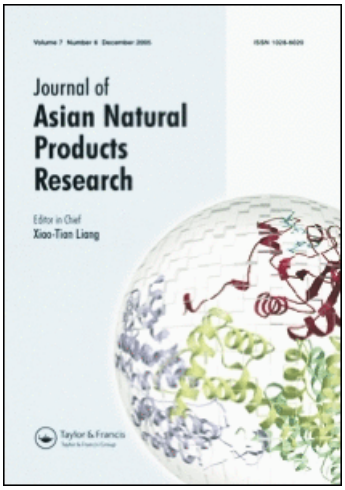

Journal of Asian Natural Products Research
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713454007

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To cite this Article Ma, Jian-Ping , Tan, Chang-Heng and Zhu, Da-Yuan(2008) 'Glycosidic constituents from *Carpesium cernuum* L.', Journal of Asian Natural Products Research, 10: 6, 565 — 569
To link to this Article: DOI: 10.1080/10286020801966724
URL: http://dx.doi.org/10.1080/10286020801966724

Journal of Asian Natural Products Research
Vol. 10, No. 6, June 2008, 565–569

Glycosidic constituents from *Carpesium cernuum* L.

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(*Received 4 April 2007; final version received 12 July 2007*)

Carpesides A (**1**) and B (**2**), two new 8-*O*-4′-neolignan glucosides, and eupatriol 9-*O*-β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranoside (**3**), one new monoterpenoid diglycoside, together with 10 known glycosidic compounds, were isolated from the aerial part of *Carpesium cernuum* L. The structures of the new glycosides are elucidated by means of chemical methods and spectroscopic studies.

Keywords: carpeside A; carpeside B; *Carpesium cernuum* L; 8-*O*-4′-neolignan glycoside; monoterpenoid glycoside

1. Introduction

The whole plant of *Carpesium cernuum* L. (Asteraceae or Compositae) has been used as Chinese folk medicine for anti-inflammation, pain relief, and detoxication.[1] Previous investigations on the title plant revealed the presence of eudesmanolides, germacranolides, and cymene derivatives.[2,3] Continuing our interest in Chinese folk herbs,[4] we investigated the chemical constituents of the title plant, leading to the isolation of 13 glycosidic compounds, including two new 8-*O*-4′-neolignan glucosides, carpesides A (**1**) and B (**2**), and one new monoterpenoid diglycoside, eupatriol 9-*O*-β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranoside (**3**). Flavonoids and 8-*O*-4′-neolignans were reported from the genus *Carpesium* for the first time. We describe herein the isolation and structural elucidation of the new glycosides **1**–**3**.

2. Results and discussion

Carpesides A (**1**) and B (**2**) have the same R_f value on TLC and the same molecular formula of $C_{26}H_{34}O_{12}$ (HRESIMS $[M + Na]^+$ at *m/z* 561.1931 for **1** and 561.1961 for **2**). The ^1H (δ 4.12, d, $J = 7.4$ Hz for **1** and δ 4.16, d, $J = 7.3$ Hz for **2**) and ^{13}C NMR (**1**: δ 101.0, 78.7, 78.4, 75.6, 72.2, 63.3; **2**: δ 101.5, 78.3, 78.3, 75.6, 72.3, 63.3) spectral data, along with acid hydrolysis and GC analysis disclosed a β-D-glucopyranosyl moiety in the molecules of both **1** and **2**.

The ^1H signals for the aglycone of **1** were attributed to two 1,3,4-trisubstituted phenyls [δ 7.11 (d, $J = 1.8$ Hz, 1H), 6.86 (dd, $J = 8.4$, 1.8 Hz, 1H), and 6.75 (d, $J = 8.4$ Hz, 1H); 6.94 (d, $J = 1.7$ Hz, 1H), 6.81 (dd, $J = 8.3$, 1.7 Hz, 1H), and 6.70 (d, $J = 8.3$ Hz, 1H)], one 1-ol-2(*E*)-propenyl [δ 6.48 (d, $J = 16.0$ Hz, 1H), 6.20 (dt, $J = 16.0$, 5.7 Hz, 1H), and 4.18 (dd, $J = 5.7$, 1.4 Hz, 2H)], two oxygenated methines [δ 5.06 (d, $J = 7.0$ Hz, 1H) and 4.43 (dt, $J = 7.0$, 4.2 Hz, 1H)], one oxygen-bearing methylene [δ 3.86 (dd, $J = 10.0$, 4.2 Hz, 1H) and 3.79 (dd, $J = 10.0$, 4.6 Hz,

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ISSN 1028-6020 print/ISSN 1477-2213 online

DOI: 10.1080/10286020801966724
http://www.informaworld.com

1H)], and two methoxyls (δ 3.77 and 3.74, each s, 3H), indicating a citrusin A-like 8-*O*-4′-neolignan glucopyranoside.[4,5] The HMBC cross-peaks of 3-OMe/C-3, 3′-OMe/C-3′, H-1a/C-7 (Figure 1) revealed the connectivities of two methoxyls with C-3 and C-3′, and the glucopyranosyloxyl with C-7, respectively. A coupling constant of 7.0 Hz between H-7 and H-8, and the negative CD absorption in the range 210–250 nm manifested the relative configuration of 7,8-*threo* and the absolute configuration of 8*R* in the molecular structure of **1**.[6] The structure of carpeside A was therefore determined to be (7*R*,8*R*)-Δ$^{7'}$-3,3′-dimethoxy-4,7,9,9′-tetrahydroxy-8-*O*-4′-neolignan-7-*O*-β-D-glucopyranoside.

The ^{1}H and ^{13}C NMR spectral data of **2** were very similar with those of **1**, except for $J_{7,8} = 4.0$ Hz for **2**, and a positive CD absorption in the range 210–250 nm, which indicated **2** to have the relative configuration of 7,8-*erythro* and the absolute configuration of 8*S*.[6] Accordingly, the stereostructure of **2** was elucidated to be (7*R*,8*S*)-Δ$^{7'}$-3,3′-dimethoxy-4,7,9,9′-tetrahydroxy-8-*O*-4′-neolignan-7-*O*-β-D-glucopyranoside.

Kraus and Spiteller reported a mixture of neolignan glucoside having the same planar structure as that of **1** and **2**.[7] Takara *et al.* also obtained a single compound of them from *Kokuto*;[8] however, their configurations of C-7 and C-8 were not defined. The reported chemical shifts of C-7 (81.6 or 81.3 ppm) and H-7 (δ 5.02, d, $J = 5.8$ or 5.05 Hz, d, $J = 5.5$ Hz) therein were obviously different from those of **1** and **2**, suggesting them to be stereoisomers of **1** and **2** at C-7.

Compound **3** was obtained as a white amorphous powder. Its HR-ESI-MS gave a molecular formula of $C_{21}H_{32}O_{12}$ ($[M + Na]^+$ at *m/z* 499.1801). The IR spectrum showed characteristic absorptions for hydroxyls (3423 cm^{-1}) and benzene ring (1626 cm^{-1}). Under acid hydrolysis and GC analysis, **3** gave D-glucose and D-apiose. The ^{1}H NMR spectrum of **3** displayed signals for anomeric protons of a β-glucopyranosyl (δ 4.28, d, $J = 8.0$ Hz) and a β-apiofuranosyl (δ 5.00, d, $J = 2.2$ Hz), one 1,3,4-trisubstituted aromatic ring [δ 7.11 (d, $J = 7.8$ Hz, 1H), 6.61 (br d, $J = 8.5$ Hz, 1H), and 6.57 (br s, 1H)], two methyls (δ 2.22 and 1.56, each s, 3H), and one isolated oxygen-bearing methylene (δ 4.17 and 3.73, d, $J = 10.8$ Hz), suggesting an eupatriol diglycoside.[9] The ^{13}C NMR spectrum exhibited a β-apiofuranosyl-(1 → 6)-β-glucopyranosyl unit as the glycosyl moiety,[4] and a downfield shift C-9 (δ 78.5 vs. 69.2 ppm) in contrast with that of eupatriol, indicating a structure of eupatriol 9-*O*-β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranoside, which was further confirmed by the HMBC correlations of the C-9/H-1a and C-6a/H-1b.

The known compounds, citrusin A (**4**),[5] (+)-angelicoidenol-2-*O*-β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranoside (**5**),[10] (3*R*,9*R*)-3-hydroxy-7,8-dihydro-β-ionyl-9-*O*-β-D-apio-

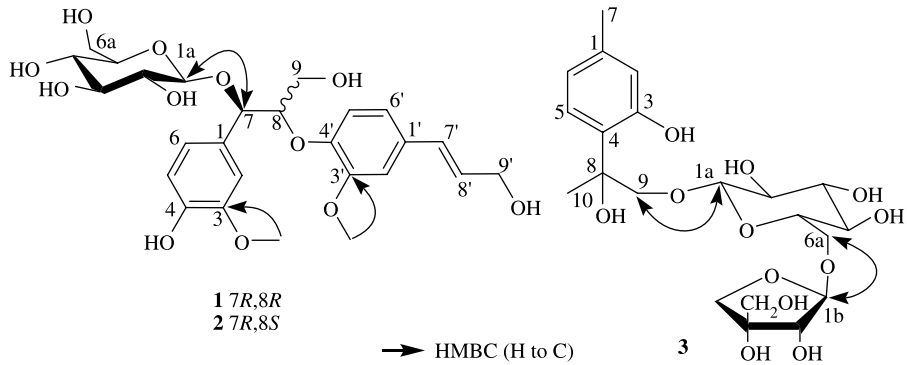

Figure 1. Structures and significant HMBC correlations of **1**–**3**.

furanosyl-(1 → 6)-β-D-glucopyranoside (**6**),[11] kaempferol-3-*O*-rutinoside (**7**),[12] luteolin-7-*O*-β-D-glucopyranoside (**8**),[13] isoquercetin (**9**),[14] kaempferol-3-*O*-β-D-glucopyranoside (**10**),[15] eugenyl-*O*-β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranoside (**11**),[16] (7*S*,7′*S*,8*S*,8′*S*)-neo-olivil-9′-*O*-β-D-glucoside (**12**),[7] and (−)-syringaresinol-4,4′-bis-*O*-β-D-glucopyranoside (**13**),[17] were identified by comparison of their ^{1}H and ^{13}C NMR, MS, and physical data with those reported in the literature.

3. Experimental

3.1 General experimental procedures

Optical rotations were measured using a Perkin–Elmer 341 polarimeter. IR spectra were recorded on a Nicolet Magna 750 FT-IR (KBr) spectrometer. ESI-MS and HR-ESI-MS data were obtained using the LCQ-Deca and Q-Tof Ultima mass spectrometers, respectively. NMR spectra were recorded on a Bruker AV500 instrument with TMS as the internal standard. Silica gel (200–300 or 400 mesh; Qingdao Haiyang, Co., China), ODS-A gel (Greenherbs Science & Technology Development Co., Ltd, Beijing, China), D-1400 macroporous resin (Yangzhou pharmaceutical factory, China), and Sephadex LH-20 (Pharmacia Biotech AB, Uppsala, Sweden) as well as precoated plates of silica gel (HSGF254) (Qingdao Haiyang Chemical Group Co., Qingdao, China) were used for column chromatography (CC) and TLC, respectively. Perkin–Elmer Sigma-115 gas chromatograph was used for GC analyses. Analytical and preparative HPLC were performed using a Varian HPLC system (pump, Prepstar SD-1; detector, UV–VIS 320; column, Merck: 5 μm, i.d. 4.6 × 250 mm and 12 μm ODS-A, i.d. 25 × 250 mm, respectively).

3.2 Plant material

The aerial part of *C. cernuum* L. was collected from Tonghai County, Yuxi, Yunnan Province, China in March 2005, and identified by Professor Da-Yuan Zhu. A voucher specimen (No. 20050305) has been deposited in the Herbarium of our institute.

3.3 Extraction and isolation

Dried snippets of *C. cernuum* L. (10 kg) were extracted with 50% EtOH for three times. After removal of the solvents by evaporation under reduced pressure, the extract was suspended in water and subjected to column chromatography (CC, macroporous resin, i.d. 10 × 80 cm, EtOH/H_2O (*v/v*) 0, 10, 30, 50, 95%) to give fractions A–E. Fraction C (30% EtOH fraction, 120 g) was separated by CC (SiO_2, $CHCl_3$/MeOH 100:0 → 0:100) to afford fractions C_1–C_{11}. Fractions C_6, C_8, and C_9 produced solids **10** (43 mg), **9** (60 mg), and **8** (50 mg), respectively. Fraction C_8 provided **3** (6 mg), **4** (10 mg), **11** (3 mg), **12** (5 mg), and **13** (6 mg) after repeated CC (1, SiO_2, $CHCl_3$/MeOH 4:1; 2, *LiChrospher Rp-18*, MeOH–H_2O 1:2; and 3, Sephadex *LH-20*, MeOH–H_2O 10:1). Compounds **1** (15 mg), **2** (24 mg), and **6** (8 mg) were obtained from fraction C_9 after CC (1, *LiChrospher Rp-18*, MeOH–H_2O 1:3; 2, Sephadex *LH-20*, MeOH–H_2O 10:1; 3, prep-HPLC, MeOH–H_2O 14:86 for **1** and **2**). Fraction C_{10} provided **5** (20 mg) and **7** (6 mg) after purification using CC (1, *LiChrospher Rp-18*, MeOH–H_2O 15:85; 2, Sephadex *LH-20*, MeOH–H_2O 10:1).

3.3.1 Carpeside A (*1*)

White amorphous powder. $[\alpha]_D^{23}$ −79 (*c* 0.24, MeOH). CD (*c* 1.05 g l^{-1}, MeOH) $\Delta\varepsilon$ (λ_{max}): 162 (203 nm), −97 (225 nm), −273 (240 nm), −136 (283 nm); IR ν_{max} KBr (cm^{-1}): 3396 (OH), 1655, 1603, 1512. ^{1}H and ^{13}C NMR spectral data, see Table 1. ESI-MS (pos./neg.) *m/z* 561.1 ([M + Na]$^+$), 583.3 ([M + HCOO]$^-$). HR-ESI-MS (pos.) *m/z* 561.1931 [M + Na]$^+$ (calcd for $C_{26}H_{34}O_{12}Na$, 561.1948).

3.3.2 Carpeside B (*2*)

White amorphous powder. $[\alpha]_D^{20}$ −26 (*c* 0.80, MeOH). CD (*c* 1.05 g l^{-1}, MeOH) $\Delta\varepsilon$ (λ_{max}):

Table 1. ^{1}H and ^{13}C NMR spectral data of **1**–**2** (CD_3OD).

Site	δ_C of **1**	δ_H of **1**	δ_C of **2**	δ_H of **2**
1	133.4 (s)	–	133.4 (s)	–
2	113.7 (d)	6.94 (d, 1.7)	113.2 (d)	7.00 (br s)
3	152.3 (s)	–	152.0 (s)	–
3	148.0 (s)	–	147.9 (s)	–
5	119.4 (d)	6.70 (d, 8.3)	118.8 (d)	6.84 (d, 7.6)
6	123.6 (d)	6.81 (dd, 8.3, 1.7)	122.4 (d)	6.85 (overlap.)
7	78.4 (d)	5.06 (d, 7.0)	78.3 (d)	5.18 (d, 4.0)
8	85.5 (d)	4.43 (dt, 7.0, 4.2)	86.3 (d)	4.39 (td, 5.8, 4.6)
9	62.7 (t)	3.86 (dd, 10.0, 4.2)	62.5 (t)	3.84 (dd, 11.2, 4.2)
		3.79 (dd, 10.0, 4.6)		3.54 (dd, 11.2, 5.9)
3-MeO	56.8 (q)	3.74 (s)	56.8 (q)	3.79 (s)
1′	130.6 (s)	–	130.7 (s)	–
2′	111.9 (d)	7.11 (d, 1.8)	111.6 (d)	7.13 (d, 1.6)
3′	149.5 (s)	–	149.8 (s)	–
4′	149.4 (s)	–	149.5 (s)	–
5′	115.9 (d)	6.75 (d, 8.4)	116.3 (d)	6.75 (d, 7.9)
6′	121.0 (d)	6.86 (dd, 8.4, 1.8)	121.1 (d)	6.86 (dd, 7.9, 1.5)
7′	132.0 (d)	6.48 (d, 16.0)	131.9 (d)	6.50 (d, 16.0)
8′	128.9 (d)	6.20 (dt, 16.0, 5.7)	130.7 (d)	6.22 (dt, 16.0, 6.0)
9′	64.3 (t)	4.18 (dd, 5.7, 1.4, 2H)	64.2 (t)	4.18 (d, 6.0, 2H)
3′-MeO	57.0 (q)	3.77 (s)	56.9 (q)	3.83 (s)
1a	101.0 (d)	4.12 (d, 7.4)	101.5 (d)	4.16 (d, 7.3)
2a	75.6 (d)	3.10 (t, 8.4)	75.6 (d)	3.10–3.14 (m)
3a	78.7 (d)	3.26–3.30 (m)	78.3 (d)	3.25–3.30 (m)
4a	72.2 (d)	3.22–3.26 (m)	72.3 (d)	3.22–3.24 (m)
5a	78.4 (d)	3.25 (dd, 8.4, 7.7)	78.3 (d)	3.20–3.30 (m)
6a	63.3 (t)	3.81 (dd, 12.0, 1.5)	63.3 (t)	3.86 (dd, 11.8, 2.1)
		3.66 (dd, 12.0, 6.0)		3.68 (dd, 11.8, 5.9)

-291 (205 nm), -112 (227 nm), $+67$ (247 nm), 73 (251 nm), 162 (282 nm); IR ν_{max} KBr (cm^{-1}): 3425 (OH), 1651, 1512. ^{1}H and ^{13}C NMR spectral data, see Table 1. ESI-MS (pos./neg.) *m/z* 561.1 $[M + Na]^+$, 583.4 $[M + HCOO]^-$. HR-ESI-MS (pos.) *m/z* 561.1961 $[M + Na]^+$ (calcd for $C_{26}H_{34}O_{12}Na$, 561.1948).

*3.3.3 Eupatriol 10-O-β-D-apiofuranosyl-(1 → 6)-β-D-glucopyranoside (**3**)*

White amorphous powder. $[\alpha]_D^{21}$ -51 (*c* 0.08, MeOH). IR ν_{max} KBr (cm^{-1}): 3423 (OH), 1626. ESI-MS (pos./neg.) *m/z*: 499.1 ($[M + Na]^+$), 475.2 ($[M - H]^-$); HR-ESI-MS (pos.) *m/z* 499.1801 $[M + Na]^+$ (calcd for $C_{21}H_{32}O_{12}Na$, 499.1791). ^{1}H NMR spectral data (400 MHz, CD_3OD): 7.11 (d, $J = 7.8$ Hz, H-5); 6.61 (br d, $J = 8.5$ Hz, H-6); 6.57 (br s, H-2); 5.00 (d, $J = 2.2$ Hz, H-1b); 4.28 (d, $J = 8.0$ Hz, H-1a); 4.17 (d, $J = 10.8$ Hz, H-9); 3.99 (dd, $J = 11.0$, 2.1 Hz, Ha-6a); 3.97 (d, $J = 9.7$ Hz, Ha-4b); 3.90 (d, $J = 2.7$ Hz, H-2b); 3.76 (d, $J = 9.7$ Hz, Hb-4b); 3.73 (d, $J = 10.8$ Hz, H-9); 3.59 (dd, $J = 11.7$, 6.6 Hz, Hb-6a); 3.57 (s, 2H, H-5b); 3.42 (ddd, $J = 9.4$, 6.5, 1.8 Hz, H-5a); 3.34 (t, $J = 8.9$ Hz, H-3a); 3.25 (dd, $J = 9.7$, 8.9 Hz, H-4a); 3.20 (dd, $J = 9.3$, 7.9 Hz, H-2a); 2.22 (s, 3H, H-7); 1.56 (s, 3H, H-10). ^{13}C NMR spectral data (100 MHz, CD_3OD): 157.1 (s, C-3), 140.1 (s, C-1), 128.3 (d, C-5), 127.4 (s, C-4), 121.7 (d, C-6), 118.7 (d, C-2), 111.4 (d, C-1b), 105.7 (d, C-1a), 81.1 (s, C-3b), 78.5 (t, C-9), 78.5 (d, C-2b), 78.3 (d, C-3a), 77.6 (s, C-8), 77.4 (d, C-5a), 75.6 (d, C-2a), 75.5 (t, C-4b), 72.2 (d, C-4a), 69.2 (t, C-6a), 66.1 (t, C-5b), 25.8 (q, C-10), 21.5 (q, C-7).

3.3.4 Acid hydrolysis of compounds 1—3

A solution of **1**–**3** (each 2 mg) in 2 M HCl–dioxane (1:1, v/v, 2 ml) was heated under reflux for 2 h. After cooling, the reaction mixture was neutralized with $NaHCO_3$ and then filtrated to remove the solid. The solution was subjected to CC (Sephadex LH-20, MeOH–H_2O 1:1) to afford a sugar fraction. The sugar fraction of **1**–**3** and standard D-glucose and D-apiose (Sigma, USA) were, respectively, treated with L-cysteine methyl ester hydrochloride (2 mg) in pyridine (1 ml) at 60°C for 1 h, after which the solution was treated with *N*,*O*-bis(trimethylsilyl)-trifluoroacetamide (0.02 ml) at 60°C for 1 h, following which the supernatant was subjected to GLC analysis (*Supelco*, 230°C; flow rate, 15 ml/min). D-Glucose (standard, $t_R = 24.3$ min; **1**, $t_R = 24.2$ min; **2**, $t_R = 24.3$ min; **3**, $t_R = 24.3$ min) was detected from the sugars of **1**–**3,** and D-apiose (standard, $t_R = 14.2$ min; **3**, $t_R = 14.2$ min) from **3**.

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