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Diarylheptanoids from the Bark of *Alnus pendula* Matsumura

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Abstract – Diarylheptanoids, (5*S*)-1,7-bis-(3,4-dihydroxyphenyl)-5-hydroxyheptane-3-one-5-*O*-β-D-xylopyranoside (**1,** Oregonin), 1,7-bis-(3,4-dihydroxyphenyl)-4-heptene-3-one (**2**, Hirsutenone), (5*S*)-7-(3,4-dihydroxyphenyl)-5-hydroxy-1-(4-hydroxyphenyl)-3-heptanone-5-*O*-β-D-xylopyranoside (**3**, Alnuside A), (5*S*)-1-(3,4-dihydroxyphenyl)-5-hydroxy-7-(4-hydroxyphenyl)-3-heptanone-5-*O*-β-D-xylopyranoside (**4**, Alnuside B), (5*S*)-1,7-bis-(3,4-dihydroxyphenyl)-5-hydroxyheptane-3-on-5-*O*-β-D-glucopyranoside (**5**) and 1,7-bis-(4-hydroxyphenyl)-5-hydroxyheptane-3-on-5-*O*-β-D-glucopyranoside (**6**, Platyphylloside) were isolated from the bark of *Alnus pendula* Matsumura. The structures of these compounds were identified based on the spectral and physicochemical data.
Keywords – *Alnus pendula* Matsumura, Diarylheptanoid

Introduction

Alnus pendula Matsumura, one of the indigenous *Alnus* species that grow in Korea, is a deciduous broad-leaved tree found in damp areas, and the bark of *Alnus* species has been used in oriental traditional medicine as a remedy for fever, hemorrhage, diarrhea and alcoholism (Lee, 1966). Several interesting biological activities of diarylheptanoids, including their anti-inflammatory (Lee *et al*., 2000a; Lee *et al*., 2000b; Kim *et al*., 2005), anti-oxidant (Lee *et al*., 2000d; Kuroyanagi *et al*., 2005b) and anti-atopic dermatitis (Choi *et al*., 2010) properties, have previously been reported. In an earlier study, quantitative analysis of diarylheptanoids was conducted using HPLC of *A. japonica*, *A. hirsuta* and *A. hirsuta* var. *sibirica* (Lim *et al*., 2005). Here, as part of our continuous search for diarylheptanoids from new natural sources (Kim *et al*., 2005a; Lee *et al*., 2000c; Jeong *et al*., 2000), we describe the isolation and identification of diarylheptanoids from the bark of *A. pendula*.

Experimental

General experimental procedures – ^{1}H-(600 MHz) and ^{13}C-(150 MHz) NMR spectra were obtained on a Varian Unity INOVA 600 spectrometer (Varian, Inc., U.S.A.). Chemical shifts were expressed in parts per million (ppm) relative to TMS as an internal standard, and coupling constants (*J*) were given in Hz. MS were obtained on a Varian Saturn 4D mass spectrometer (Varian, Inc., U.S.A.) and JEOL JMS HX-110/110A tandem mass spectrometer (JEOL Ltd., Japan). TLC was carried out on Merck silica gel F_{254}-precoated aluminum plates.

Plant material – The dried and powdered bark (300 g) of *A. pendula* (bar code; PB 2368.2) was purchased from the Korea Plant Extract Bank in October 2008.

Extraction and isolation – The dried and powdered bark (300 g) of *A. pendula* was extracted using 80% aqueous acetone at room temperature for 3 days. The filtrate was concentrated and applied to a Sephadex LH-20 column (25 - 100 μm, 8 × 150 cm, Pharmacia, Uppsala, Sweden) containing increasing proportions of MeOH (60% - 100%) to afford four fractions, I (3.68 g), II (3.84 g), III (23.87 g) and IV (8.48 g). Repeated column chromatography of fraction II on the MCl-Gel CHP 20P (75 - 150 μm, 5 × 80 cm, Mitsubishi Chemical Co., Tokyo, Japan) with 60% - 100% methanol gradient and Disogel (40 - 60 μm, 3 × 50 cm, Daiso Co., Osaka, Japan) with 30% - 80% and 30% - 100% methanol gradient in middle pressure liquid chromatography (MPLC) system (5 ml/min, 280 nm) provided compounds **3** (0.06 g), **4** (0.07 g), **5** (0.16 g) and **6** (0.74 g). Column chromatography of fraction III on the Sephadex LH-20 column with 60% - 100% methanol gradient and MCl-Gel with 30% - 100% methanol gradient yielded compound **1** (13.26 g). Finally, Disogel MPLC of fraction IV with 30% - 80% methanol

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gradient, MCl-Gel with 60% - 100% methanol gradient and Sephadex LH-20 with 60% - 100% methanol gradient provided compound **2** (0.25 g).

Oregonin (**1**) – Brown amorphous powder, negative FAB MS: *m/z* 477 $[M-H]^-$, ^{1}H-NMR (600 MHz, DMSO-d_6 + D_2O): δ 6.67-6.60 (4H in total, H-2′, 2″, 5′, 5″), 6.48-6.45 (2H in total, H-6″, 6′), 4.19 (1H, br d, *J* = 7.8 Hz, xyl-1), 4.03 (1H, m, H-5), 3.76 (1H, dd, *J* = 11.4 Hz, xyl-5e), 3.35 (1H, m, xyl-4), 3.08-2.56 (8H in total, H-1, 2, 4, 7), 1.74-1.68 (2H in total, m, H-6). ^{13}C-NMR (150 MHz, DMSO-d_6 + D_2O): see Table 1.

Hirsutenone (**2**) – Brown oil, negative FAB MS: *m/z* 345 $[M-H]^-$, ^{1}H-NMR (600 MHz, DMSO-d_6 + D_2O) : δ 6.87-6.83 (1H in total, m, H-5), 6.65-6.59 (4H in total, m, H-2′, 2″, 5′, 5″), 6.47-6.44 (2H in total, m, H-6′, 6″), 6.12 (1H, d, *J* = 15.6 Hz, H-4), 2.79-2.43 (8H in total, m, H-1, 2, 6, 7), ^{13}C-NMR (150 MHz, DMSO-d_6 + D_2O): see Table 1.

Alnuside A (**3**) – Brown amorphous powder, negative FAB MS: *m/z* 461 $[M-H]^-$, ^{1}H-NMR (600 MHz, DMSO-d_6 + D_2O): δ 6.98 (2H, d, *J* = 8.4 Hz, H-2′, 6′), 6.67 (2H, d, *J* = 8.4 Hz, H-3′, 5′), 6.65 (1H, d, *J* = 7.8 Hz, H-5″), 6.61 (1H, d, *J* = 2.4Hz, H-2″), 6.47 (1H, m, H-6″), 4.22 (1H, d, *J* = 7.8 Hz, xyl-1), 4.11 (1H, *J* = 5.0 Hz, H-5), 3.86 (1H, xyl-5), 3.46 (1H, m, xyl-4), 3.29 (1H, xyl-3), 3.16 (1H, xyl-5), 3.13 (1H, xyl-2), 2.79 (1H, dd, *J* = 16.8, 7.2 Hz, H-4), 2.72 (4H, s, H-1, H-2), 2.56 (1H, dd, *J* = 16.8, 5.4 Hz, H-4), 2.50 (2H, m, H-7), 1.78 (1H, m, H-6), 1.73 (1H, m, H-6), ^{13}C-NMR (150 MHz, DMSO-d_6 + D_2O): see Table 1.

Alnuside B (**4**) – Brown amorphous powder, negative FAB MS: *m/z* 461 $[M-H]^-$, ^{1}H-NMR (600nMHz, DMSO-d_6 + D_2O): δ 6.98 (2H, d, *J* = 8.4 Hz, H-2″, 6″), 6.67 (2H, d, *J* = 8.4 Hz, H-3″, 5″), 6.65 (1H, d, *J* = 7.8 Hz, H-5′), 6.61 (1H, d, *J* = 2.4 Hz, H-2′), 6.47 (1H, m, H-6′), 4.22 (1H, d, *J* = 7.8 Hz, xyl-1), 4.11 (1H, m, H-5), 3.84 (1H, dd, *J* = 11.4, 5.4 Hz, xyl-5), 3.46 (1H, m, xyl-4), 3.29 (1H, xyl-3), 3.16 (1H, xyl-5), 3.12 (1H, xyl-2), 2.79 (1H, dd, *J* = 16.8, 7.2 Hz, H-4), 2.73 (2H, m, H-1), 2.68 (2H, m, H-2), 2.57 (1H, dd, *J* = 16.8, 5.4 Hz, H-4), 2.51 (2H, m, H-7), 1.77 (1H, m, H-6), 1.73 (1H, m, H-6), ^{13}C-NMR (150 MHz, DMSO-d_6 + D_2O): see Table 1.

(5S)-1,7-bis-(3,4-dihydroxyphenyl)-5-hydroxyheptane-3-one-5-O-β-D-glucopyranoside (**5**) – Brown amorphous powder, negative FAB MS: *m/z* 507 $[M-H]^-$, ^{1}H-NMR (600 MHz, DMSO-d_6 + D_2O): δ 6.68-6.61 (4H in total, H-2″, 2′, 5″, 5′), 6.50-6.47 (2H in total, dd, *J* = 7.8 Hz, H-6″,6′), 4.28 (1H, br d, *J* = 7.2 Hz, glc-1), 4.16 (1H, m, H-5), 3.89 (1H, dd, *J* = 12.0, 1.8 Hz, glc-5), 3.72 (1H, dd, *J* = 12.0, 5.4 Hz, glc-6), 3.26 (1H, m, glc-2), 2.79-2.51 (8H in total, H-1, 2, 4, 7), 1.84 - 1.69 (2H in total, m, H-6), ^{13}C-NMR (150 MHz, DMSO-d_6 + D_2O): see Table 1.

Platyphylloside (**6**) – Brown amorphous powder, negative FAB MS: *m/z* 475 $[M-H]^-$, ^{1}H-NMR (600 MHz, DMSO-d_6 + D_2O): δ 7.00-6.96 (4H in total, m, H-2″, 6″, 2′, 6′), 6.69-6.65 (4H in total, m, H-3″, 5″, 3′, 5′), 4.29 (1H, br d, *J* = 7.8 Hz, glc-1), 4.17 (1H, m, H-5), 3.87-3.15 (5H in total, m, glc-H), 2.81 - 2.58 (8H in total, m, H-1, 2, 4, 7,), 1.85-1.73 (2H in total, H-6), ^{13}C-NMR (150 MHz, DMSO-d_6 + D_2O): see Table 1.

Table 1. ^{13}C-NMR spectra of compounds **1** - **6**

Carbon No.	Comp. **1**	Comp. **2**	Comp. **3**	Comp. **4**	Comp. **5**	Comp. **6**
C-1	28.7	29.3	28.6	28.4	28.6	28.4
C-2	45.1	41.6	45.0	45.0	44.9	47.2
C-3	209.6	199.7	210.6	210.5	210.8	210.6
C-4	47.5	130.6	47.9	47.6	48.5	48.0
C-5	76.9	147.3	75.0	74.8	76.4	76.2
C-6	39.7	34.2	37.2	37.1	36.9	37.0
C-7	30.5	33.4	30.2	30.3	30.1	30.0
C-1′	132.4	132.2	133.7	132.9	132.6	131.8
C-1″	133.3	132.4	132.9	133.7	132.7	132.9
C-2′	115.8	115.7	128.9	115.2	114.9	114.8
C-2″	115.8	115.8	115.1	128.9	115.0	114.6
C-3′	145.1	145.2	115.0	144.6	144.5	129.0
C-3″	145.1	145.2	144.6	115.0	144.6	129.0
C-4′	143.2	143.5	155.0	142.7	142.6	155.0
C-4″	143.4	143.6	142.9	154.7	142.9	154.7
C-5′	116.0	116.0	114.8	114.9	115.2	128.9
C-5″	116.0	116.0	115.0	114.7	115.4	128.9
C-6′	119.2	119.3	131.8	119.2	119.2	114.8
C-6″	119.3	119.2	119.3	131.8	119.4	114.6
Xyl-1	102.8		.102.8	102.8		
Xyl-2	74.7		73.6	73.6		
Xyl-3	77.0		76.4	76.4		
Xyl-4	69.8		69.8	69.8		
Xyl-5	66.0		65.5	65.5		
Glc-1					101.8	102.0
Glc-2					74.5	75.4
Glc-3					76.5	76.5
Glc-4					70.1	70.2
Glc-5					75.8	76.3
Glc-6					61.3	61.3

* 150 MHz (DMSO-d_6 + D_2O)

Results and discussion

Dried and powdered barks of *A. pendula* were extract-

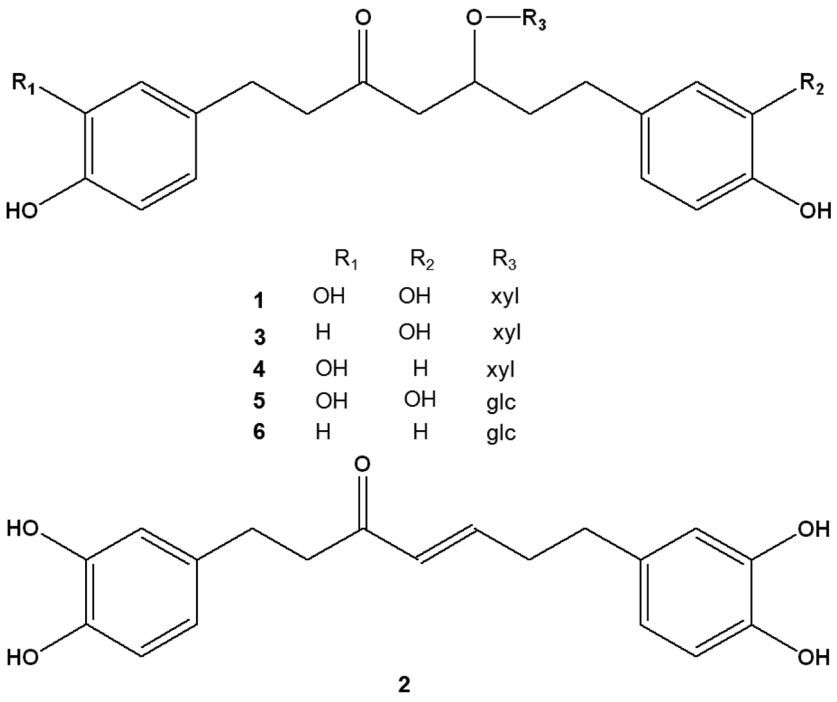

Fig. 1. The Structures of compounds **1** - **6**.

ed with aqueous acetone and the extract was subjected to a combination of Sephadex LH-20, MCl-Gel and Disogel chromatography to afford six known diarylheptanoids (**1** - **6**).

Compound **1** was a brown amorphous powder (Negative FAB MS: *m/z* 477 $[M - H]^-$); on TLC, the green spot was detected by spraying with $FeCl_3$ and the violet spot was detected by spraying 10% H_2SO_4 solution with subsequent heating. The ^{1}H-NMR spectrum of **1** showed the presence of one methylene over δ 1.74-1.68, another four methylenes over δ 3.08-2.56, a hydroxyl group in methane signals of δ 4.03, and two sets of aromatic ABX-spin systems, which were the *meta*- and *ortho*-coupled aromatic signals at δ 6.67-6.60 (4H in total, H-2′, 2″, 5′, 5″) and 6.48-6.45 (2H in total, H-6″, 6′). Finally, the doublet signal of anomeric proton δ 4.19 (J = 7.8 Hz) was observed in the ^{1}H-NMR spectrum. The ^{13}C-NMR spectrum revealed a heptanoid moiety that was substituted by ketone (δ 209.6, C-3). Comparing the ^{13}C-NMR data of an aglycone with those of compound **2** (hirsutenone), a xylose shift (δ 102.8, 74.7, 77.0, 69.8, 66.0) was observed in the diarylheptanoid glycoside. Thus, compound **1** was identified as (5*S*)-1,7-bis-(3,4-dihydroxyphenyl)-5-hydroxyheptane-3-on-5-*O*-β-D-xylopyranoside (Oregonin) by comparing the spectral data with values reported in the literature (Lee *et al*., 1992).

Compound **2** was a brown oil (negative FAB MS: *m/z* 345 $[M - H]^-$); on TLC, the green spot was detected by spraying with $FeCl_3$ and the violet spot was detected by spraying 10% H_2SO_4 solution with subsequent heating, respectively. The signals of four more methylene protons δ 2.79-2.43, which were ketone C-3 (δ 6.12), were adjacent to the alkene proton doublet (J = 15.6 Hz, H-4) and two sets of aromatic ABX-spin system, which were *meta*- and *ortho*-coupled aromatic signals δ 6.65-6.59 (4H in total, m, H-2′, 2″, 5′, 5″), and *ortho*-*meta*-coupled aromatic signals δ 6.47-6.44 (2H in total, m, H-6′, 6″) were observed in ^{1}H-NMR spectrum, as well as two hydroxy-bearing carbon signals of C-3′, 3″ (δ 145.2 × 2) and C-4′, 4″ (δ 143.5, 143.6) in the ^{13}C-NMR spectrum. The ^{13}C-NMR spectra of one catechol ring and one ketone (δ 199.7), according to one alkene group carbon (δ 130.6, 147.3), indicated diarylheptanoid. Thus, compound **2** was identified as hirsutenone by comparing the spectral data with values reported in the literature (Lee *et al*., 1992).

Compound **3** was a brown amorphous powder (negative FAB MS: *m/z* 461 $[M - H]^-$); on TLC, the green spot was detected by spraying with $FeCl_3$ and the violet spot was detected by spraying 10% H_2SO_4 solution with subsequent heating, respectively. The ^{1}H-NMR spectrum showed the presence of one methylene over δ 1.73 - 1.78 (1H, m, H-6), and another four methylenes over δ 2,72, 2.50, 2.79, a hydroxy group in methane signals of δ 2.56, one aromatic ABX-spin system, which was the *meta*- and *ortho*-coupled aromatic signal at δ 6.67 (2H, d, J = 9 Hz,

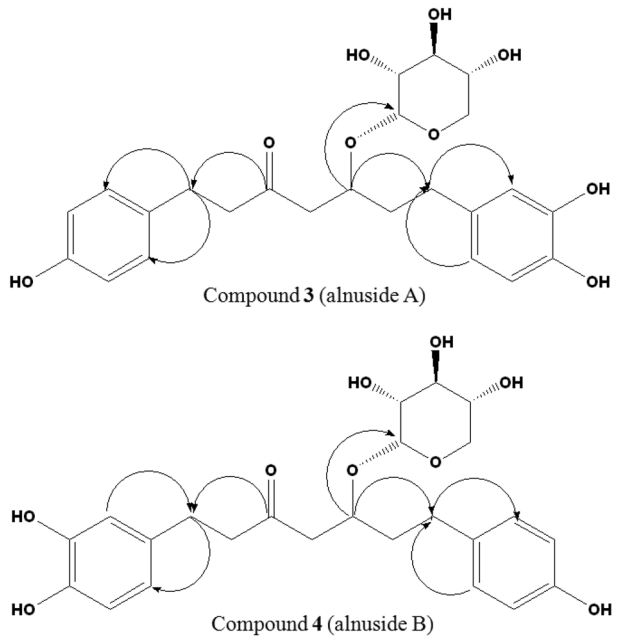

Fig. 2. HMBC correlations of compounds **3** and **4**.

H-3′, 5′), 6.98 (2H, d, J = 8.4 Hz, H-2′, 6′), and one A_2B_2 system, which was the *meta*- and *ortho-meta*-coupled aromatic signals at δ 6.47 (1H, H-6″), 6.61 (1H, d, J = 2.4 Hz, H-2″), and 6.65 (1H, d, J = 7.8 Hz, H-5″), Finally, the doublet signals of the anomeric proton at δ 4.22 (1H, d, J = 7.8 Hz, xyl-1) were observed in the ^{1}H-NMR spectrum. The ^{13}C-NMR spectrum revealed a heptanoid moiety substituted by ketone (δ 210.6, C-3). Comparing the ^{13}C-NMR data, the four methylenes and xylopyranosyl moiety were the same in compounds **1** and **4**. The connectivity of above four moieties was confirmed by heteronuclear multiple bond connectivity (HMBC) experiment. The H-1 showed a correlation with C-2″ and 6″ of 3,4-dihydroxyphenyl group as well as C-3. And, H-7 showed a correlation with 2′ and 6′ of 4-hydroxyphenyl group as well as C-5. In addition, H-5 showed a correlation with the anomeric carbon and C-3. Thus, compound **3** was identified as 1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl)-5-*O*-β-D-xylopyranosyl-heptane-3-one (Alnuside A) (Kuroyanagi *et al*., 2005).

Compound **4** was a brown amorphous powder (negative FAB MS: *m/z* 461 $[M - H]^-$); on TLC, the green spot was detected by spraying with $FeCl_3$ and the violet spot were detected by spraying 10% H_2SO_4 solution with subsequent heating. Its ^{1}H/^{13}C-NMR spectra had almost the same signal patterns as those of **3**, and suggested that **4** was also diarylheptanoid glycoside composed with 3,4-dihydroxyphenyl group, 4-hydroxyphenyl group, xylose and keto-enol type heptane moiety. In contrast of **3**, H-1 showed a correlation with 2″ and 6″ of 4-hydroxyphenyl group as well as C-3, and H-7 showed a correlation with 2′ and 6′ of 3,4-dihydroxyphenyl group as well as C-5 on HMBC. Thus, **4** was identified as 1-(4-hydroxyphenyl)-7-(3,4-dihydroxyphenyl)-5-*O*-β-D-xylopyranosyl-heptane-3-one (Alnuside B) (Kuroyanagi *et al*., 2005).

Compound **5** was a brown amorphous powder (negative FAB MS: *m/z* 507 $[M - H]^-$); on TLC, the green spot was detected by spraying with $FeCl_3$ and the violet spot was detected by spraying 10% H_2SO_4 solution with subsequent heating. The ^{1}H-NMR and ^{13}C-NMR spectra of compound **1** were very similar to those of compound **5** except for the presence of a glucose moiety instead of the glycoside. The spectrum of compound **5** showed the presence of four methylenes over δ 2.79 - 2.51 (8H in total, H-1, 2, 4, 7) and two pairs of 1,3,4-trisubstituted aromatic rings over δ 6.68 - 6.61 (4H in total, H-2″, 2′, 5″, 5′) and 6.50-6.47 (2H in total, dd, J = 7.8 Hz, H-6″,6′). The ^{1}H-NMR spectrum of compound **5** revealed a glucoside. The ^{13}C-NMR data revealed a glycoside compared with those of its xylose (compound **1**). The doublet signals of anomeric proton at δ 4.16 (1H, m, H-5) were observed in the ^{1}H-NMR spectrum, and the ^{13}C-NMR spectrum revealed two catechol rings and a heptanoid moiety substituted by ketone (δ 210.8, C-3). Comparing the ^{13}C-NMR data of the glycoside with those of its aglycone (compound **1**), the downfield shift of C-5 signal (+ 05 ppm) at δ 76.4 and the upfield shift of C-4 at δ 48.5, which is larger than that of C-6 at δ 36.9, indicate that glycose is linked to C-5 of the heptanoid and allow assignment of the configuration of C-5 of the glycoside. Thus the structure of compound **5** was identified as (5*S*)-1,7-bis-(3,4-dihydroxyphenyl)-5-hydroxyheptane-3-on-5-*O*-β-D-glucopyranoside (Lee *et al*., 2000d).

Compound **6** was a brown amorphous powder (negative FAB MS: *m/z* 475 $[M - H]^-$); on TLC, the green spot was detected by spraying with $FeCl_3$ and the violet spot was detected by spraying 10% H_2SO_4 solution with subsequent heating. The ^{1}H-NMR spectrum of compound **6** revealed one methylene over δ 1.85 - 1.73 and another four methylenes over 2.81 - 2.58, a hydroxy group in the methane signals of δ 4.17, and two sets of aromatic ABX-spin systems, which were present in *meta*- and *ortho*-coupled aromatic signals at δ 7.00 - 6.96 (4H in total, m, H-2″, 6″, 2′, 6′) and 6.69 - 6.65 (4H in total, m, H-3″, 5″, 3′, 5′). Finally, the doublet signals of anomeric proton at δ 4.29 (J = 7.8 Hz) were observed in the ^{1}H-NMR spectrum. The ^{13}C-NMR spectrum showed two *p*-coumaroyl rings and a heptanoid moiety substituted by ketone (δ 210.6, C-

3). Thus, compound **6** was identified as 1,7-bis-(4-hydroxyphenyl)-heptane-3-on-5-*O*-β-D-xylopyranoside (platyphlloside) by comparing the spectral data with values reported in the literature (Smite *et al*., 1993; Nomura *et al*., 1981). These compounds (**1 - 6**) have not been previously isolated from this plant.

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