Studies on the Constituents of Turkish Plants. I. Flavonol Triglycosides from the Fruit of *Rhamnus thymifolius*

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Two new flavonol glycosides have been isolated from the fruit of Turkish *Rhamnus thymifolius* (Rhamnaceae) and their structures were elucidated as kaempferol-3-*O*-α-L-rhamnopyranosyl(1→3)-(4-*O*-acetyl)-*O*-α-L-rhamnopyranosyl-(1→6)-*O*-β-D-galactopyranoside and kaempferol-4′-*O*-α-L-rhamnopyranosyl(1→3)-*O*-α-L-rhamnopyranosyl(1→6)-*O*-β-D-galactopyranoside based on spectral and chemical evidence.

Keywords *Rhamnus thymifolius*; Rhamnaceae; kaempferol triglycoside; Turkish plant

There are 21 species of *Rhamnus* in Turkey, of which seven are endemic.[1] From the dried fruits of *Rhamnus thymifolius* BORNM collected at Adapazari in Turkey, two new flavonoid glycosides (**2** and **3**) were isolated together with kaempferol-7-*O*-methyl-3-*O*-α-L-rhamnopyranosyl-(1→3)-*O*-α-L-rhamnopyranosyl(1→6)-*O*-β-D-galactopyranoside (**1**),[2] kaempferol-7-*O*-methyl ether (rhamnocitrin, **4**), kaempferol (**5**), emodin (**6**), emodin-8-*O*-β-D-glucopyranoside (**7**), *p*-hydroxybenzoic acid (**8**), and protocatechuic acid (**9**). This paper deals with the isolation of these products and the elucidation of the structures of compounds **1**, **2** and **3**.

Compounds **1**, **2** and **3** were obtained as yellow needles exhibiting characteristic chemical properties of flavonoid glycosides (positive color reaction with Mg–HCl, $FeCl_3$ and anthrone).

Compound **1** has the molecular formula $C_{34}H_{42}O_{19}$, as ascertained from the secondary ion mass spectrum (SIMS). The proton nuclear magnetic resonance (^{1}H-NMR, pyridine-d_5) spectrum of **1** exhibited proton signals due to kaempferol, a methoxyl group [δ 3.73 (3H, s)] and anomeric protons [each 1H, at δ 5.19 br s, 5.91 br s, 5.99 (d, J=8 Hz)] along with other proton signals assignable to a sugar moiety. On hydrolysis with 3% HCl, **1** gave kaempferol-7-*O*-methyl ether as the aglycone, which was identical with an authentic sample (rhamnocitrin, **4**) by direct comparison, and D-galactose ($[\alpha]_D$ +74° in H_2O) and L-rhamnose ($[\alpha]_D$ +10° in H_2O) as component sugars. A comparison of the ultraviolet (UV) shifts of **1** with those of **4** in MeOH solution and on the addition of NaOAc and $AlCl_3$ suggested that the sugar moiety was bound to the C-3 hydroxyl group of kaempferol.[3] The sugar sequence and the anomeric configurations were established as described below. In the carbon-13-nuclear magnetic resonance (^{13}C-NMR, pyridine-d_5) spectrum of **1**, the signals corresponding to three anomeric carbons [δ 102.07 ($^1J_{CH}$ 167.9), 104.88 ($^1J_{CH}$ 156.9), 104.13 ($^1J_{CH}$ 168.1)] and the terminal carbons of the hexoses (δ 67.05, 18.52, 18.43) in the sugar moiety indicated that the sugar moiety consisted of one galactose and two rhamnoses. Moreover, intense differential nuclear Overhauser effects (NOEs) in the ^{1}H-NMR spectrum of **1** were observed between the anomeric proton (1‴-H) of the inner rhamnose and 6″-H of galactose and between the anomeric proton (1⁗-H) of the terminal rhamnose and the 3‴-H of the inner rhamnose. From these findings and $^1J_{CH}$ values of the three anomeric carbon atoms,[4] it is clear that the terminal rhamnose is linked to the hydroxyl group at C-3 of the inner rhamnose in α-configuration and the inner rhamnose is located at the hydroxyl group on C-6 of galactose in α-configuration, while the galactose is β-linked to the C-3 hydroxyl group of kaempferol. The assignments of all signals due to the sugar moieties (Tables I and II) were determined by decoupling experiment, means of ^{1}H–^{1}H or ^{13}C–^{1}H two dimensional correlation spectroscopy (2D COSY). Therefore, compound **1** was established to be kaempferol-7-*O*-methyl-3-*O*-α-L-rhamnopyranosyl(1→3)-*O*-α-L-rhamnopyranosyl(1→6)-*O*-β-D-galactopyranoside. This compound is identical with catharticin isolated from *Rhamnus catharticus*, and also with alaternin from *R. alatenus*.[2]

Compound **2** gave the molecular formula $C_{35}H_{42}O_{20}$. The appearance of a signal at 1.96 ppm (3H, s) in the

TABLE I. ^{1}H-NMR Chemical Shifts (δ) of the Sugar Moieties of Compounds **1** and **2** (Pyridine-d_5)

	1	**2**
Gal		
1″	5.99 (d, 8)	6.00 (d, 8)
2″	4.73 (dd, 8, 8)	4.75 (dd, 8, 8)
3″	*ca.* 4.19	4.25 (dd, 10, 8)
4″	*ca.* 4.39	*ca.* 4.44
5″	4.15 m	*ca.* 4.18
6″	4.03 (dd, 10, 7)	4.00 (dd, 10, 7)
	ca. 4.39	*ca.* 4.40
Rha		
1‴	5.19 (br s)	5.19 (br s)
2‴	*ca.* 4.55	4.57 (dd, 3, 2)
3‴	4.45 (dd, 9, 3)	*ca.* 4.43
4‴	*ca.* 4.25	5.74 (t, 10, 10)
5‴	*ca.* 4.21	*ca.* 4.21
6‴	1.45 (d, 6)	1.17 (d, 6)
Rha		
1⁗	5.91 (br s)	5.46 (br s)
2⁗	4.66 (dd, 3, 2)	*ca.* 4.48
3⁗	4.49 (dd, 9, 3)	*ca.* 4.37
4⁗	*ca.* 4.19	*ca.* 4.15
5⁗	*ca.* 4.55	*ca.* 4.51
6⁗	1.54 (d, 6)	1.51 (d, 6)
4‴-OAc	1.96 (3H, s)	

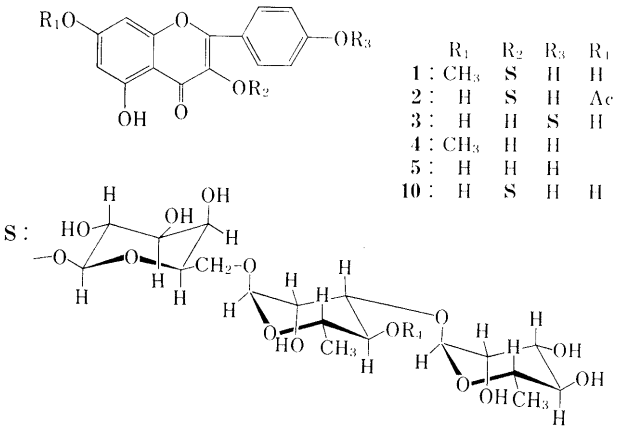
Figures in parentheses are coupling constants in hertz (Hz).

Table II. ^{13}C-NMR Chemical Shifts (δ) of Compounds **1**, **2**, **3**, and **10** (Pyridine-d_5)

	1	2	3	10
Aglycone moiety				
2	158.25	157.82	146.40	158.12
3	135.60	135.54	138.12	135.52
4	178.86	178.72	177.24	178.70
5	162.28	162.72	162.25	162.42
6	98.58	99.93	99.21	99.96
7	165.91	166.06	165.55	166.20
8	92.55	94.65	94.59	94.69
9	157.33	157.65	157.32	157.61
10	106.21	105.15	104.36	105.10
1′	121.80	121.82	125.92	121.81
2′	132.08	131.97	130.01	131.97
3′	116.12	116.05	116.70	116.05
4′	161.89	161.77	159.64	161.78
5′	116.12	116.05	116.70	116.05
6′	132.08	131.97	130.01	131.97
Sugar moiety				
Gal				
1″	104.88 (156.9)	105.06 (157.0)	102.62 (156.9)	104.93
2″	73.12	73.12	71.95	73.11
3″	75.19	75.20	75.59	74.91
4″	69.65	69.61	70.13	69.57
5″	75.19	74.99	75.04	75.16
6″	67.05	67.31	67.55	66.99
Rha				
1‴	102.07 (167.9)	101.95 (169.0)	102.29 (167.9)	101.90
2‴	71.79	71.47	71.83	71.90
3‴	79.85	78.12	79.68	79.76
4‴	72.67	73.73	72.45	72.75
5‴	69.97	67.25	69.90	69.83
6‴	18.52	17.82	18.71	18.55
Rha				
1⁗	104.13 (168.1)	104.09 (167.9)	104.13 (167.8)	104.13
2⁗	72.38	72.51	72.85	72.29
3⁗	72.67	72.39	72.53	72.56
4⁗	74.14	73.77	74.20	73.92
5⁗	69.97	70.16	69.90	70.26
6⁗	18.43	18.43	18.49	18.45

Figures in parentheses are $^1J_{CH}$ values in hertz (Hz).

^{1}H-NMR spectrum and signals at 20.71 and 170.16 ppm in the ^{13}C-NMR spectrum, together with an ester carbonyl band at 1706 cm^{-1} in the infrared (IR) spectrum, indicated the presence of an acetyl group located in the sugar moiety. The alkaline hydrolysis of **2** yielded compound **10**, which afforded kaempferol, D-galactose and L-rhamnose of acidic hydrolysis. The ^{13}C-NMR signals of the sugar moiety of **10** were quite similar to those of **1**, suggesting that **10** has the same sugar sequence as **1** (Table II). In a comparison of the ^{13}C-NMR spectrum of **2** with that of **10**, acetylation shifts[5] were observed at the C-3‴ (−1.64 ppm), C-4‴ (+0.98 ppm), and C-5‴ (−2.58 ppm) signals of **2**. Furthermore, the NOEs in the ^{1}H-NMR spectrum of **2** were observed between the anomeric proton (1⁗-H) of the terminal rhamnose and 2⁗-H, 3‴-H and a methyl proton of the acetyl group, and between the methine proton bearing the acetyl group (4‴-H) and 6‴-H, 5‴-H and the methyl proton of the acetyl group, while the heteronuclear multiple bond connectivity (HMBC) spectrum of **2** showed that 4‴-H was correlated with C-3‴, C-5‴, and carbon signals of the



	R1	R2	R3	R4
1	CH3	S	H	H
2	H	S	H	Ac
3	H	H	S	H
4	CH3	H	H	
5	H	H	H	
10	H	S	H	H

Chart 1

acetyl group (C$\underline{H}_3$C=O). These findings indicated the acetyl group to be bound to the C-4‴ hydroxyl group of the inner rhamnose. Accordingly, **2** was concluded to be kaempferol-3-*O*-α-L-rhamnopyranosyl(1→3)-(4-*O*-acetyl)-*O*-α-L-rhamnopyranosyl(1→6)-*O*-β-D-galactopyranoside. The same trisaccharide bearing the acetoxyl group at C-4‴ (C-4 in the inner rhamnose) has already been found in other flavonol triglycoside isolated from *Rhamnus saxatilis*, but in that case, the aglycone was quercetin-7-*O*-methyl ether (rhamnetin).[2]

Compound **3** showed the molecular formula $C_{33}H_{40}O_{19}$, and contained kaempferol and the same component sugars as **10**. As a comparison of the ^{13}C-NMR spectrum of the sugar moiety of **3** with that of **10** revealed close similarity, except for the signals corresponding to C-1″ (−2.31 ppm) and C-2″ (−1.16 ppm), **3** has the same sugar sequence as **10**. The position of the linkage between the sugar moiety and kaempferol was also determined by comparison of the carbon chemical shifts due to the aglycone moiety of **3** with those of **10**. The C-2 (−11.72 ppm), C-3 (+2.60 ppm), and C-4 (−1.46 ppm) signals of **3** indicated that the C-3 hydroxyl group of kaempferol is unsubstituted,[6] and the location of the sugar moiety at the C-4′ hydroxyl group of kaempferol was established by the glycosylation shifts[6] at the C-1′ (+4.11 ppm) and C-4′ (−2.14 ppm) signals. Thus, compound **3** was assigned as kaempferol-4′-*O*-α-L-rhamnopyranosyl(1→3)-*O*-α-L-rhamnopyranosyl(1→6)-*O*-β-D-galactopyranoside.

Experimental

The following instruments were used to obtain physical data: melting point, Yanagimoto micro-melting point apparatus (values are uncorrected); optical rotation, JASCO DIP-360 automatic polarimeter; IR spectra, Hitachi 270-30 IR spectrometer; UV spectra, Hitachi 150-20 spectrophotometer; SIMS, Hitachi M-2000A double-focus high-resolution mass spectrometer with polyethylene glycol (No. 1000) as a standard; ^{1}H-NMR spectra, Hitachi R-600 FT-NMR spectrometer (60 MHz) and JEOL GSX-400 FT-NMR spectrometer (400 MHz) with tetramethylsilane as an internal standard (s, singlet; d, doublet; t, triplet; m, multiplet); ^{13}C-NMR spectra, JEOL GSX-400 FT-NMR spectrometer and JEOL GSX-500 FT-NMR spectrometer with tetramethylsilane as an internal standard. Gas-liquid chromatography (GLC) was done with a Hitachi gas chromatograph model 163 using a capillary column (25 m × 0.25 mm i.d., OV-1701); thin layer chromatography (TLC) was run on precoated TLC plates (Merck, Kieselgel 60F-254); for column chromatography, Kieselgel 60 (70—230 mesh, Merck), Sephadex LH-20 (Pharmacia), or MCI-CHP20P (Mitsubishi Chemical Ltd.), Polyamide C-200 (Wako Pure Chemical) was used. Silylating Reagent, TMS-HT Kit [hexamethyldisila-

zane and trimethylchlorosilane in pyridine (Tokyo Kasei Kogyo Co., Ltd.)] was used for silylation.

Extraction and Isolation Dried fruits (540 g) of *Rhamnus thymifolius* (Rhamnaceae), collected at Adapazari, Turkey in October, 1980, were extracted with MeOH (2 l) in a Soxhlet extractor for 10 h. The solvent was evaporated off under reduced pressure to give the MeOH extract (240 g), which was partitioned into $CHCl_3$–MeOH–H_2O (5 : 3 : 8), and the H_2O layer was extracted with EtOAc and then with *n*-BuOH. Each solvent was evaporated off under reduced pressure to yield the $CHCl_3$ extract (5.39 g), the EtOAc extract (60.2 g) and the *n*-BuOH extract (30.5 g). The $CHCl_3$ extract was subjected to column chromatography on silica gel (100 g) using gradient elution with $CHCl_3$–MeOH (100 : 0→17 : 3). The $CHCl_3$–MeOH (95 : 5) fraction was chromatographed on a Sephadex LH-20 column (MeOH) to furnish emodin (**6**, 15 mg) and rhamnocitrin (**4**, 20 mg) and the $CHCl_3$–MeOH (9 : 1) fraction was chromatographed on polyamide (MeOH) and Sephadex LH-20 (MeOH) columns to provide rhamnocitrin (**4**, 55 mg) and kaempferol (**5**, 150 mg). The EtOAc extract was subjected to column chromatography on silica gel (EtOAc–MeOH–H_2O, 88 : 7 : 5) to yield fractions A—D. Fraction A was subjected to repeated chromatographies on polyamide (MeOH) and Sephadex LH-20 (MeOH) to afford emodin-8-*O*-*β*-D-glucoside (**7**, 40 mg). Fraction B was separated by repeated column chromatographies on silica gel ($CHCl_3$–MeOH, 8 : 1) and Sephadex LH-20 (MeOH) to give *p*-hydroxybenzoic acid (**8**, 20 mg) and protocatechuic acid (**9**, 18 mg). Fraction C was purified by repeated column chromatographies on polyamide (MeOH) and Sephadex LH-20 (MeOH–H_2O, 2 : 1) to provide compound **2** (30 mg). Fraction D was chromatographed on polyamide (MeOH), followed by Sephadex LH-20 (MeOH–H_2O, 2 : 1) to give compound **1** (20 mg). The *n*-BuOH extract was subjected to repeated column chromatographies on MCI-CHP20P (20% aqueous MeOH and finally MeOH), silica gel [1) EtOAc–MeOH–H_2O, 88 : 7 : 5, 2) $CHCl_3$–MeOH–H_2O, 30 : 9 : 1] and Sephadex LH-20 (MeOH–H_2O, 2 : 1) to furnish compounds **1** (200 mg), **2** (90 mg), and **3** (150 mg), respectively. The physical data for compounds **4**—**9** were identical with those of authentic samples by direct comparison.

Compound **1**: Yellow needles from a mixture of MeOH and H_2O, mp 225—227 °C, SIMS *m/z*: 755.2345 ($[M+H]^+$) $C_{34}H_{43}O_{19}$; requires 755.2395. $[\alpha]_D^{24}$ −36.6° (*c* = 1.0, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3428 (OH), 2904, 1660 (C=O), 1598, 1494, 1454, 1352, 1216, 1172, 1140. UV λ_{max} nm (log ε): (MeOH) 266.3 (4.01), 350.4 (3.95); (+NaOMe) 268.6, 395.4; (+NaOAc) 266.2, 359.6; (+NaOAc/H_3BO_3) 266.2, 297.5 sh, 353.5; (+$AlCl_3$) 274.8, 304.0, 355.2, 396.0; (+$AlCl_3$/HCl) 275.1, 302.6, 351.0, 395.4. ^{1}H-NMR (pyridine-d_5) δ: aglycone moiety (kaempferol); 3.73 (3H, s, 7-OC<u>H</u>$_3$), 6.59 (1H, d, *J* = 2 Hz, 8-H), 6.63 (1H, d, *J* = 2 Hz, 6-H), 7.27 (2H, d, *J* = 8 Hz, 3′-H, 5′-H), 8.51 (2H, d, *J* = 8 Hz, 2′-H, 6′-H), 13.08 (1H, br s, 5-O<u>H</u>), sugar moiety; shown in Table I. ^{13}C-NMR (pyridine-d_5) δ: shown in Table II.

Acid Hydrolysis of Compound 1 Compound **1** (70 mg) was treated with 3% aqueous HCl (10 ml) at 80 °C for 5 h. After cooling, the reaction mixture was neutralized with IRA-45 (OH^- form) and the resin was filtered off. The filtrate was extracted with EtOAc, and the organic solution was concentrated. The solution was chromatographed (SiO_2, 10 g, $CHCl_3$–MeOH, 19 : 1) to give kaempferol 7-methyl ether, which was identical with an authetic sample (rhamnocitrin **4**). The water layer was concentrated and the residue was purified by column chromatography (SiO_2, 1 g, EtOAc–MeOH–H_2O, 77 : 13 : 10) to yield D-galactose {2 mg, $[\alpha]_D^{24}$ +74° (*c* = 0.2, H_2O)} and L-rhamnose {5 mg, $[\alpha]_D^{24}$ +10° (*c* = 0.5, H_2O)}. Its trimethylsilyl ether was identical with an authentic sample by GLC analysis. [t_R (galactose) 4.03, 5.64, 6.52; t_R (rhamnose) 2.51, 3.12 temp. 185 °C].

Compound **2**: Yellow needles from a mixture of MeOH and H_2O mp 225—227 °C. SIMS *m/z*: 783.2359 ($[M+H]^+$) $C_{35}H_{43}O_{20}$; requires 783.2348. $[\alpha]_D^{24}$ −37.1° (*c* = 2.08, H_2O). IR ν_{max}^{KBr} cm^{-1}: 3444 (OH), 1706 (CH_3CO), 1654, 1604, 1560, 1488, 1452, 1282, 1170, 1140, 1078, 1048. UV λ_{max} nm (log ε): (MeOH) 266.5 (4.01), 352.0 (3.94); (+NaOMe) 274.5, 326.0, 402.5; (+NaOAc) 274.5, 388.5; (+NaOAc/H_3BO_3) 266.8, 354.5; (+$AlCl_3$) 274.0, 305.0, 354.3, 396.5; (+$AlCl_3$/HCl) 275.0, 303.7, 350.8, 397.0. ^{1}H-NMR (pyridine-d_5) δ: aglycone moiety (kaempferol); 6.72 (1H, d, *J* = 2 Hz, 6-H), 6.74 (1H, d, *J* = 2 Hz, 8-H), 7.19 (2H, d, *J* = 9.5 Hz, 3′-H, 5′-H), 8.48 (2H, d, *J* = 9.5 Hz, 2′-H, 6′-H), 13.15 (1H, br s, 5-O<u>H</u>), sugar moiety; shown in Table I. ^{13}C-NMR (pyridine-d_5) δ: shown in Table II.

Alkaline Hydrolysis of 2 A mixture of **2** (70 mg) and 0.17 N NaOMe in MeOH (3 ml) was treated at 1 °C for 30 min. The mixture was diluted with H_2O (17 ml), then neutralized with Dowex 50W × 8 and the resin was filtered off. The filtrate was evaporated under reduced pressure to yield a product (60 mg), which was purified by column chromatography (SiO_2, 7 g, $CHCl_3$–MeOH–H_2O, 20 : 9 : 1) to afford compound **10** (42 mg).

Acid Hydrolysis of 10 Compound **10** (30 mg) was hydrolyzed as described for **1**. Kaempferol as the aglycone moiety and D-galactose and L-rhamnose as sugar moieties were identified by direct comparison with authentic samples.

Compound **3**: Yellow needles from a mixture of MeOH and H_2O, mp 205—207 °C. SIMS *m/z*: 741.2241 ($[M+H]^+$) $C_{33}H_{41}O_{19}$; requires 741.2242. $[\alpha]_D^{24}$ −88.6° (*c* = 0.87, H_2O). IR ν_{max}^{KBr} cm^{-1}: 3404 (OH), 2928, 1656 (C=O), 1620, 1604, 1510, 1370, 1318, 1244, 1074, 1046. UV λ_{max} nm (log ε): (MeOH) 267.0 (4.28), 317.7 (4.07), 363.5 (4.27); (+NaOMe) 280.5, 413.0; (+NaOAc) 276.0, 401.0; (+NaOAc/H_3BO_3) 268.0, 367.0; (+$AlCl_3$) 269.0, 305.7 sh, 344.6, 419.0; (+$AlCl_3$/HCl) 269.3, 305.7 sh, 344.4, 419.0. ^{1}H-NMR (pyridine-d_5) δ: 1.65 (3H, d, *J* = 6 Hz, Rha-6‴-H), 1.72 (3H, d, *J* = 6 Hz, Rha-6⁗-H), 4.10—5.05 (m, sugars-H), 5.42 (1H, br s, Rha-1‴-H), 5.58 (1H, d, *J* = 7 Hz, Gal-1″-H), 6.12 (1H, br s, Rha-1⁗-H), 6.71 (1H, d, *J* = 2 Hz, 8-H), 6.97 (1H, d, *J* = 2 Hz, 6-H), 7.50 (2H, d, *J* = 9 Hz, 3′-H, 5′-H), 8.59 (2H, d, *J* = 9 Hz, 2′-H, 6′-H). ^{13}C-NMR (pyridine-d_5) δ: shown in Table II.

Acid Hydrolysis of 3 Compound **3** (40 mg) was hydrolyzed as described for **1**. Kaempferol as the aglycone moiety and D-galactose and L-rhamnose as sugar moieties were identical by direct comparison with authentic samples.

Acknowledgements We are grateful to Miss N. Sawabe, Faculty of Pharmaceutical Sciences, Science University of Tokyo, for measurement of some of the ^{13}C-NMR spectra. We thank Miss Y. Konuma, Miss I. Shinko, and Mr. T. Ōta for their help in the isolation of constituents.

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