Two New Guaiane-Type Sesquiterpene Glycosides from the Fruits of *Daucus carota* L.

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Two new guaiane-type sesquiterpene glycosides, 11-*O*-acetyl-torilolone 8-*O*-*β*-D-glucopyranoside (1) and 1*β*-hydroxytorilolone 11-*O*-*β*-D-glucopyranoside (2), were isolated from the fruits of *Daucus carota* L. Their chemical structures were elucidated on the basis of MS, NMR spectroscopic analyses coupled with chemical degradation.

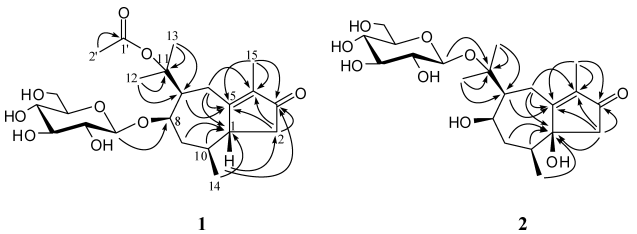
Key words *Daucus carota*; Umbelliferae; sesquiterpene glycoside; glycoside

Daucus carota L. (Umbelliferae) is extensively distributed throughout the world, which fruits (common name: wild carrot fruits) are widely used as a traditional Chinese medicine for the treatment of ancylostomiasis, dropsy, chronic kidney diseases and bladder afflictions, *etc.*[1] Pharmacological studies on the plant of *D. carota* have demonstrated antibacterial,[2] antifungal,[3] anthelmintic, hepatoprotective[4] and cytotoxic[5] activities. The previous research on chemical constituents of *D. carota* has carried out the presence of sesquiterpenes,[6—8] chromones,[9] flavonoids,[10,11] coumarins[6,12] and anthocyanins.[13,14] As a part of our ongoing investigation on bioactive constituents,[15—18] we initiated a phytochemical investigation on the fruits of *D. carota* L., which resulted in the isolation of two new guaiane-type sesquiterpene glycosides, 11-*O*-acetyl-torilolone 8-*O*-*β*-D-glucopyranoside (**1**) and 1*β*-hydroxytorilolone 11-*O*-*β*-D-glucopyranoside (**2**). In this paper, we report the isolation and structure elucidation of them.

Results and Discussion

A 95% EtOH extract of the fruits of *D. carota* L. was suspended in H_2O and then partitioned successively with petroleum ether, $CHCl_3$, EtOAc and *n*-BuOH. The *n*-BuOH soluble fraction, on chromatographic separation over silica gel column chromatography (CC), followed by Sephadex LH-20 CC and HPLC purification, afforded two new compounds **1** and **2** (Fig. 1). They were completely established by UV, mass and NMR spectroscopy including 1D and 2D NMR techniques.

Compound **1** was obtained as an amorphous powder, $[\alpha]_D^{22}$ −25.4° (c=1.0, MeOH). The molecular formula was established as $C_{23}H_{36}O_9$ by positive-ion HR-electrospray ionization (ESI)-MS (m/z 479.2243 $[M+Na]^+$). Its UV spectrum was characteristic as an *α*,*β*-unsaturated ketone with an absorption maximum at 244 nm. The ^{1}H- and ^{13}C-NMR spectra of **1** displayed the presence of an acetoxyl group (δ_H 2.02; δ_C 22.9, 172.6). In addition, the ^{13}C-NMR data (Table 1) combined with analysis of the heteronuclear multiple quantum coherence (HMQC) spectrum revealed the remaining 21 carbon signals due to four quaternary carbons, nine methines, four methylenes and four methyls, of which 15 were assigned to the aglycone part including one ketonic carbonyl carbon at δ_C 212.4 along with two olefinic carbons at δ_C 179.5, 137.1 and the remaining 6 were ascribed to a glucopyranosyl unit at δ_C 63.1—104.9. Enzymatic hydrolysis of **1**, in addition to the aglycone (**1a**), it also gave D-glucose as a component sugar, which was confirmed by GC-MS analysis following conversion to the trimethylsilylthiazolidine derivatives.[19] The ^{1}H-NMR spectrum of **1** exhibited a set of signals assignable to a *β*-glucopyranosyl moiety with an anomeric proton resonanced at δ_H 4.32 (d, J=7.5 Hz). The HMQC spectrum of the aglycone moiety showed four methyl proton signals [δ_H 1.66 (d, J=1.2 Hz), 1.59 (s), 1.51 (s) and 1.04 (d, J=6.5 Hz)] and one carbinylic proton signal [δ_H 4.04 (ddd, J=6.0, 6.0, 3.0 Hz)], coupled with the corresponding carbon signals at δ_C 7.9, 23.6, 24.9, 23.4 and 80.8 as well as one additional oxygenated quaternary carbon signal at δ_C 86.5. The partial structure of C6–C7–C8–C9–C10(–C14)–C1–C2 was deduced from the ^{1}H–^{1}H correlation spectroscopy (COSY) and HMQC spectral data. An *α*,*β*-unsaturated cyclopentenone unit bearing one methyl group was confirmed by the heteronuclear multiple bond connectivity (HMBC) correlations of H-1 (δ_H 2.36)/C-2 (δ_C 43.1) and C-3 (δ_C 212.4), H_2-2 (δ_H 2.57, 2.05)/C-3, C-4 (δ_C 137.1) and C-5 (δ_C 179.5) as well as Me-15 (δ_H 1.66)/C-3, C-4 and C-5. The presence and location of the isopropyl group at C-7 was elucidated by the HMBC correlations between Me-12 (δ_H 1.59)/C-7 (δ_C 53.0), C-11 (δ_C 86.5) and Me-13 (δ_H 1.51)/C-7, C-11. The connectivity of the two rings was indicated by the HMBC correlations from Me-14 (δ_H 1.04) to C-1 (δ_C 51.7) and H-10 (δ_H 1.77) to C-1, along with H_2-6 (δ_H 2.89, 2.24) to C-1, C-4 and C-5. The correlations between H-8 (δ_H 4.04) and C-1′ (δ_C 172.6) through $^3J_{CH}$ was not observed, indicating the acetoxyl group and C-11 was connected through an oxygen atom. The *β*-D-glucopyranosyl moiety linked to C-8 in **1** was deduced from the HMBC correlation between Glc-H-1 (δ_H 4.32) and



1 **2**

Fig. 1. The Key HMBC (H→C) Correlations of **1** and **2**

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Table 1. ^{1}H- and ^{13}C-NMR Data of **1**, **1b** and **2** (δ in ppm, J in Hz)

Position		**1**[a]		**1**[b]	**1b**[b]	**2**[a]		**2**[b]
		δ_H[c]	δ_C[d]	δ_C[d]	δ_C[d]	δ_H[d]	δ_C[d]	δ_C[d]
1	β	2.36 (ddd, 10.5, 6.0, 1.5)	51.7	50.3	52.0		80.8	79.4
2	α	2.05 (dd, 19.0, 1.5)	43.1	42.0	41.7	2.54 (d, 18.1)	50.6	50.5
	β	2.57 (dd, 19.0, 6.0)				2.35 (d, 18.1)		
3			212.4	208.0	207.8		210.0	206.8
4			137.1	135.6	134.0		135.9	134.2
5			179.5	175.5	177.0		178.2	176.3
6	α	2.89 (dd, 13.5, 5.0)	29.3	28.3	25.0	2.88 (d, 13.8)	23.1	22.5
	β	2.24 (t, 13.5)				2.60 (dd, 13.8, 11.1)		
7	α	2.26 (ddd, 13.5, 6.0, 5.0)	53.0	52.5	49.7	1.75 (ddd, 11.1, 7.0, 3.2)	51.5	51.2
8	α	4.04 (ddd, 6.0, 6.0, 3.0)	80.8	80.1	70.1	4.26 (td, 7.0, 3.2)	70.0	68.7
9	α	2.23 (ddd, 13.0, 7.0, 3.0)	40.2	39.6	44.7	1.76 (ddd, 14.8, 7.0, 3.2)	40.3	40.2
	β	1.80 (ddd, 13.0, 10.5, 6.0)				2.06 (ddd, 14.8, 9.8, 7.5)		
10	α	1.77 (m)	34.5	33.5	33.8	1.74[e]	38.7	38.0
11			86.5	85.1	73.2		82.0	80.7
12		1.59 (s)	23.6	23.2	29.0	1.40 (s)	25.2	26.6
13		1.51 (s)	24.9	24.7	29.6	1.42 (s)	25.9	24.6
14	β	1.04 (d, 6.5)	23.4	23.1	23.2	1.06 (d, 6.9)	19.3	19.4
15		1.66 (d, 1.2)	7.9	7.9	8.3	1.72 (s)	8.5	8.2
1′			172.6	170.3				
2′		2.02 (s)	22.9	22.7				
Glc-1		4.32 (d, 7.5)	104.9	105.1		4.53 (d, 7.8)	98.6	98.4
2		3.09 (dd, 9.0, 7.5)	75.4	75.3		3.14 (dd, 9.1, 7.8)	75.5	75.4
3		3.29 (t, 9.0)	78.5	78.8		3.35 (t, 9.1)	78.7	79.2
4		3.27 (t, 9.0)	71.8	71.7		3.22 (t, 9.1)	72.2	72.2
5		3.23 (ddd, 9.0, 5.0, 2.0)	78.1	78.4		3.24 (ddd, 9.1, 5.6, 2.0)	78.0	78.5
6		3.66 (dd, 11.5, 5.0)	63.1	63.1		3.53 (dd, 11.5, 5.6)	63.3	63.2
		3.84 (dd, 11.5, 2.0)				3.80 (dd, 11.5, 2.0)		

a) In CD_3OD. *b*) In C_5D_5N. *c*) At 500 MHz. *d*) At 125 MHz. *e*) Overlapped signals.

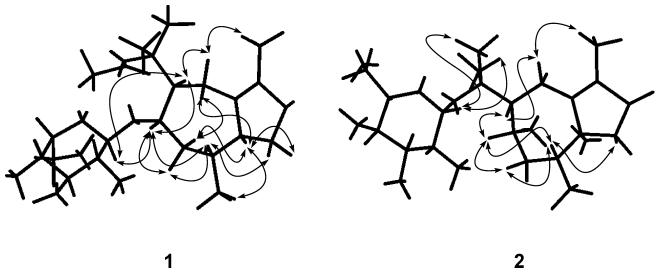

Fig. 2. The Key NOESY Correlations (H↔H) of **1** and **2**

C-8 (δ_C 80.8). Based on the above spectral data, the gross molecular structure of **1** was established. The stereochemistry of **1** was confirmed by careful analyses of nuclear Overhauser effect spectroscopy (NOESY) data and the coupling constants (Fig. 2). The coupling constants of H_β-6 in the axial orientation with H-7 and H_α-6 in the equatorial orientation with H-7 were 13.5 and 5.0 Hz, respectively, indicating the stereochemistry of H-7 was α, which was supported by the NOESY correlations between H-7 and H_α-6. The α configuration of H-8 was suggested by a small coupling constant of 6.0 Hz (H-7 with H-8) and the obvious NOESY correlations of β-D-Glc-H-1 with H-7 and H-8, H-7 with H-8 as well as H-8 with H_α-9. The orientations of H-1 and H-10 were determined to be β and α configurations on the basis of the NOESY correlations between H-1/H_β-6, H_β-9, H_β-2 and Me-14, and by comparison of the NMR data of **1** with those of similar compound published.[20] The α configuration of H-10 was also confirmed by the NOESY correlations from H_α-2 to H-10 and H_α-9 to H-10. Thus, compound **1** was an 8-epimer of 11-*O*-acetyl-8-*epi*-torilolone 8-*O*-β-D-glucopyranoside isolated from the methanolic extract of *Torillis japonica* D. C. fruit.[20] In addition, the deacetate derivative of the aglycone (**1b**) obtained using acid hydrolysis of **1**, was revealed to be torilolone by comparison of its ^{13}C-NMR data (Table 1) with those previously reported.[20] This suggestion was supported by the downfield shifts of C-6 (by −3.8 ppm), C-7 (by −5.3 ppm) and by the upfield shifts of C-12 (by +3.0 ppm), when compared with those of 8-*epi*-torilolone.[20] Based on the above results, the structure of **1** was determined as (1β,7β,8β,10β)-11-*O*-acetyl-8,11-dihydroxy-4-guaien-3-one 8-*O*-β-D-glucopyranoside, namely 11-*O*-acetyl-torilolone 8-*O*-β-D-glucopyranoside, which is a new compound.

Compound **2** was obtained as an amorphous powder, $[\alpha]_D^{22}$ −24.9° (c=0.4, MeOH). The molecular formula was determined as $C_{21}H_{34}O_9$ from the data of HR-ESI-MS (m/z 453.2078 $[M+Na]^+$). The UV spectrum showed an absorption maximum of an α,β-unsaturated ketone at 240 nm as similar as **1**. A careful analysis of their NMR spectra suggested that two compounds **1** and **2** were closely related guaiane-type sesquiterpenoids.[21—24] In comparison with **1**, the resonance signals of **2** for an acetoxy group and one methine disappeared in the ^{1}H- and ^{13}C-NMR spectra, but one more oxygenated quaternary carbon at δ_C 80.8 (C-1) appeared in the ^{13}C-NMR spectrum. In addition, the anomeric carbon at δ_C 98.6 was shifted by −6.3 ppm than that of **1**, suggesting that a β-glucopyranosyl moiety of **2** was attached to the tertiary alcohol group. Therefore, compound **2** had a similar structure as **1**, except for disappearance of an acetoxyl group assigned to C-11 and appearance of an extra hydroxy group, combined with a β-D-glucopyranosyl moiety located at dif-

ferent position compared to **1** (Fig. 1). The HMBC correlations from H_2-2 (δ_H 2.54, 2.35), H_2-6 (δ_H 2.88, 2.60), Me-14 (δ_H 1.06) and H-10 (δ_H 1.74) to C-1 (δ_C 80.8) were observed, respectively, indicating the hydroxy group was ascribed to C-1. The β-D-glucopyranosyl moiety located at C-11 in **2** was determined by the HMBC correlation between Glc-H-1 (δ_H 4.53) and C-11 (δ_C 82.0) along with the downshift anomeric carbon signal at δ_C 98.6.[20] From the above data, the gross planar structure of **2** was deduced as 1-hydroxytorilolone 11-*O*-β-D-glucopyranoside. The stereochemistry of H-7, H-8 and H-10 was determined to be the same as that of **1**, on the basis of the NOESY spectrum (Fig. 2) and coupling constants. The β-configuration of OH-1 was confirmed by the signals of Me-14 and H-10 at δ_H 1.06 and 1.74 in the ^{1}H-NMR spectrum, since the values of the chemical shifts of Me-14 and H-10 are δ_H 1.07, 1.74 for β-configuration and δ_H 0.77, 2.31 for α-orientation.[22,24] It was also supported by comparison of the optical rotation of the aglycone of **2** (**2a**, $[\alpha]_D^{22}$ −5.1°) with those of the similar compounds ($[\alpha]_D^{20}$ −13.7° for 1β-hydroxytorilin, whereas +24.4° for 1α-hydroxytorilin).[24] Thus, the structure of **2** was established as 1β-hydroxytorilolone 11-*O*-β-D-glucopyranoside, namely (1β,7β,8β,10β)-1,8,11-trihydroxy-4-guaien-3-one 11-*O*-β-D-glucopyranoside.

Experimental

General Experimental Procedures Optical rotations were measured using a Rudolph Autopol IV digital polarimeter with a 0.5 dm length cell. HR-ESI-MS was taken on a Bruker Daltonics Apex III mass spectrometer. All NMR spectra were recorded on a Bruker ARX-500 and ARX-125 MHz NMR spectrometer equipped with a CH dual 5ϕ probe. Samples were dissolved in 0.6 ml CD_3OD or C_5D_5N and transferred into a 5 mm NMR tube. All chemical shifts are expressed as δ (ppm) relative to the internal standard trimethylsilyl (TMS) (δ=0 ppm), and scalar coupling constants are reported in Hz. Silica gel (200—300 mesh, Qingdao Haiyang Chemical Co. Ltd., China), Sephadex LH-20 (Ammersham Pharmacia Biotech) and octadecyl silica (ODS) (35—50 μm, Alltech) were used for column chromatography. Preparative HPLC was performed using ODS column (Waters Sunfire ODS-C_{18}, 10 mm i.d.×250 mm).

Plant Material The fruits of *Daucus carota* L. were purchased in September 2007 from Hangzhou, Zhejiang Province, P. R. of China, and identified by one of the authors (Lin Zhang). A voucher specimen was deposited in the Herbarium of the College of Biomedical Engineering and Instrument Sciences, Zhejiang University, People's Republic of China.

Extraction and Isolation The air-dried fruits of *D. carota* L. (3 kg) were refluxed two times with 95% aqueous EtOH. The combined EtOH extracts were concentrated, suspended in H_2O, and then partitioned with petroleum ether, $CHCl_3$, EtOAc and *n*-BuOH successively to give four different polar parts. The *n*-BuOH layer (10.2 g) was subjected to silica gel CC with a gradient of $CHCl_3$/MeOH (15 : 1—8 : 1) to give eight fractions (1—8). Fraction 2 was loaded on silica gel CC with $CHCl_3$/MeOH (8 : 1) to give three fractions (A1—A3). Fraction A2 (0.35 g) was purified by Sephadex LH-20 CC with $CHCl_3$/MeOH (1 : 1), followed by silica gel CC with $CHCl_3$/$(CH_3)_2CO$ (1 : 1) to obtain **1** (9.2 mg). Fraction 5 (0.2 g) was chromatographed on silica gel CC with $CHCl_3$/MeOH (9 : 1) and then further separated by repeated HPLC purification with 20% aqueous MeOH to afford **2** (7.0 mg).

11-*O*-Acetyl-torilolone 8-*O*-β-D-Glucopyranoside (**1**): Amorphous powder; $[\alpha]_D^{22}$ −25.4° (*c*=1.0, MeOH); UV (MeOH) λ_{max}: 244 nm; ^{1}H-NMR (CD_3OD, 500 MHz) and ^{13}C-NMR (CD_3OD, 125 MHz), see Table 1; positive-ion HR-ESI-MS *m/z* 479.2243 (Calcd for $C_{23}H_{36}O_9Na$, 479.2252).

1β-Hydroxytorilolone 11-*O*-β-D-Glucopyranoside (**2**): Amorphous powder; $[\alpha]_D^{22}$ −24.9° (*c*=0.4, MeOH); UV (MeOH) λ_{max}: 240 nm; ^{1}H-NMR (CD_3OD, 500 MHz) and ^{13}C-NMR (CD_3OD, 125 MHz), see Table 1; positive-ion HR-ESI-MS *m/z* 453.2078 (Calcd for $C_{21}H_{34}O_9Na$, 453.2095).

Acid Hydrolysis and Determination of the Absolute Configuration of the Monosaccharides A solution of **1** (3.5 mg) in 1 M HCl (dioxane–H_2O, 1 : 1, 2 ml) was heated at 80 °C for 3 h under an Ar atmosphere. After dioxane was removed, the solution was extracted with EtOAc (2 ml×3) to obtain the deacetate derivative of the aglycone **1b** (1.5 mg). The H_2O layer was concentrated under reduced pressure to dryness, to give a residue of the sugar fraction. The residue was dissolved in pyridine (0.1 ml), to which 0.08 M L-cysteine methyl ester hydrochloride in pyridine (0.15 ml) was added. The mixture was kept at 60 °C for 1.5 h. After the reaction mixture was dried *in vacuo*, the residue was trimethylsilylated with 1-trimethylsilylimidazole (0.1 ml) for 2 h. The mixture was partitioned between *n*-hexane and H_2O (0.3 ml each) and then the *n*-hexane extract was analyzed by GC-MS under the following conditions: capillary column, EQUITY^{TM}-1 (30 m×0.25 mm×0.25 mm, Supelco); column temperature, 230 °C; injection temperature, 250 °C; carrier N_2 gas; detection in EI mode, ionization potential, 70 eV; ion-source temperature, 280 °C.[16,19] D-Glucose in **1** was confirmed by comparison of the retention times of its derivatives with those of standard D-glucose and L-glucose derivatives prepared in a similar way which showed retention times of 11.25 and 10.79 min, respectively. Sugar in **2** (1.0 mg) was also identified by the same method.

Enzymatic Hydrolysis A solution of **1** (3.5 mg) in 0.1 M acetate buffer (pH 4.0, 1.0 ml) was treated with naringinase (Sigma Chemical Co., 2 units), and then the reaction mixture was stirred at 40 °C for 72 h. The reaction mixture was passed through a Sep-Pak ODS cartridge (Waters) and washed with H_2O and CH_3OH to give the aglycone **1a** (1.8 mg). Through a similar procedure, enzymatic hydrolysis of **2** (3.5 mg) was carried out to afford the aglycone **2a** (1.6 mg).

(1β,7β,8β,10β)-11-*O*-Acetyl-8,11-dihydroxy-4-guaien-3-one (**1a**): Colorless oil. $[\alpha]_D^{22}$ −20.6° (*c*=0.16, $CHCl_3$: MeOH=1 : 1); positive-ion HR-ESI-MS *m/z* 317.1720 (Calcd for $C_{17}H_{26}O_4Na$, 317.1729); ^{1}H-NMR (C_5D_5N, 500 MHz) δ: 5.65 (1H, m, H-8), 3.22 (1H, d, *J*=12.5 Hz, H-6), 2.95 (1H, m, H-2), 2.88 (1H, dd, *J*=12.5, 10.0 Hz, H-6), 2.60 (1H, m, H-2), 2.29 (1H, m, H-9), 2.28 (1H, m, H-1), 2.12 (1H, m, H-9), 2.10 (3H, s, Me-1′), 2.06 (1H, m, H-7), 1.99 (3H, s, Me-15), 1.86 (1H, m, H-10), 1.52 (3H, s, Me-13), 1.48 (3H, s, Me-12), 1.19 (3H, d, *J*=7.0 Hz, Me-14); ^{13}C-NMR (C_5D_5N, 125 MHz) δ: 207.5 (C-3), 175.6 (C-5), 171.1 (C-1′), 134.8 (C-4), 73.1 (C-8), 72.0 (C-11), 51.3 (C-1), 48.7 (C-7), 41.6 (C-2), 40.9 (C-9), 33.9 (C-10), 28.6 (C-12), 27.0 (C-13), 25.9 (C-6), 23.2 (C-14), 21.5 (C-2′), 8.1 (C-15).

(1β,7β,8β,10β)-1,8,11-Trihydroxy-4-guaien-3-one (**2a**): Colorless oil. $[\alpha]_D^{22}$ −5.1° (*c*=0.14, $CHCl_3$: MeOH=1 : 4); positive-ion HR-ESI-MS *m/z* 291.1579 (Calcd for $C_{15}H_{24}O_4Na$, 291.1572); ^{1}H-NMR (C_5D_5N, 500 MHz) δ: 4.72 (1H, dt, *J*=7.1, 3.0 Hz, H-8), 3.17 (1H, dd, *J*=13.5, 10.0 Hz, H-6), 3.10 (1H, d, *J*=13.5 Hz, H-6), 2.95 (1H, m, H-9), 2.92 (1H, d, *J*=18.0 Hz, H-2), 2.79 (1H, d, *J*=18.0 Hz, H-2), 2.10 (1H, ddd, *J*=14.5, 7.1, 1.5 Hz, H-9), 1.87 (3H, s, Me-15), 1.86 (1H, m, H-10), 1.76 (3H, s, Me-13), 1.72 (1H, m, H-7), 1.62 (3H, s, Me-12), 1.34 (3H, d, *J*=7.0 Hz, Me-14); ^{13}C-NMR (C_5D_5N, 125 MHz) δ: 206.7 (C-3), 176.0 (C-5), 133.7 (C-4), 79.0 (C-1), 73.3 (C-11), 70.4 (C-8), 50.6 (C-2), 50.6 (C-7), 39.4 (C-9), 38.1 (C-10), 29.4 (C-12), 29.2 (C-13), 22.4 (C-6), 19.1 (C-14), 8.1 (C-15).

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