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FUROCOUMARIN GLUCOSIDES OF *ANGELICA ARCHANGELICA* SUBSPECIES *LITORALIS*

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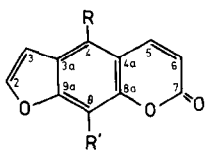
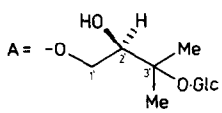
Key Word Index—*Angelica archangelica* subsp. *litoralis*; Umbelliferae; psoralens; furocoumarins; furocoumarin glycosides; ^{13}C NMR.

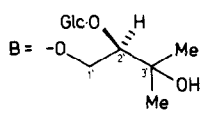
Abstract—From the roots of *Angelica archangelica* subsp. *litoralis* three new furocoumarin glycosides, *tert.* *O*-β-D-glucopyranosyl-(*R*)-byakangelicin, *sec.*-*O*-β-D-glucopyranosyl-(*R*)-byakangelicin and *tert.*-*O*-β-D-glucopyranosyl-(*R*)-isobyakangelicin were isolated and their structures established mainly by spectroscopic methods. Additionally, *tert.*-*O*-β-D-glucopyranosyl-(*R*)-heraclenol was obtained and characterized.

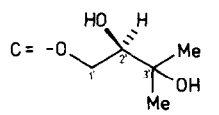
INTRODUCTION

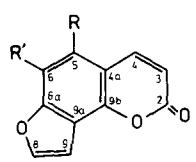
Previously we have reported on the isolation and structure elucidation of dihydrofurocoumarin glycosides from *Angelica archangelica* subsp. *litoralis* [1]. Examination of a remaining fraction of yellow fluorescent glycosides from this plant and careful separations by reversed phase HPLC have now led to the isolation of *tert.*-*O*-β-D-glucopyranosyl-(*R*)-heraclenol, (**1**) and three new furocoumarin glycosides (**2**–**4**) structurally related to **1**.











1	R = H	R' = A
2	R = OMe	R' = A
3	R = OMe	R' = B
4	R = A	R' = OMe
5	R = H	R' = OMe
6	R = OMe	R' = H
7	R = OMe	R' = OMe
11	R = H	R' = C
12	R = OMe	R' = C
13	R = C	R' = OMe
14	R = C	R' = H
8	R = H	R' = OMe
9	R = OMe	R' = H
10	R = OMe	R' = OMe

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RESULTS AND DISCUSSION

D-Glucose was the only sugar liberated by hydrolysis of the four glycosides, **1**–**4**. Their strong yellow fluorescence, and signals observed in the aromatic region of their ^{1}H NMR spectra were typical of furocoumarins [2]. The shapes of their UV curves indicated 9-oxygenated and 4,9-dioxygenated psoralen skeletons [3], and this was confirmed by comparison of ^{13}C NMR data of the glycosides with those of suitable linear and angular furocoumarin model compounds (Table 1). Assigned ^{13}C NMR data of some of these models (**5**–**7**) have been reported previously [4]. Data of other models (**8**–**10**) were obtained during this study (see Experimental). Assignment of all signals in the ^{1}H NMR spectra (DMSO-d_6 solution) of **1**–**4** was possible by consideration of the multiplicities of hydroxyl signals, by acid decoupling of these signals and by supplementary double resonance experimentation (Table 2). In all cases the δ-values and especially the coupling patterns observed for sugar proton signals were found to be typical of β-D-glucopyranosides. For each of the four glycosides, the presence of an aromatic 2,3-dioxygenated isopentyloxy substituent also was indicated by characteristic AMX patterns in the region δ 3.8–4.7 together with pairs of *gem*-dimethyl singlets near δ 1.2.

The site of sugar attachment in these modified prenyloxy side chains was defined in consequence of the assignment of all hydroxyl resonances. Furthermore, the spectra of **2**–**4** indicated the presence of aromatic methoxy substituents.

The evidence presented above defined the constitutions of all glycosides as depicted, except for an uncertainty left in the case of glycosides **2**–**4** as to the relative placement of their C-4 and C-9 substituents. This remaining problem was solved by NOE experiments. Thus, in the case of **2** and **3** the clear NOE observed for H-3 (13 and 10%) and for H-5 (both 2%) upon irradiation of their methoxy signals at δ 4.16, is concordant only with placement of the methoxy groups at C-4 in these two compounds. Conversely, in glycoside **4**, it is the modified prenyloxy group which is situated at C-4, because irradiation of the

Table 1. ^{13}C NMR spectra (67.9 MHz in DMSO-d_6, 30°, TMS as int. standard)

	1	2	3	4	5	7
C-2	147.9	146.2	146.2	146.3	147.8	146.3
C-3	107.1	105.4	105.6	105.5	107.1	105.7
C-3_a	125.9	114.5	114.4	115.8	126.0	114.4
C-4	113.8	144.1	144.1	143.8	113.9	144.3
C-4_a	116.5	106.9	106.8	107.9	116.4	106.8
C-5	145.4	139.6	139.6	140.2	145.3	139.7
C-6	114.2	112.5	112.5	112.4	114.2	112.5
C-7	160.0	159.5	159.4	159.6	159.8	159.6
C-8_a	142.7	143.2	142.9	142.8	142.5	143.1
C-9	131.6	126.8	126.4	127.5	131.9	127.2
C-9_a	147.2	149.6	149.2	149.0	147.0	149.5
C-1′	76.7*	76.5*	76.6*	76.6	—	—
C-2′	76.8*	76.7*	82.7	76.6	—	—
C-3′	78.2	78.1	76.4*	77.9	—	—
Me	23.8	23.5	27.1	24.3	—	—
	21.6	21.5	25.2	20.9	—	—
MeO	—	60.8†	60.8†	61.2	61.0	61.3
						60.8
Glucose						
C-1″	96.8	96.6	101.8	96.8	—	—
C-2″	73.8	73.6	73.7	73.6	—	—
C-3″	75.2†	75.3‡	75.4	75.5	—	—
C-4″	70.3	70.2	70.2	70.2	—	—
C-5″	75.1†	75.0‡	75.4	74.9	—	—
C-6″	61.2	61.1†	61.2†	61.2	—	—

*,†,‡Assignments with similar signs may be interchanged.

signal, δ 4.68, arising from one of its C-1′ protons effected NOE of H-3 (3%), and because no NOE was observed upon irradiation of the methoxy signal at δ 4.03. It may be noted, that the distinctly different δ-values, 4.16 and 4.03, observed for OMe-4 and OMe-9, respectively, in the spectra of **2**–**4**, (2% in DMSO-d_6), are observed also in isopimpinellin, **7**, (checked by NOE). Thus, a simple basis for differentiation between other 4-oxygenated 9-methoxypsoralens and 9-oxygenated 4-methoxypsoralens appears to be provided.

As all four glycosides provided dextrorotatory aglycones upon enzymic hydrolysis, the chirality, *R*, may tentatively be assigned to their hemiterpenoid side chains by optical comparison with (+)-(*R*)-oxypeucedanin hydrate, (**14**) [5]. Accordingly, **1** is the known compound *tert.*-*O*-β-D-glucopyranosyl-(*R*)-heraclenol [6, 7], the spectral data of which are tabulated here for comparison, and because those reported earlier are very sparse. The glycosides **2** and **3** are the previously unknown *tert.*-*O*- and *sec.*-*O*-β-D-glycopyranosyl-(*R*)-byakangelicin, respectively. The glycoside **4** and its aglycone **13** are both new. In anticipation, however, of the natural occurrence of **13**, its racemic modification was earlier synthesized and named (±)-isobyakangelicin [8]. Thus, **4** is *tert.*-*O*-β-D-glucopyranosyl-(*R*)-isobyakangelicin.

EXPERIMENTAL

D-Glucose was identified by TLC and by the D-glucose oxidase test.

Extraction and isolation. Extraction of dried roots (1350 g) of *A. archangelica* subsp. *litoralis* (Fr.) Thell. and gross fractio-

Table 2. ^1H NMR spectra (270 MHz in DMSO-d_6, 30°, TMS as int. standard)

	1	2	3	4
H-2	8.14*d* (2.2)	8.08*d* (2.4)	8.08*d* (2.4)	8.06*d* (1.8)
H-3	7.10*d* (2.2)	7.36*d* (2.4)	7.36*d* (2.4)	7.31*d* (1.8)
H-4	7.67*s*	—	—	—
H-5	8.15*d* (9.4)	8.19*d* (9.8)	8.19*d* (9.8)	8.34*d* (9.8)
H-6	6.44*d* (9.4)	6.34*d* (9.8)	6.34*d* (9.8)	6.36*d* (9.8)
H-$1'_a$	4.60*dd* (10.3, 2.3)	4.43*dd* (10.4, 2.8)	4.67*dd* (10.5, 3.2)	4.68*dd* (9.8, 1.3)
H-$1'_b$	4.40*m*	4.19*dd* (10.4, 7.6)	4.34*dd* (10.5, 6.0)	4.11*dd* (9.8, 8.6)
H-2′	3.87*dd* (7.4, 2.3)	3.87*dd* (7.6, 2.8)	3.92*dd* (6.0, 3.2)	3.84*dd* (8.6, 1.3)
Me	1.22*s*	1.22*s*	1.24*s*	1.22*s*
	1.21*s*	1.19*s*	1.15*s*	1.19*s*
MeO	—	4.16*s*	4.16*s*	4.03*s*
OH-2′	5.22*d* (3.2)	4.90*d* (4.6)	—	5.19*d* (5.5)
OH-3′	—	—	4.35*s*	—
Glucose				
H-1″	4.40*d* (7.9)	4.41*d* (8.0)	4.70*d* (7.6)	4.40*d* (7.9)
H-2″	2.91*t* (8.5)	2.91*t* (8.0)	2.98*t* (7.8)	2.92*t* (8.1)
H-3″	3.16*t* (8.8)	3.17*t* (8.5)	3.18*t* (8.9)	3.17*t* (8.8)
H-4″	3.04*t* (8.8)	3.03*t* (8.7)	3.07*t* (8.3)	3.05*t* (8.4)
H-5″	3.12*m*	3.13*m*	3.16*m*	3.12*m*
H-$6''_a$	3.61*dd* (11.5, 1.8)	3.61*dd* (11.4, 1.9)	3.65*dd* (11.2, 1.6)	3.62*dd* (11.5, 1.7)
H-$6''_b$	3.39*dd* (11.5, 5.8)	3.40*dd* (11.4, 5.6)	3.44*dd* (11.2, 5.1)	3.37*dd* (11.5, 5.7)
OH-2″	5.01 *d* (4.7)	5.13*d* (4.4)	4.54*d* (3.7)	5.08*d* (4.4)
OH-3″	4.93*d* (4.4)	4.86*d* (5.0)	4.83*d* (4.7)	4.87*d* (4.8)
OH-4″	4.88*d* (4.8)	4.83*d* (4.5)	4.82*d* (4.9)	4.83*d* (4.8)
OH-6″	4.40*m*	4.30*t* (5.4)	4.31*t* (5.5)	4.28*t* (4.8)

Except for hydroxyl signals, multiplicities are for acid decoupled spectra (1% CF_3COOD added). Figures in parentheses are coupling constants in Hz.

nations leading to a fraction, B (0.7 g), containing yellow fluorescent glycosides were described earlier [1]. Subsequent fractionation of B was by reversed phase HPLC on a Spherisorb ODS column (7 μm, 0.8 i.d. × 25 cm) with eluent A, (H_2O–MeOH–HOAc, 72:28:1), stepwise changed to eluent B, (H_2O–MeOH–HOAc, 60:40:1) for elution of late peaks. B (30 mg) dissolved in 100 μl of eluent, could be separated for each injection. Appropriate pooled fractions upon rechromatography afforded **1** (35 mg), **2** (9 mg), **3** (14 mg) and **4** (21 mg), all except **4** crystalline upon removal of solvent. In eluent A, **1**–**4** exhibited capacity ratios, $k' = 11$, 19, 36 and 13, respectively.

tert.-*O*-β-D-*Glucopyranosyl*-(R)-*heraclenol* (**1**). $[\alpha]_D^{25} + 4°$ (H_2O; *c* 0.1); [lit. [6]; $[\alpha]_D^{25} + 9°$ (in H_2O)]; UV λ_{max}^{MeOH} nm (log ε): 220 (4.40), 249 (4.37), 263 (sh) (4.14), 300 (4.07), no NaOMe shift; *IR* ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1690 (C=O), 1586 and 1470 (aromatic).

tert.-*O*-β-D-*Glucopyranosyl*-(R)-*byakangelicin* (**2**). Mp 170–173°; $[\alpha]_D^{25} - 8°$ (H_2O; *c* 0.1); UV λ_{max}^{MeOH} nm (log ε): 228 (4.34), 242 (4.19), 250 (4.19), 272 (4.30), 3.15 (4.11), no NaOMe shift; *IR* ν_{max}^{KBr} cm^{-1}: 3300–3400 (*OH*), 1710 (*C*–*O*), 1590 and 1480 (aromatic).

sec.-*O*-β-D-*Glucopyranosyl*-(R)-*byakangelicin* (**3**). MP 111–114°; $[\alpha]_D^{25} - 15°$ (MeOH; *c* 0.1); UV λ_{max}^{MeOH} nm (log ε): 228 (4.34), 242 (4.21), 250 (4.21), 273 (4.29), 3.14 (4.11), no NaOMe shift; IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 1710 (C=O), 1585 and 1470 (aromatic).

tert.-*O*-β-D-*Glucopyranosyl*-(R)-*isobyakangelicin* (**4**). Noncrystalline; $[\alpha]_D^{25} + 29°$ (MeOH; *c* 0.09); UV λ_{max}^{MeOH} nm (log ε): 227 (4.31), 242 (4.18), 251 (4.15), 271 (4.28), 310 (4.05), no NaOMe shift; IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 1708 (C=O), 1582 and 1480 (aromatic).

Enzymic hydrolysis of **1**–**4**. Performed by the procedure described earlier [1]. The resultant aglycones, **11**–**13** described below, were purified by CC on Si gel (CH_2Cl_2–EtOAc–*tert*.BuOH, 82:15:3).

(R)-*Heraclenol* (**11**). Mp 115.0–116.5°; $[\alpha]_D^{23} + 16°$, $[\alpha]_{436}^{23} + 33°$ (pyridine; *c* 0.2) [lit. [7] mp. 117–118°; $[\alpha]_D^{32} + 16.5°$ (pyridine)]; ^{1}H NMR (90 MHz, δ in $CDCl_3$, TMS int. standard): 7.78 (1H, *d*, $J = 9.7$ Hz, H-5), 7.70 (1H, *d*, $J = 2.2$ Hz, H-2), 7.40 (1H, *s*, H-4), 6.84 (1H, *d*, $J = 2.2$ Hz, H-3), 6.38 (1H, *d*, $J = 9.7$ Hz, H-6), 4.77 (1H, *dd*, $J = 10.1$, 2.9 Hz, H-1′$_a$), 4.41 (1H, *dd*, $J = 10.1$, 7.7 Hz, H-1′$_b$), 3.86 (1H, *dd*, $J = 7.7$, 2.9 Hz, H-2′), 1.34 (3H, *s*, Me), 1.30 (3H, *s*, Me).

(R)-*Byakangelicin* (**12**). Mp 124.5–125.5°, $[\alpha]_D^{23} + 10°$, $[\alpha]_{426}^{23} + 30°$ (pyridine; *c* 0.05) [lit. [9] mp 117–118°; $[\alpha]_D^{25} + 24.62°$ (pyridine)]; ^{1}H NMR (270 MHz, δ in $CDCl_3$, TMS int. standard): 8.13 (1H, *d*, $J = 9.8$ Hz, H-5), 7.64 (1H, *d*, $J = 2.3$ Hz, H-2), 7.02 (1H, *d*, $J = 2.3$ Hz, H-3), 6.30 (1H, *d*, $J = 9.8$ Hz, H-6), 4.60 (1H, *dd*, $J = 10.2$, 2.7 Hz, H-1′$_a$), 4.28 (1H, *dd*, $J = 10.2$, 7.8 Hz, H-1′$_b$), 4.19 (3H, *s*, OMe), 3.84 (1H, *m*, H-2′), 1.33 (3H, *s*, Me), 1.29 (3H, *s*, Me).

(R)-*Isobyakangelicin* (**13**). Mp 132.5–133.0°, $[\alpha]_D^{23} + 16°$, $[\alpha]_{436}^{23} + 39°$ (pyridine; *c* 0.1); ^{1}H NMR (270 MHz, δ in $CDCl_3$, TMS int. standard): 8.16 (1H, *d*, $J = 9.8$ Hz, H-5), 7.64 (1H, *d*, $J = 2.4$ Hz, H-2), 6.98 (1H, *d*, $J = 2.4$ Hz, H-3), 6.33 (1H, *d*, $J = 9.8$ Hz, H-6), 4.36 (1H, *dd*, $J = 9.9$, 3.1 Hz, H-1′$_a$), 4.34 (1H, *dd*, $J = 9.9$, 7.6 Hz, H-1′$_b$), 4.19 (3H, *s*, OMe), 3.89 (1H, *m*, H-2′), 1.35 (3H, *s*, Me), 1.30 (3H, *s*, Me).

^{13}C *NMR data of furocoumarin models*, **8**–**10**. These data, recorded below, were obtained from proton noise decoupled spectra. They were assigned by comparison with angelicin [10] and by consideration of line intensities as dependent on pulse delay time.

Sphondin (**8**). ^{13}C NMR (67.9 MHz, δ in DMSO-d_6, 30°, TMS int. standard) 160.1 (C-2), 147.4 (C-8), 146.1 (C-6$_a$), 145.3 (C-4), 142.5 (C-6 or C-9$_b$), 142.3 (C-9$_b$ or C-6), 117.7 (C-9$_a$), 114.1 (C-3), 113.8 (C-4$_a$), 104.8 (C-5), 104.2 (C-9), 56.4 (OMe).

Isobergapten (**9**). ^{13}C NMR (67.9 MHz, δ in $CDCl_3$, TMS int. standard): 160.8 (C-2), 157.8 (C-6$_a$), 154.1 (C-5), 148.6 (C-9$_b$), 144.2 (C-8), 139.7 (C-4), 112.0 (C-3), 109.9 (C-9$_a$), 105.7 (C-4$_a$), 103.8 (C-9), 90.4 (C-6), 56.2 (OMe).

Pimpinellin (**10**). ^{13}C NMR (67.9 MHz, δ in DMSO-d_6, 30°, TMS int. standard): 159.5 (C-2), 149.1 (C-6$_a$), 146.9 (C-8), 144.2 (C-9$_b$), 142.6 (C-5), 140.0 (C-4), 134.6 (C-6), 113.7 (C-3), 113.4 (C-9$_a$), 109.0 (C-4$_a$), 103.8 (C-9), 62.3 (OMe), 61.0 (OMe).

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