2 d	71.7 d
4′	74.1 d	74.1 d	74.1 d	73.8 d	74.3 d
5′	70.3 d	70.3 d	70.4 d	69.9 d	70.2 d
6′	16.5 q	16.5 q	16.6 q	16.2 q	16.5 q

[a] Obtained as a mixture of isomers at C-10.
[b–d] Interchangeable signals.

The aglycones of **1** and **2** were isolated previously from *Schistostephium crategifolium* (Bohlmann *et al.*, 1983) and *Achillea odorata* (Barrero *et al.*, 1990) but only scarce ^1H NMR data were reported for them (Bohlmann *et al.*, 1983). In addition, the chemical shifts for the side chain showed a correspondence with those of the bisabolane hydroperoxides from *Rosa rugosa* (Hashidoko *et al.*, 1991) and *Alpina densibracteata* (Zingiberaceae) (Sy and Brown, 1997).

Finally, the structures were confirmed by chemical transformation of the main sesquiterpenoid fucoside **5**, which was photooxidized to yield a mixture of hydroperoxides (Scheme 1). They were proved to be identical with **1** and **2** on the basis of the ^1H and ^{13}C NMR data. Further reduction of the reaction mixture yielded the corresponding alcohols **3** and **4**. Previously, Feliciano *et al.* (1990a) performed photooxidation of the triacetate of **5** to obtain the acetates of **1** and **2**, which were further



Scheme 1.

reduced to acetates of the alcohols **3** and **4**. However, no spectral data were reported for the peroxide acetates of **1** and **2**. Based on the above data **1** and **2** are deduced to be 10-hydroperoxy-bisabola-2,11-diene 7-*O*-*β*-D-fucopyranoside and 11-hydroperoxy-bisabola-2,9-diene 7-*O*-*β*-D-fucopyranoside. The isolated hydroperoxides are probably derived from **5**, but we suggest them being metabolites of *C. lanatus* and not artefacts, because they were found in fresh leaves.

In addition to the bisabolane hydroperoxides, another two compounds **3** and **4** were also obtained. The NMR data (Table I and Experimental) were indicative of the alcoholic equivalent of the hydroperoxides **1** and **2**. Both compounds gave similar ESIMS spectra with clusters at *m/z* 407 $[M+Na]^+$ and 423 $[M+K]^+$and protonated molecular ions at *m/z* 385 $[M+H]^+$. The NMR spectral data showed similarity to those of **1** and **2**. Some differences typical for alcohol functions rather than peroxide ones (Appendino *et al.*, 1985; Sy and Brown, 1997) were observed. Thus, the ^{13}C chemical shifts of compound **3** at the C-10 position (including the neighbouring positions) were consistent with a 10-OH group (C-10: δ_c 75.6 d; C-11: 147.5 s; C-12: 110.4/110.8 t) and for **4** with a 11-OH group (C-9: δ_c 122.2 d; C-10: 140.3 d; C-11: 70.4 d; C-12: 29.4 q), respectively. Compound **3**, like **1**, appeared to be a mixture of epimers at C-10.

The NMR data of the aglycone part of **3** and **4** showed resemblance with the isolated from *Achillea odorata* 2,11-bisaboladiene-7,10-diol and 2,9-bisaboladiene-7,11-diol (Barrero *et al.*, 1990) and the NMR data of the side chain, with those of 7,11-dihydroxy-2,11-bisaboladiene-15-oic acid methyl ester and 7,10-dihydroxy-2,11-bisaboladiene-15-oic acid methyl ester from *Rosa rugosa* (Hashidoko *et al.*, 1993).

Furthermore as stated above, **1** and **2** by reduction with NaI afforded alcohols, which were proved to be identical with **3** and **4** (Scheme I). Therefore, the structures of **3** and **4** were elucidated as 10-hydroxy-bisabola-2,11-diene 7-*O*-*β*-D-fucopyranoside and 11-hydroxy-bisabola-2,9-diene 7-*O*-*β*-D-fucopyranoside.

Unexpectedly, compound **6** was assigned as the iridoid glucoside, asperuloside. Until recently, the Asteraceae were considered to lack iridoids. However, Changzeng and Dequan (1997) isolated a secoiridoid from *Aster auriculatus* and now asperuloside is isolated from *Carthamus lanatus.* Grayer *et al.* (1999) assumed that the gene to produce iridoids is latent but not lost in the Asteraceae and could be switched on if it is necessary or by chance. We presume that the iridoid metabolic pathway still exists in the representatives of the family resulting in production of compounds in very small amounts, which are difficult to be detected. Apparently, most of the available isoprane precursors are used in the synthesis of other terpenoids (sesquiterpenoids) with a larger potential as protective substances in the plants.

Biological activity

The aglycone of **5**, *α*-bisabolol, is a well-known bioactive compound with anti-inflammatory, bactericidal and anti-mycotic properties (Harborne *et al.*, 1999). To our knowledge no data are reported for *α*-bisabolol *β*-D-fucopyranoside (**5**) which appears as the main sesquiterpene glycoside of *C. lanatus.*

Table II. Antimicrobial activity and cytotoxicity of *α*-bisabolol *β*-D-fucopyranoside (**5**)[a].

Sample	Antimicrobial activity			Cytotoxycity
	Staphylococcus aureus	*Escherichia coli*	*Candida albicans*	LD_{50} [*μ*M]
	Zone of inhibition in diameter [mm]			
5	38.7 ± 1.1	–[b]	–	0.0760 ± 0.0288
Reference[c]	28.0 ± 1.0	–	–	0.0025 ± 0.0003

[a] Results are the mean of three replications.
[b] –: no activity (diameter of the inhibitory zone less than 10 mm means absence of activity).
[c] Reference: streptomycin for the antimicrobial activity; caffeic acid phenethyl ester (CAPE) for the cytotoxicity.

5 was studied for antibacterial and antifungal activity by the modified disk diffusion method (Kujumgiev *et al.*, 1993) The Gram-positive bacteria *Staphylococcus aureus*, the Gram-negative bacteria *Escherichia coli* and the fungus *Candida albicans* were used as test microorganisms. Action of significance against *S. aureus* (38.7 ± 1.1) was detected (see Table II). No activity against *E. coli* and *C. albicans* was shown. The cytotoxicity of **5** was investigated by the *Artemia salina* assay (Solis e*t al.*, 1993) and considerable activity was evaluated (LD_{50} 0.0760 ± 0.0288 μM, 27.97 ± 10.67 μg/ml).

The pure α-bisabolol β-D-fucopyranoside (**5**) showed significantly higher antimicrobial and cytotoxic activity than the previously studied diethyl ether fraction of the methanol extract (Taskova *et al.*, 2002), where **5** is the main constituent.

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