Studies on the Constituents of *Epimedium koreanum*. III

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A new flavonol glycoside, epimedin I (1), a new chromone, 5,7-dihydroxy-2-(*p*-hydroxy-phenoxy)-6-prenyl-chromone (2), and icariside A_7 (3) were isolated from the aerial parts of *Epimedium koreanum* NAKAI (Berberidaceae) together with six known compounds, chaohuoside A (epimedin L) (4), 8-prenylkaempferol (5), anhydroicaritin (6), ginkgetin (7), isoginkgetin (8) and bilobetin (9). Their structures were established by spectroscopic methods and chemical evidence.

Key words *Epimedium koreanum*; Berberidaceae; epimedin I; chromone derivative; icariside A_7

The aerial parts of several plants of the genus *Epimedium* (Berberidaceae) are used mainly as a tonic. Studies on the constituents of *Epimedium* species have been carried out and many new compounds have been reported. They are mainly flavones, lignans, dihydrophenanthrenes, ionones, terpene glycosides and phenyl ethanoids.[1)]

In our previous paper,[2,3)] the isolation and structural determination of two new flavonol glycosides named epimedoside and epimedin K, together with three known compounds, icariside A_1, maltol and salidroside, were reported as constituents of the aerial parts of *Epimedium* (E.) *koreanum* NAKAI. Further investigation of *E. koreanum* revealed three other new compounds, epimedin I (**1**), 5,7-dihydroxy-2-(*p*-hydroxyphenoxy)-6-prenylchromone (**2**) and icariside A_7 (**3**), in addition to six known constituents, chaohuoside A (epimedin L) (**4**),[4)] 8-prenylkaempferol (**5**),[5)] anhydroicaritin (**6**),[6)] ginkgetin (**7**), isoginkgetin (**8**) and bilobetin (**9**).[7)] Their structures were determined from chemical evidence and spectral data. The last five compounds were isolated for the first time from this species. Epimedin L was presented at the 43rd Annual Meeting of the Japanese Society of Pharmacognosy 1996[8)] and also described by another group as chaohuoside A.

Compound **1**, a yellow powder, gave a positive reaction with Molish and Mg–HCl reagents. Its UV spectrum was characteristic of a flavonoid. The FAB-MS showed a molecular ion peak at *m/z* 880. Combining this information with the results of elemental analysis, its molecular formula was deduced as $C_{41}H_{52}O_{21}$. Its ^{1}H-NMR spectrum exhibited a singlet signal of 5-OH at δ 12.52 (1H, s) and five proton signals in the aromatic region. A signal at δ 6.65 (1H,s) was due to the proton attached to C-6, and a set of *ortho*-coupled doublet signals of four protons at δ 7.93 (2H, d, J=8.5 Hz) and 7.19 (2H, d, J=8.5 Hz) corresponded to an AA′BB′ spin system assignable to the 4′-substituted ring B. A signal at δ 55.4 ppm in the ^{13}C-NMR spectrum and a signal at δ 3.88 (3H, s) in the ^{1}H-NMR spectrum showed the presence of a methoxyl group. The methoxyl group was deduced to be attached at the C-4′ position based on the correlation between the proton signal of a methoxyl group and the C-4′ signal at δ 161.5 ppm observed in the heteronuclear multiple bond correlation (HMBC) spectrum. Signals at δ 131.0, 122.0, 25.4, 21.3, 17.7 ppm in the ^{13}C-NMR spectrum and signals at δ 5.18 (1H, t, J=7.3 Hz), 3.43 (2H, m), 1.68, 1.61 (3H, each s) indicated the presence of a prenyl group. The chemical shift values of the relevant protons and carbons of **1** were similar to those of anhydroicaritin except for the presence of signals due to the sugar moieties and an acetyl group. Therefore, the aglycone of **1** was deduced to be (8-γ,γ-dimethylallyl-3,5,7-trihydroxy -4′-methoxy-flavone (anhydroicaritin). This conclusion was further supported by acidic hydrolysis of the compound, because the aglycone obtained was identical to authentic anhydroicaritin. In the ^{1}H-NMR and ^{13}C-NMR spectra, signals due to one L-rhamnopyranosyl moiety and two D-glucopyranosyl moieties were observed. In the ^{1}H-NMR spectrum, the signal of the anomeric proton of the L-rhamnopyranosyl group appeared at δ 5.34 (1H, br s), and that of the D-glucopyranosyl was observed at δ 4.24 (1H, d, J=7.5 Hz) and 5.01 (1H, d, J=6.5 Hz). The β-glucosidic and α-rhamnosidic linkages of these sugars were inferred from the coupling constants of the anomeric protons. In the HMBC spectrum, the anomeric proton at δ 5.01 (H-1 of glucose, d, J=6.5 Hz) was correlated with C-7 (δ 160.6) of the aglycone. A correlation between the anomeric proton at δ 5.34 (H-1 of rhamnose, br s) and the carbon signal at δ 133.6 due to the C-3 of the aglycone was observed. Moreover, the anomeric proton of another β-D-glucopyranose group at δ 4.24 (1H, d, J=7.5 Hz) was correlated with the carbon signal at δ 76.4 which was assigned to C-3 of the α-L-rhamnopyranose. Therefore, it was deduced that the β-D-glucopyranosyl moiety with an anomeric proton signal at δ 4.24 ppm was substituted at C-3 of the α-L-rhamnopyranosyl moiety. The proton signal at 1.95 (3H, s) and the carbon signals at δ 20.6, 169.6 ppm showed the presence of one acetyl moiety. The acetyl group was determined to be at R_4-C because the carbonyl signal (δ 169.6) was correlated with the proton signal of R_4 at δ 4.83 (1H, t, J=10.0 Hz) and the chemical shift of H-R_4 at δ 4.83 was shifted downfield by 1.68 ppm, compared with the H-R_4 of icarisid II[9)] at δ 3.15 ppm.

From the above data, we concluded that compound **1** was anhydroicaritin 3-*O*-β-D-glucopyranosyl (1→3)-α-L-(4-*O*-acetyl) rhamnopyranoside-7-*O*-β-D-glucopyranoside.

It was named epimedin I according to our previous classification[3)] of constituents of *Epimedium* plants.

2-Phenoxychromones possess a unique flavone-like skeleton in which the A/C ring is linked to the B-ring *via*

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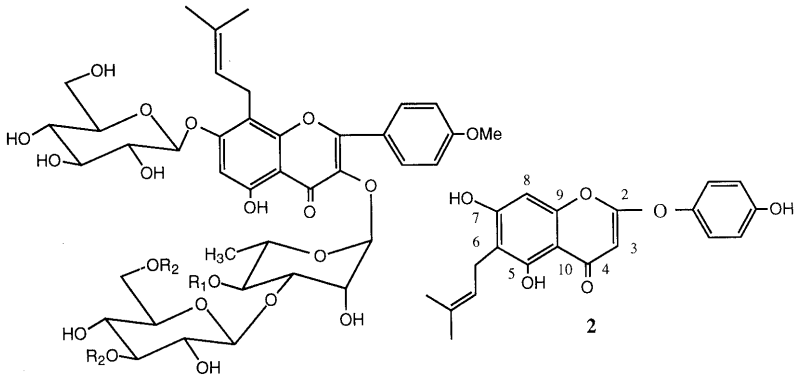
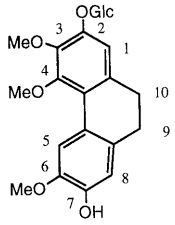
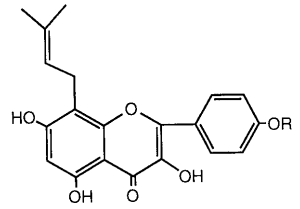


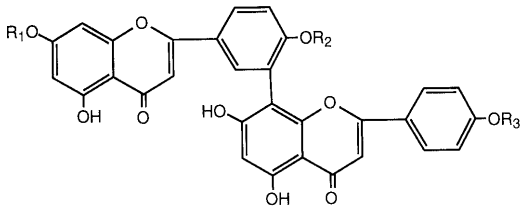
	R1	R2
1	COCH3	H
4	COCH3	COCH3



3



	R
5	H
6	CH3



	R1	R2	R3
7	CH3	CH3	H
8	H	CH3	CH3
9	H	H	CH3

an oxygen atom. Only two Compositae members, one Rosaceae and one Berberidaceae are so far known as a source of this rare group of natural products.[10-12] Spectroscopic data on compound **2** was similar to that of 2-phenoxychromones obtained from *Artemisia capillaris* (Compositae)[10] and *Rosa rugosa* (Rosaceae).[11] The signals at δ 5.04 (1H, s) and 86.7 ppm were characteristic of the H-3 and C-3 in such 2-phenoxychromones.[12] The signals of C-2 (δ 167.6) and C-1′ (δ 143.0) are also characteristic of 2-phenoxychromone derivatives. The chemical shifts of the relevant protons and carbons of **2** were similar to those of 5,7-dihydroxy-2-(*p*-hydroxyphenoxy)chromone except for the presence of signals due to the prenyl group which appeared at δ 130.6, 122.0, 25.4, 20.8, 17.6 ppm in the ^{13}C-NMR spectrum and at δ 5.15 (1H, t, J=7.0 Hz), 3.20 (2H, m), 1.71, 1.62 (3H, each s) in the ^{1}H-NMR spectrum. To confirm the position of the prenyl group attached to the C-6 or C-8 of the A ring, **2** was subjected to ordinary acetylation to give **2a**. The ^{1}H-NMR spectrum (2.33, 2.35 and 2.41 ppm, each 3H, s) of **2a** showed the existence of three acetoxyl groups, suggesting that **2** possessed three hydroxyl groups. The H-8 proton signal at δ 7.15 of **2a** was down-shifted by 0.72 ppm, compared with the corresponding one of **2** at δ 6.43. The position of the prenyl group was assigned from HMBC experiments on **2**. The proton at δ 13.04 (5-OH) showed cross-peaks with the carbons at δ 111.2 (C-6) and 101.5 (C-10), and the proton at δ 6.43 (H-8) showed cross-peaks with the carbons at δ 111.2 (C-6) and δ 152.5 (C-9). This supported the position of the prenyl group of **2** as being at C-6, and the structure was assigned as 5,7-dihydroxy-2-(*p*-hydroxyphenoxy)-6-prenylchromone.

Compound **3** was obtained as a white powder. The UV spectrum showed absorption maxima at 281, 302 and 313 nm, suggesting the presence of a 9,10-dihydrophenanthrene skeleton. The ^{1}H-NMR spectrum exhibited a multiplet signal due to benzylic methylene protons at δ 2.66 (4H), three singlet signals due to methoxyl protons at δ 3.857, 3.863 and 4.08 (each 3H), a doublet signal due to an anomeric proton at δ 5.70 (1H, d, J=7.0 Hz), three singlet signals due to aromatic protons at δ 7.13, 7.37 and 8.32 (each 1H) and a singlet signal of a hydroxyl group at δ 11.08. The ^{13}C-NMR spectrum showed two carbon signals of the benzylic methylene at δ 30.9 and 29.5 ppm besides carbon signals of two benzene rings.

From these data, **3** was deduced to be a 9,10-dihydrophenanthrene derivative having three methoxyl groups

and a glycosyl residue. The ^{13}C-NMR spectrum exhibited three methoxyl carbon signals at δ 56.3, 60.6 and 61.4; the latter two signals might be due to *ortho*-disubstituted methoxyl groups because of the downfield shifts.[13,14] Acid hydrolysis of **3** afforded glucose as the sugar moiety. By comparison of the carbon signals of **3** with those of epimedoicarisoside A,[14] we concluded that the skeletons of the two compounds were similar except for the C-8 signal (δ 116.2 ppm) which was shifted downfield by 4.55 ppm compared with the corresponding signal of epimedoicarisoside A (δ 111.6 ppm). This phenomenon is due to the presence of a hydroxyl group instead of a methoxyl group at C-7. Thus, the β-D-glucopyranosyl residue was deduced to be attached at C-2. Methylation of compound **3** with $(CH_3)_2SO_4$–K_2CO_3 afforded epimedoicarisoside A. The identity of the product was established by comparison of the reported physical and spectral data (mp, ^{1}H-NMR).

From above analysis, compound **3** was found to be 7-hydroxy-3,4,6-trimethoxy-9,10-dihydro-phenanthrene-2-*O*-β-D-glucopyranoside. It is a new compound and was named icariside A_7.

Experimental

General Procedures ^{1}H- and ^{13}C-NMR spectra, with tetramethylsilane (TMS) as internal standard, were recorded on a JEOL α-500 FT-NMR. EI-MS was measured on a JEOL JMS-SX 102. UV spectra were measured on a Shimadzu UV-260. Silica-gel was from the Qingdao Marine Chemical Factory, Shandong Province, China. High performance liquid chromatography (HPLC) was carried out on a Shimadzu LC-10 instrument. The plant was purchased from Liaoning Crude Drug Co., Ltd. in October 1992 in Liaoning Province, China. Voucher specimens have been deposited at the herbarium of the Shenyang Pharmaceutical University.

Isolation The aerial parts of *E. koreanum* NAKAI (25 kg) were extracted twice with 70% ethanol. After removal of the ethanol, the extract was absorbed on Amberlite D 101 and the resin was eluted successively with water, 40% and 95% ethanol. Part of the 95% ethanol eluate (127 g) was chromatographed on silica-gel with a chloroform–methanol gradient. The chloroform–methanol (20 : 1) eluate was subjected to silica-gel column chromatography with cyclohexane–ethyl acetate–acetone 4 : 1 : 1, and 2 : 1 : 1. Compound **2** (5 mg), Compound **5** (7 mg), **6** (17 mg), **7** (21 mg), **8** (19 mg) and **9** (20 mg) were obtained. The chloroform–methanol (10 : 1) eluate was subjected to silica-gel column chromatography with acetone–benzene–ethyl acetate (2 : 1 : 1) to give compound **4** (25 mg). Chloroform–methanol (3 : 1) eluate was further fractionated by HPLC on an ODP-501E column (acetonitrile–water 28 : 72) to give compound **1** (9 mg) . Part of the 40% ethanol eluate (250 g) was chromatographed on silica-gel with a chloroform–methanol gradient. The chloroform–methanol (10 : 1) eluate was subjected to silica-gel column chromatography with cyclohexane–ethyl acetate–acetone (1 : 1 : 1). The eluate was further fractionated by HPLC on an ODP-501E column (acetonitrile–water 30 : 70) to give compound **3** (12 mg).

Epimedin I A yellow powder, gave a positive reaction with Molish and Mg–HCl reagents. UV λ_{max}^{MeOH} (nm): 270, 313, 349; 272, 354; (+NaOMe): 279, 306, 343, 409; (+$AlCl_3$): 280, 305, 338, 411; (+$AlCl_3$/HCl): 270, 313; (+NaOAc): 270, 313, 348; (+NaOAc/H_3BO_3). FAB-MS *m/z*: 880. EI-MS *m/z*: 368, 353, 313, 300, 165, 135. ^{1}H-NMR (DMSO-d_6) δ: 12.52 (1H, s, 5-OH), 7.93 (2H,d, J=8.5 Hz, H-2′, 6′), 7.19 (2H, d, J=8.5 Hz, H-3′, 5′), 6.65 (1H, s, H-6), 5.18 (1H, t, J=7.3 Hz, H-12), 3.57, 3.43 (2H, m, H-11), 1.68 (3H, s, H-15), 1.61 (3H, s, H-14); G′: 5.01 (1H,d, J=6.5 Hz, H-1), 3.32 (2H, m, H-2,3), 3.19 (1H, m, H-4), 3.45 (1H, m, H-5), 3.73 (1H, m, H-6a), 3.47 (1H, m, H-6b); R: 5.34 (1H, br s, H-1), 4.10 (1H, m, H-2), 3.82 (1H, dd, J=2.4, 9.7 Hz, H-3), 4.83 (1H, t, J=10.0 Hz, H-4), 3.26 (1H, m, H-5), 0.74 (3H, d, J=6.0 Hz, CH_3-6) ; G″: 4.24 (1H, d, J=7.5 Hz, H-1), 3.41 (2H, m, H-2, H-3), 3.21 (1H, m, H-4), 3.61 (1H, m, H-5), 3.74 (1H, m, H-6a) , 3.44 (1H, m, H-6b), 3.88 (3H, s, 4′-OCH_3), 1.95 (3H, s, R_4-Ac) . ^{13}C-NMR (DMSO-d_6): 178.1 (C-4), 161.5 (C-4′), 160.6 (C-7), 159.0 (C-5), 157.3 (C-2), 153.0 (C-9), 133.6 (C-3), 131.0 (C-13), 130.6 (C-2′, 6′), 122.0* (C-12), 121.9* (C-1′), 114.1 (C-3′, 5′), 108.3 (C-8), 105.5 (C-10), 98.1 (C-6), 25.4 (C-14), 21.3 (C-11), 17.7 (C-15); G′: 100.5 (C-1), 73.2 (C-2), 76.5 (C-3), 69.6 (C-4), 77.1 (C-5), 60.5 (C-6); R: 100.9 (C-1), 69.1 (C-2), 76.4 (C-3), 71.2 (C-4), 68.0 (C-5) 16.9 (C-6); G″: 101.6 (C-1), 73.2 (C-2), 73.9 (C-3), 70.2 (C-4), 73.7 (C-5), 60.7 (C-6); 55.4 (4′-OCH_3), 169.6, 20.6 (R_4-Ac), (note: * assignment may be interchanged, G′, G″ and R are those of the glucose at C-7 and the exo-glucose and *endo*-rhamnose at C-3, respectively). *Anal.* Calcd for $C_{41}H_{52}O_{21}$: C, 55.91; H, 5.95. Found: C, 55.96; H, 5.92.

Acid Hydrolysis **1** (0.5 mg) was dissolved in 0.1 ml methanol and concentrated HCl (3—4 drops). The solution was taken up in capillaries and heated for 3 h at 60 °C, then subjected to silica-gel TLC analysis together with authentic samples (glucose, rhamnose and anhydroicaritin). 1) Developing solvent: $CHCl_3$–CH_3OH 2 : 1. Glucose and rhamnose were detected. 2) Developing solvent: cyclohexane–ethyl acetate 1 : 1. The aglycone of the compound had the same *Rf* as anhydroicaritin.

Compound 2 (5,7-Dihydroxy-2-(*p*-hydroxyphenoxy)-6-prenylchromone) A colorless powder. UV λ_{max}^{MeOH} (nm): 290. EI-MS *m/z*: 368, 353, 313, 300, 165. ^{1}H-NMR (DMSO-d_6) δ: 13.04 (1H, s, 5-OH), 9.77 (1H, s, 4′-OH), 7.18 (2H,d, J=8.5 Hz, H-2′, 6′), 6.87 (2H, d, J=8.5 Hz, H-3′, 5′), 6.43 (1H, s, H-8), 5.15 (1H, t, J=7.0 Hz, H-12), 5.04 (1H, s, H-3), 3.20 (2H, m, H-11), 1.71 (3H, s, H-15), 1.62 (3H, s, H-14). ^{13}C-NMR (DMSO-d_6): 183.0 (C-4), 167.6 (C-2), 161.4 (C-7), 158.2 (C-5), 156.0 (C-4′), 152.5 (C-9), 143.0 (C-1′), 130.6 (C-13), 122.0 (C-12), 121.7 (C-2′, 6′), 116.4 (C-3′, 5′), 111.2 (C-6), 101.5 (C-10), 93.0 (C-8), 86.7 (C-3), 25.4 (C-14), 20.8 (C-11), 17.6 (C-15) . *Anal.* Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.84; H, 5.18.

Compound 2a Compound **2** (4.5 mg) was dissolved in pyridine and acetic anhydride (each 0.3 ml), and the reaction mixture was left at room temperature. The reagents were evaporated *in vacuo* and a triacetate **2a** (4 mg) was obtained. ^{1}H-NMR ($CDCl_3$) δ: 7.16 (4H, m, H-2′, 3′, 5′, 6′), 7.15 (1H, s, H-8), 5.35 (1H, s, H-3), 5.00 (1H, t, J=7.3 Hz, H-12), 2.34 (2H, m, H-11), 2.33, 2.35, 2.41 (9H, each s, OAc), 1.72 (3H, s, H-15), 1.67(3H, s, H-14). ^{13}C-NMR ($CDCl_3$): 177.5 (C-4), 169.1, 168.6, 167.8 (OAc), 166.2 (C-2), 153.0 (C-7), 152.5 (C-5), 148.9 (C-4′), 148.7 (C-9), 132.8 (C-1′), 125.3 (C-13), 123.5 (C-2′, 6′), 121.7 (C-3′, 5′), 120.5 (C-12), 117.5 (C-6), 114.3 (C-10), 109.5 (C-8), 91.5 (C-3), 25.5 (C-14), 21.1 (OAc), 20.9, 20.9 (OAc), 20.7 (C-11), 17.9 (C-15).

Compound 3 (Icariside A_7) A white powder, gave a positive reaction with Molish reagent. UV λ_{max}^{MeOH} (nm): 281, 302, 313. ^{1}H-NMR (pyridine-d_5) δ: 11.08 (1H, s, OH-2) , 8.32 (1H, s, H-5), 7.37 (1H, s, H-1), 7.13 (1H, s, H-8), 5.70 (1H, d, J=7.0 Hz, H-1′), 3.857, 3.863, 4.08 (each 3H, s, 3-OCH_3/4-OCH_3/6-OCH_3), 2.66 (4H, m, H_2-9/H_2-10). ^{13}C-NMR (pyridine-d_5) δ: 151.8 (C-4), 150.8 (C-2), 147.2, 147.1 (C-6/C-7), 143.0 (C-3), 134.5 (C-10a), 132.0 (C-8), 124.4 (C-4b), 122.8 (C-4a), 116.2 (C-8), 112.6, 112.6 (C-1/C-5), 102.7 (C-1′), 79.1, 78.7 (C-3′/C-5′), 75.0 (C-2′), 71.4 (C-4′), 62.5 (C-6′), 61.4, 60.6 (3-OCH_3/4-OCH_3), 56.3 (6-OCH_3), 30.9 (C-10), 29.5 (C-9).

Methylation of Compound 3 A mixture of compound **3** (4 mg), dimethyl sulfate (0.2 ml) and anhydrous potassium carbonate (40 mg) in dry acetone (2 ml) was refluxed for 3 h with stirring. After removal of the precipitate by filtration, the filtrate was concentrated to give a syrup (3 mg), which showed four singlets due to methoxyl protons at δ 3.84, 3.79, 3.78 and 3.72 (each 3H) in the ^{1}H-NMR spectrum (DMSO-d_6).

Chaohuoside A (Epimedin L) A yellow powder, gave a positive reaction with Molish and Mg–HCl reagents. ^{1}H-NMR (DMSO-d_6) δ: 12.49 (1H, s, 5-OH), 7.89 (2H, d, J=8.6 Hz, H-2′, 6′), 7.16 (2H, d, J=8.6 Hz, H-3′, 5′), 6.64 (1H, s, H-6), 5.17 (1H, t, J=7.0 Hz, H-12), 1.68 (3H, s, H-15), 1.60 (3H, s, H-14), G′; 5.04 (1H, d, J=7.0 Hz, H-1); R: 5.36 (1H, br s, H-1), 4.83(1H, t, J=9.8 Hz, H-4), 0.72 (3H, d, J=6.0 Hz, H-6), 2.02 (3H, s, R_4-Ac) ; G″: 4.40 (1H, d, J=7.3 Hz, H-1), 3.88 (3H, s, 4′-OCH_3), 1.99[a] (3H,s, G″$_3$-Ac), 1.94[a] (3H, s, G″$_6$-Ac). ^{13}C-NMR (DMSO-d_6); 178.0 (C-4), 161.5 (C-4′), 161.6 160.5 (C-7), 159.0 (C-5), 157.3 (C-2), 153.0 (C-9), 133.8 (C-3), 131.0 (C-13), 130.4 (C-2′, 6′), 122.0 (C-12), 122.0 (C-1′), 114.1 (C-3′, 5′), 108.4 (C-8), 105.5 (C-10), 98.2 (C-6), 25.4 (C-14), 21.3 (C-11), 17.7 (C-15); G′: 100.5 (C-1), 73.3 (C-2), 76.5 (C-3), 69.6 (C-4), 77.1 (C-5), 60.6 (C-6); R: 101.0 (C-1), 69.4 (C-2), 77.1 (C-3), 70.9 (C-4), 68.3 (C-5), 16.9 (C-6); G″: 104.5 (C-1), 70.7 (C-2), 77.6 (C-3), 68.1 (C-4), 73.3[b] (C-5), 63.4 (C-6), 55.5 (4′-OCH_3), 170.2, 20.4[c] (R_4-Ac), 169.7, 21.0[c] (G″$_3$-Ac), 169.5, 20.6[c] (G″$_6$-Ac).

(note: a,b,c assignments may be interchanged, G′, G″ and R are those of the glucose at C-7 and the *exo*-glucose and *endo*-rhamnose at C-3,

respectively).

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