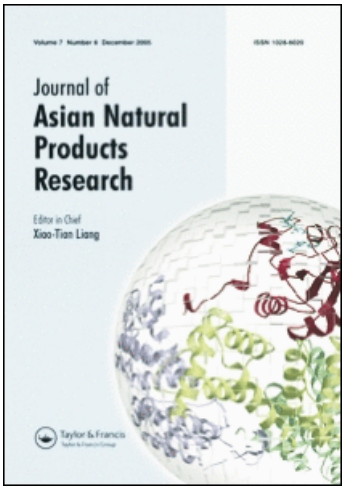

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ORIGINAL ARTICLE

Two new dihydrobenzofuran lignans from *Rabdosia lophanthoides* (Buch.-Ham.ex D.Don) Hara

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Two new dihydrobenzofuran lignanosides, (7*R*,8*S*)-4,3′,9′-trihydroxyl-3-methoxyl-7,8-dihydrobenzofuran-1′-propylneolignan-9-*O*-(6-*O*-syringoyl)-β-D-glucopyranoside, named lophanthoside B (**1**) and (7*R*,8*S*)-4,9,9′-trihydroxyl-3-methoxyl-7,8-dihydrobenzofuran-1′-propylneolignan-3′-*O*-β-D-glucopyranoside (**2**), an enantiomer of umbroside, along with four known dihydrobenzofuran lignans (**3**–**6**), were isolated from 50% acetone extract of *Rabdosia lophanthoides* (Buch.-Ham.ex D.Don) Hara. Their structures were elucidated by NMR and MS experiments.

Keywords: Lamiaceae; *Rabdosia lophanthoides*; dihydrobenzofuran lignans

1. Introduction

Isodon (=*Rabdosia*) is a cosmopolitan and important genus of the Labiatae (=Lamiaceae) family. About 150 species of undershrubs, sub-undershrubs, or perennial herbs are found mainly in tropical and subtropical Asia. The use of the *Isodon* species in the Chinese popular folk medicine has a long history. Most herbs of this species have obvious biological activities and low toxicity. *Rabdosia lophanthoides* (Buch.-Ham.ex D. Don) Hara. has been used for the treatment of acute icteric hepatitis, acute cholecystitis, esophagitis, gynecopathia [1], and so on. However, few of the phytochemical studies of this plant, especially lignans, have been reported previously. In this paper, we report two new dihydrobenzofuran lignanosides, (7*R*,8*S*)-4,3′,9′-trihydroxyl-3-methoxyl-7,8-dihydrobenzofuran-1′-propylneolignan-9-*O*-(6-*O*-syringoyl)-β-D-glucopyranoside, named lophanthoside B (**1**) and (7*R*,8*S*)-4,9,9′-trihydroxyl-3-methoxyl-7,8-dihydrobenzofuran-1′-propylneolignan-3′-*O*-β-D-glucopyranoside (**2**), an enantiomer of umbroside, along with four known lignans (7*R*,8*S*)-4,9′-dihydroxyl-3,3′-dimethoxyl-7,8-dihydrobenzofuran-1′-propylneolignan-9-*O*-β-D-glucopyranoside (**3**) [2], (7*R*,8*S*)-9,3′,9′-trihydroxyl-3-methoxyl-7,8-dihydrobenzofuran-1′-propylneolignan-4-*O*-β-D-glucopyranoside (**4**) [3], (7*R*,8*S*)-4,3′,9,9′-tetrahydroxyl-3-methoxyl-7,8-dihydrobenzofuran-1′-propylneolignan (**5**) [4], and (7*R*,8*S*)-4,9,9′-trihydroxyl-3,3′-dimethoxyl-7,8-dihydrobenzofuran-1′-propylneolignan (**6**) [5], among which, compounds **3**–**6** were obtained from this plant for the first time (Figure 1).

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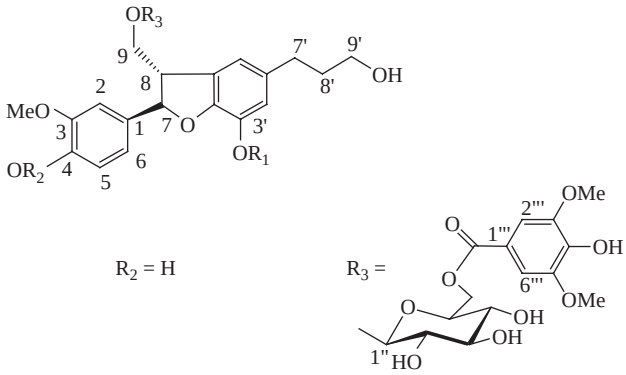

1 R_1 = H R_2 = H R_3 =

2 R_1 = β-D-glucoside R_2 = H R_3 = H

3 R_1 = Me R_2 = H R_3 = β-D-glucoside

4 R_1 = H R_2 = β-D-glucoside R_3 = H

5 R_1 = H R_2 = H R_3 = H

6 R_1 = Me R_2 = H R_3 = H

Figure 1. The structures of compounds **1**–**6**.

2. Results and discussion

Compound **1** was obtained as a white amorphous powder, with the molecular formula of $C_{34}H_{40}O_{15}$, as deduced from the $[M + Na]^+$ peak at *m/z* 711.2260 by HR-ESI-MS. The IR spectrum exhibited the absorption of hydroxyls (3423 cm^{-1}), carbonyl (1697 cm^{-1}), and aromatic rings (1612, 1516 cm^{-1}). The UV spectrum showed absorption maximum at 280 nm. The ^1H NMR spectrum of **1** (Table 1) exhibited characteristic proton signals of dihydrobenzofuran skeleton, including the protons of an ABX system at δ 6.94 (1H, d, $J = 1.8$ Hz), 6.69 (1H, d, $J = 8.0$ Hz), and 6.80 (1H, dd, $J = 1.8$, 8.0 Hz), and the protons at δ 5.54 (1H, d, $J = 5.8$ Hz), 3.59 (2H, m), 3.99 (2H, m) as one of the C_6—C_3 moieties, along with the other C_6—C_3 moiety at δ 6.56 (1H, br s), 2.51 (2H, t, $J = 8.0$ Hz), 1.77 (2H, m), 3.53 (2H, t, $J = 6.8$ Hz), one glucose moiety at δ 4.41 (1H, d, $J = 7.5$ Hz), 3.30 (1H, m), 3.58 (1H, m), 3.42 (1H, m), 4.39 (1H, m), 4.76 (1H, m), and the signals of a syringoyl moiety at δ 7.29 (2H, s), 3.74 (6H, s). By comparison of its NMR spectral data with those reported [6], the ^{13}C NMR spectral data (Table 1) confirmed the presence of dihydrobenzofuran skeleton, a syringoyl fragment at δ 121.0, 108.2, 149.2, 142.5, 168.1, and 56.7 and glucose signals at δ 104.0, 75.1, 75.6, 72.0, 78.0, and 65.3. In the HMBC spectrum, H-6″ (δ 4.39, 4.76) was correlated with the carbonyl signal at δ 168.1, H-1″ (δ 4.41) with C-9 (δ 72.7), and the MeO at δ 3.76 with C-3 (δ 149.2). Based on the above description, the syringoyl moiety could be located at C-6″ of the glucose moiety, the *O*-glucopyranosyl located at C-9 and the methoxyl at C-3, respectively. In addition, a *trans*-configuration between C-7 and C-8 was determined from the coupling constant ($J = 6.0$ Hz) [6]. The absolute configurations of C-7 (δ 89.4) and C-8 (δ 54.1) were proved by means of their chemical shifts. According to the report [6,7], C-7 at δ 88.0–89.5 and C-8 at δ 53.5–55.0 were 7*R*,8*S*; C-7 at δ 86.5–87.5 and C-8 at δ 56.5–57.5 were 7*S*,8*R*. The CD spectra of compound **1** exhibited a positive Cotton effect at 222 nm ($\Delta\varepsilon + 2.01$). A positive Cotton effect at 223 nm ($\Delta\varepsilon + 1.19$) was

Table 1. ^{1}H and ^{13}C NMR spectral data for compounds **1** and **2** (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR, methanol-d_4).

	1		**2**	
Position	δ_H (*J*, Hz)	δ_C	δ_H (*J*, Hz)	δ_C
1		135.0		134.2
2	6.94 (d, $J = 1.8$)	110.7	6.85 (d, $J = 1.7$)	110.8
3		149.2		149.1
4		147.2		147.6
5	6.69 (d, $J = 8.0$)	116.0	6.66 (d, $J = 8.1$)	116.2
6	6.80 (dd, $J = 8.0, 1.8$)	119.6	6.74 (dd, $J = 8.1, 1.7$)	120.0
7	5.54 (d, $J = 6.0$)	89.4	5.50 (d, $J = 6.2$)	89.4
8	3.59 (m)	54.1	3.41 (m)	54.9
9	3.99 (m)	72.7	3.76 (m)	64.8
3-OCH_3	3.76 (s)	56.4	3.80 (s)	56.4
1′		136.8		137.1
2′	6.56 (br s)	116.8	6.81 (br s)	117.9
3′		141.9		142.4
4′		148.9		147.3
5′		129.1		130.5
6′	6.56 (br s)	117.1	6.70 (br s)	119.5
7′	2.51 (t, $J = 8.0$)	32.6	2.60 (t, $J = 8.0$)	32.7
8′	1.77 (m)	35.7	1.80 (m)	35.5
9′	3.53 (t, $J = 6.8$)	62.3	3.52 (t, $J = 6.8$)	62.4
Glc				
1″	4.41 (d, $J = 7.5$)	104.0	5.01 (d, $J = 7.5$)	102.7
2″	3.30 (m)	75.1	3.32 (m)	74.8
3″	3.58 (m)	75.6	3.34 (m)	77.6
4″	3.42 (m)	72.0	3.40 (m)	71.3
5″	3.42 (m)	78.0	3.29 (m)	78.0
6″	4.76, 4.39 (m)	65.3	3.65, 3.76 (m)	62.2
Syringoyl				
1‴		121.0		
2‴, 6‴	7.29 (s)	108.2		
3‴, 5‴		149.2		
4‴		142.5		
MeO	3.74 (s)	56.7		
CO		168.1		

reported for the compound (2*R*,3*S*)-2,3-dihydro-2-(4′-hydroxy-3′-methoxy-phenyl)-3-hydroxymethyl-7-methoxy-5-benzofuranpropanol-4′-*O*-β-D-glucopyranoside [3]. These data also suggested that the absolute configurations of C-7 and C-8 in compound **1** were *R* and *S*, respectively. Thus, the structure of compound **1** was elucidated as (7*R*,8*S*)-4,3′,9′-trihydroxyl-3-methoxyl-7,8-dihydrobenzofuran-1′-propylneolignan-9-*O*-(6-*O*-syringoyl)-β-D-glucopyranoside, named lophanthoside B.

Compound **2** was obtained as a white amorphous powder, with the molecular formula of $C_{25}H_{32}O_{11}$, as deduced from the $[M + Na]^+$ peak at *m/z* 531.1841 by HR-ESI-MS. The IR spectrum exhibited the absorption of hydroxyls (3400–3500 cm^{-1}) and aromatic rings (1608, 1510 cm^{-1}). The UV spectrum showed absorption maxima at 214, 233, and 282 nm. The ^{1}H NMR and ^{13}C NMR spectra of **2** (Table 1) were very similar to those of **1**, except for the absence of the syringoyl group. In the HMBC spectrum,

H-1″ (δ 5.01) was correlated with C-3′ (δ 142.4), indicating that the *O*-glucopyranosyl moiety was located at C-3′. The structure of **2** was almost identical to that of umbroside, except for the obvious difference from ^{1}H NMR and ^{13}C NMR spectral data of 7 and 8 positions. The absolute configurations of C-7 (δ 89.4) and C-8 (δ 54.9) were confirmed using the same methods as compound **1**, and thus the structure of compound **2** was elucidated as (7*R*,8*S*)-4,9,9′-trihydroxyl-3-methoxyl-7,8-dihydrobenzofuran-1′-propylneolignan-3′-*O*-β-D-glucopyranoside, an enantiomer of umbroside.

3. Experimental

3.1 General experimental procedures

Melting points were determined with Kofler micro-melting point apparatus and are uncorrected. Optical rotations were obtained on a Perkin-Elmer 341 polarimeter. UV spectra were measured with a Shimadzu UV–vis 2201 spectrophotometer. CD spectra were determined using a Jasco J715 spectropolarimeter. IR spectra were obtained on a Shimadzu FTIR-8201 PC spectrometer. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker DPX-400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) with tetramethylsilane as an internal standard. The HR-ESI-MS were measured on a Bruker APEX II spectrometer in positive-ion mode. Column chromatography was performed on Diaion HP-20 (Mitsubishi Chemical Corp., Tokyo, Japan), silica gel (160–200 mesh, Haiyang Chemical Co. Ltd, Qingdao, China), Toyopearl HW-40C (TOSOH Corp., Tokyo, Japan). The chemical reagents were purchased from Beijing Chemical Plant (Beijing, China) and Tianjin No. 3 Reagent Plant (Tianjin, China).

3.2 Plant material

Dried *R. lophanthoides* were collected from Jiyuan County, Henan Province in China, and identified by Prof. Cheng-Ming Dong of the Henan University of Traditional Chinese Medicine. A voucher specimen (No. 20060609) has been deposited in the herbarium of Henan University of TCM, Zhengzhou, China.

3.3 Extraction and isolation

Dried plants of *R. lophanthoides* (9.5 kg) were extracted by 50% aqueous acetone twice at room temperature, and concentrated under reduced pressure below 40°C. The water-soluble part was chromatographed over Diaion HP-20 with H_2O containing increasing amounts of MeOH. The 20% MeOH eluate (10.6 g) was chromatographed on Toyopearl HW-40, (coarse grade) developing with 10% MeOH–50% MeOH. The 20% MeOH eluate was rechromatographed on Toyopearl HW-40 (MeOH) and on silica gel ($CHCl_3$–MeOH–H_2O, 4:1:0.1) to yield compounds **1** (15 mg) and **2** (32 mg). The 30% MeOH eluate was chromatographed on Toyopearl HW-40 (coarse grade), developing with 10% MeOH–50% MeOH. The 10% MeOH eluate was rechromatographed on Toyopearl HW-40 (MeOH) and on silica gel (EtOAc–EtOH–H_2O, 12:2:1) to yield compound **3** (20 mg). The 40% MeOH eluate was chromatographed on Toyopearl HW-40 (coarse grade), developing with 10% MeOH–50% MeOH. The 10% MeOH eluate was rechromatographed on Toyopearl HW-40 (MeOH) and on silica gel ($CHCl_3$–MeOH–H_2O, 8:1:0.05) to yield compounds **4** (20 mg), **5** (20 mg), and **6** (16 mg).

3.3.1 (7R,8S)-4,3′,9′-trihydroxyl-3-methoxyl-7,8-dihydrobenzofuran-1′-propylneolignan-9-O-(6-O-syringoyl)-β-D-glucopyranoside (1)

A white powder; mp 232–233°C. $[\alpha]_D^{20} = -11.6$ ($c = 0.16$, MeOH). IR (KBr) ν_{max}: 3423, 2936, 1697, 1611, 1516, 1336, 1116, 1031, 764 cm^{-1}; UV (MeOH) λ_{max}: 280 nm. ^{1}H and ^{13}C NMR spectral

data are shown in Table 1. HR-ESI-MS (pos.): *m/z* 711.2260 $[M + Na]^+$(calcd for $C_{34}H_{40}O_{15}Na$, 711.2265).

3.3.2 (7R,8S)-4,9,9′-trihydroxyl-3-methoxyl-7,8-dihydrobenzofuran-1′-propylneolignan-3′-O-β-D-glucopyranoside

A white powder; mp 214–216°C. $[\alpha]_D^{20} = -9.6$ ($c = 0.11$, MeOH). IR (KBr) ν_{max}: 3369, 2930, 1606, 1518, 1276, 1208, 1156 cm^{-1}; UV (MeOH) λ_{max}: 214, 233, 282 nm. ^1H and ^{13}C NMR spectral data are shown in Table 1. HR-ESI-MS (pos.): *m/z* 531.1833 $[M + Na]^+$(calcd for $C_{25}H_{32}O_{11}Na$, 531.1841).

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