Labdane Diterpenes and Flavonoids from *Leonurus japonicus*

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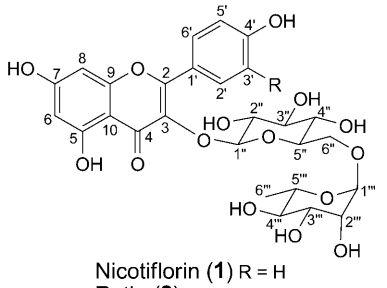
Chemical investigation of the aerial part of *Leonurus japonicus* led to the isolation and characterization of a new labdane-type diterpene, named 3α-acetoxy-15-*O*-methylleopersin C (**3**), and a new acylated rutin derivative, named 2‴-syringylrutin (**9**), along with seven known compounds, including a labdane-type diterpene and six flavonoids. The structures of the new compounds were established by spectroscopic methods.

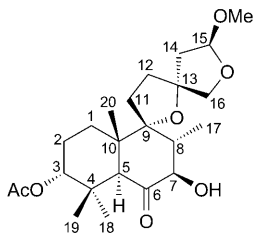
Introduction. – *Leonuri Herba* is the dried aboveground part of *Leonurus japonicus* HOUTT. (Lamiaceae) collected in summer when the plant is growing rapidly but has not bloomed. *Leonuri Herba* is a traditional Chinese medicine used in the treatment of gynecologic disorders such as menorrhagia, menostasia, and other irregular menstruation disorders [1][2]. This plant has been used for centuries in Korea and is said to be the most important crude drug in gynecological medicine [3][4]. It is officially listed in the Korean Pharmacopoeia. Several metabolites such as labdane-type diterpenes [5][6], flavonoids [6–10], monoterpene glucosides [8], coumarin [8], leonurenosides I and II [8], alkaloids [8], iridoid [10], lignan [6], and phenolic compounds [9][10] have been isolated from this plant. As a part of our continuing studies of bioactive constituents [11], we initiated a chemical investigation of this plant. In this article, we report the isolation and structural elucidation of a new labdane-type diterpene and a new flavonoid, as well as of seven known compounds.

Results and Discussion. – The MeOH extract of the aerial parts of *L. japonicus* was partitioned successively with H_2O, and hexane, AcOEt, and BuOH. The AcOEt and BuOH extracts were subjected to sequential column chromatography over silica gel and *RP-18* gel to yield **1** and **2** from BuOH extract and **3**–**9** from AcOEt extract. The known compounds were identified as nicotiflorin (**1**) [12], rutin (**2**) [12], leosibirinone A (**4**) [13], genkwanin (**5**) [14], tiliroside (**6**) [15], cosmosiin (**7**) [16], and isoquercitrin (**8**) [12], respectively, by comparing spectral and physical data with those in the literature.

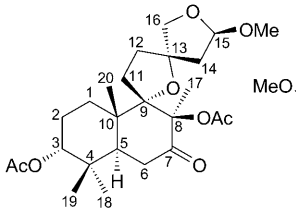
3α-Acetoxy-15-*O*-methylleopersin C (**3**) was analyzed for the molecular formula, $C_{23}H_{36}O_7$, by HR-FAB-MS (positive-ion mode; $[M+H]^+$ at *m*/*z* 425.2525 (calc. 425.2539)), which was supported by the NMR data. The IR spectrum showed diagnostic absorption bands at 3465 (OH), 1732 (ester), 1710 (C=O), and 1242 (acetate). Fragment ion peaks at *m*/*z* 406 ($[M-H_2O]^+$), 393 ($[M-MeO]^+$), 364



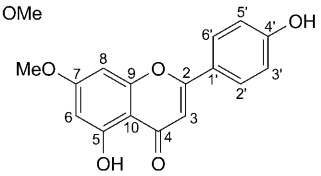
Nicotiflorin (**1**) R = H
Rutin (**2**) R = OH



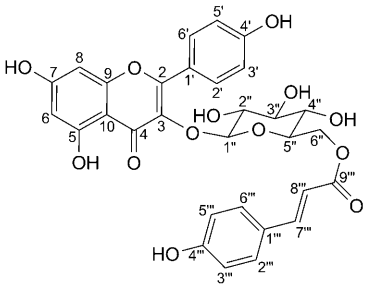
3α-Acetoxy-15-*O*-methylleopersin C (**3**)



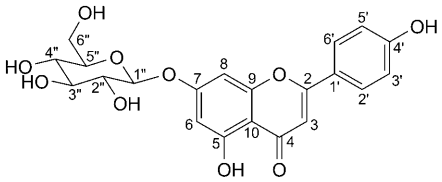
Leosibirinone A (**4**)



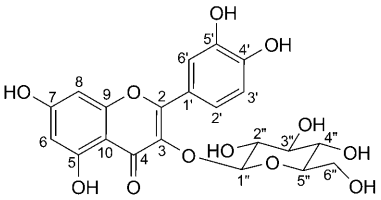
Genkwanin (**5**)



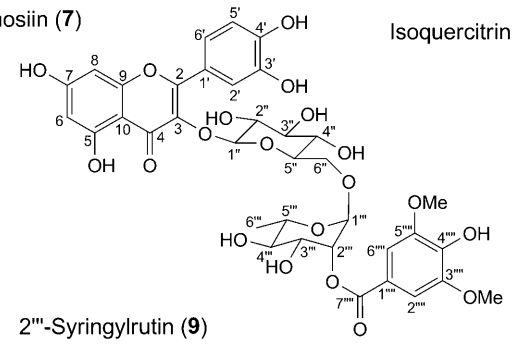
Tiliroside (**6**)



Cosmosiin (**7**)



Isoquercitrin (**8**)



2'''-Syringylrutin (**9**)

([M – AcOH]$^+$), and 347 ([M – H_2O – AcOH]$^+$) in the EI-MS indicated the presence of OH, MeO, and AcO groups in its structure. The ^{1}H-NMR spectrum (*Table 1*) displayed signals due to three tertiary Me groups (δ(H) 0.85, 0.95, 1.31), one secondary Me group (δ(H) 1.17), one AcO group (δ(H) 2.08), one MeO group (δ(H) 3.31), two O-bearing CH_2 groups (δ 4.04, 3.86), and three O-bearing CH H-atoms (δ(H) 4.52, 3.85, 5.07). The ^{13}C-NMR (*Table 1*) spectrum exhibited 23 C-atom signals, including

Table 1. *^{1}H- and ^{13}C-NMR Data*[a]) (500 and 125.8 MHz, resp., $CDCl_3$) *of* **3**. δ in ppm, J in Hz; asterisks (*) indicate overlapping signals.

Position	δ(H)	δ(C) (DEPT)	HMBC (H → C)
CH_2(1)	1.73*, 1.17*	25.8 (CH_2)	
CH_2(2)	1.88*, 1.73*	22.1 (CH_2)	C(3), C(10)
H–C(3)	4.52 (br. *s*, $W_{1/2}$ = 8.6)	77.9 (CH)	C(1), C(5), AcO
C(4)		35.7 (C)	
H–C(5)	3.23 (*s*)	51.7 (CH)	C(4), C(6), C(9), C(10), Me(18), Me(19), Me(20)
C(6)		211.7 (C)	
H–C(7)	3.85 (*d*, *J* = 10.9)	77.8 (CH)	C(6), C(8), Me(17)
H–C(8)	1.85*	46.5 (CH)	
C(9)		92.1 (C)	
C(10)		47.9 (C)	
CH_2(11)	1.98–2.06 (*m*), 1.87–1.94 (*m*)	28.9 (CH_2)	C(13)
CH_2(12)	2.25–2.32 (*m*), 2.08–2.16 (*m*)	38.6 (CH_2)	C(9), C(11), C(13), C(14), C(16)
C(13)		90.9 (C)	
CH_2(14)	2.46 (*dd*, *J* = 5.4, 13.8), 2.04 (br. *d*, *J* = 13.8)	47.6 (CH_2)	C(12), C(13), C(15)
H–C(15)	5.07 (*d*, *J* = 5.2)	105.3 (CH)	C(13), C(14), C(16), MeO
CH_2(16)	4.04 (*d*, *J* = 8.6), 3.86 (*d*, *J* = 8.6)	77.6 (CH_2)	C(12), C(13), C(14), C(15)
Me(17)	1.17 (*d*, *J* = 6.4)	13.3 (Me)	C(7), C(8), C(9)
Me(18)	0.95 (*s*)	26.6 (Me)	C(3), C(5)
Me(19)	1.31 (*s*)	21.9 (Me)	C(3), C(5)
Me(20)	0.85 (*s*)	20.0 (Me)	C(1), C(5), C(9)
MeO	3.31 (*s*)	54.8 (Me)	C(15)
AcO	2.08 (*s*)	21.3 (Me), 170.3 (C)	AcO

[a]) All δ(H) and δ(C) assignments are based on 2D-NMR (^{1}H,^{1}H-COSY, DEPT, HMQC, HMBC).

those of an AcO C-atom (δ(C) 170.3, 21.3), a C=O C-atom (δ(C) 211.7), an acetal C-atom (δ(C) 105.3), a MeO C-atom (δ(C) 54.8), two O-bearing CH groups (δ(C) 77.9, 77.8), an O-bearing CH_2 group (δ(C) 77.6), and two O-bearing quaternary C-atoms (δ(C) 92.1, 90.9). The ^{1}H,^{1}H-COSY spectrum of **3** (*Fig.*) revealed four partial structures, *i.e.*, fragment *A*, (CH_2(1)–CH_2(2)–CH(3)), in which C(3) was an O-bearing CH group, fragment *B*, (CH(7)–CH(8)–Me(17)), in which C(7) was an O-bearing CH group, fragment *C*, (CH_2(11)–CH_2(12)), and fragment *D*,

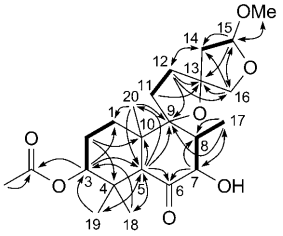


Fig. 1. *^{1}H,^{1}H-COSY* (—) *and key HMBC* (→) *data of 3α-acetoxy-15-*O*-methylleopersin C* (**3**)

(CH_2(14)–CH(15)), in which C(15) was an acetal bearing CH group. Connections between these partial fragments and other skeletal C-atoms were determined on the basis of HMBC data (*Fig.*). HMBCs were observed from the geminal Me(18) and Me(19) groups to C(3) and C(5); from H–C(3) to C(1), C(5), and AcO; from Me(20) to C(1), C(5), and C(9); from H–C(5) to Me(18), Me(19), C(4), C(9), C(10), Me(20), and C(6)=O; from H–C(7) to C(6)=O, C(8), and Me(17); and from Me(17) to C(7), C(8), and C(9). As C(5) and C(9) were common to both of these fragments *A* and *B*, they could be connected to generate decaline-type rings *A*/*B*. Further correlations from CH_2(12) to C(11), C(9), C(13), C(14), and C(16), and from H–C(15) to C(13), C(14), C(16), and MeO indicated that fragments *C* and *D* were connected to generate two spiro-tetrahydrofuran rings. These spectroscopic data, coupled with the six degrees of unsaturation, suggested that **3** was a labdane-type diterpenoid possessing two spiro-tetrahydrofuran rings [17][18]. The positions of an AcO, a C=O, a OH, and a MeO group at C(3), C(6), C(7), and C(15), respectively, were established by HMBC experiments. The relative configuration of C(3), C(5), C(7), C(8), C(9), C(10), and C(13) in **3** were assigned on the basis of NOE interactions and ^{1}H,^{1}H-coupling patterns. The observation of cross-peaks in the NOESY spectrum between Me(18) and H–C(5); H–C(5) and H–C(7); and H–C(7) and Me(17) indicated that they were all on the same face of the molecule (α), while interactions between Me(19) and H–C(3); Me(19) and Me(20); and H–C(11) and Me(20) revealed that these were on the opposite face (β). The configuration of H–C(3) was confirmed to be equatorial (β) due to the width of the broad *singlet* at half height ($W_{1/2}$ = 8.6 Hz) [19][20]. It was also evident from the 10.9-Hz coupling between H–C(7) and H–C(8) that these two H-atoms have a *trans*-diaxial relationship. Additional NOE interactions between CH_2(16) and Me(17) supported the relative (*R*)-configuration at C(13) [18][21]. A correlation peak in the NOESY spectrum between CH_2(16) and H–C(15) was not detected, suggesting the MeO group at C(15) as β-oriented. The β-orientation of the MeO group at C(15) was also supported on the basis of the comparison of the ^{1}H-NMR chemical-shift difference ($\Delta\delta$) between H_a–C(14) and H_b–C(14) with that of the 15-epimer. In the case of **3**, the chemical shift difference ($\Delta\delta$ 0.42) was larger than that of 15α-epimer ($\Delta\delta$ 0.04–0.05), which was in agreement with that observed for 15β-epimer [18]. Based on the above evidence, 3α-acetoxy-15-*O*-methylleopersin C (**3**) was assigned the structure of 3α-acetoxy-7β-hydroxy-9α,13;15,16-diepoxy-15β-methoxylabdan-6-one.

2‴-Syringylrutin (**9**) was isolated as yellow needles. The HR-FAB-MS (positive-ion mode) showed a *pseudo*-molecular-ion peak at *m*/*z* 791.2012 ($[M+H]^+$) indicating a molecular formula of $C_{36}H_{38}O_{20}$ (calc. 791.2035). The IR spectrum exhibited absorption bands typical of OH (3397 cm^{-1}), α,β-unsaturated C=O (1652 cm^{-1}), aromatic C=C groups (1608, 1513 cm^{-1}), and an *O*-glycosidic linkage (1067 cm^{-1}). The UV data of **9** showed the characteristic maxima of quercetin 3-*O*-glycosides at 260 (sh, 4.49), 266 (4.49), 293 (sh, 4.29), and 360 (4.30) nm. Use of standard shift reagents showed that the OH groups at C(5), C(7), C(3′), and C(4′) of quercetin were free, and that the OH group at C(3) was substituted. The ^{1}H-NMR spectrum of **9** (*Table 2*) showed two *meta*-coupled signals in the aromatic region at δ(H) 6.18 (*d*, *J* = 1.8) and 6.35 (*d*, *J* = 1.8), suggesting the presence of a 5,7-dihydroxy-substituted *A* ring of the flavonoid skeleton. A *doublet* of *doublet*s at δ(H) 7.50 (*dd*, *J* = 2.0, 8.4) and two *doublet*s at δ(H) 7.54 (*d*,

Table 2. *^{1}H- and ^{13}C-NMR Data*[a]) (400 MHz and 100.6 MHz, resp., (D_6)DMSO) *of* **9**. δ in ppm, J in Hz; asterisks (*) mark overlapping signals.

	δ(H)	δ(C)		δ(H)	δ(C)
Aglycon			*Glucose*		
C(2)		156.6	H–C(1″)	5.36 (*d*, *J* = 7.1)	101.2
C(3)		133.3	H–C(2″)	3.11–3.40*	74.1
C(4)		177.4	H–C(3″)	3.23 (*t*, *J* = 9.5)	76.4
C(5)		161.3	H–C(4″)	3.11–3.40*	69.9
H–C(6)	6.18 (*d*, *J* = 1.8)	98.7	H–C(5″)	3.11–3.40*	75.8
C(7)		164.1	CH_2(6″)	3.74 (br. *d*, *J* = 10.8), 3.11–3.40*	67.1
C(8)	6.35 (*d*, *J* = 1.8)	93.7	*Rhamnose*		
C(9)		156.5	H–C(1‴)	4.54 (br. *s*)	97.7
C(10)		104.1	H–C(2‴)	4.92 (*dd*, *J* = 1.9, 3.1)	72.6
C(1′)		121.3	H–C(3‴)	3.60 (*dd*, *J* = 3.1, 9.7)	68.7
H–C(2′)	7.54 (*d*, *J* = 2.0)	116.4	H–C(4‴)	3.11–3.40*	72.5
C(3′)		144.8	H–C(5‴)	3.11–3.40*	68.5
C(4′)		148.4	Me(6‴)	1.06 (*d*, *J* = 6.1)	17.9
H–C(5′)	6.78 (*d*, *J* = 8.4)	115.2	*Syringyl*		
H–C(6′)	7.50 (*dd*, *J* = 2.0, 8.4)	121.5	C(1⁗)		119.5
5-OH	12.61		H–C(2⁗,6⁗)	7.18 (br. *s*)	107.1
			H–C(3⁗,5⁗)		147.5
			H–C(4⁗)		140.8
			H–C(7⁗)		164.8
			MeO	3.81 (*s*)	56.1

[a]) All δ(H) and δ(C) assignments are based on 2D-NMR (^{1}H,^{1}H-COSY, DEPT, HMQC, HMBC).

J = 2.0) and 6.78 (*d*, *J* = 8.4), which were observed as an *ABX* system, revealed the 3′,4′-dihydroxy functional structure of a flavonoid *B* ring. The appearance of a sharp *singlet* H-atom signal at δ(H) 7.18 (2 H) for the magnetically equivalent H–C(2⁗) and H–C(6⁗) H-atoms, together with a MeO *singlet* signal at δ(H) 3.81 (6 H), indicated the presence of a syringyl group. The ^{13}C-NMR spectrum (*Table 2*) displayed the corresponding C-atom resonances at δ(C) 107.1 (2 C) plus a CO signal at δ(C) 164.8, a two-MeO signal at δ(C) 56.1, and three quaternary C-atom signals at δ(C) 119.5, 147.5 (2 C), and 140.8. These observations indicated the presence of a syringyl moiety in compound **9** [9][22]. The anomeric-H-atom resonances at δ(H) 5.36 (*d*, *J* = 7.1) and 4.54 (br. *s*), together with a secondary Me signal at δ(H) 1.06 (*d*, *J* = 6.1), and the C-resonances in the ^{13}C-NMR spectrum indicated that **9** contained one β-glucopyranosyl and one α-rhamnopyranosyl moiety. The connectivity was established from the HMBC experiment, in which correlation of H–C(1″) of the glucopyranosyl unit with C(3) of the aglycon, and that of H–C(1‴) of the rhamnopyranosyl unit with C(6″) of the glucopyranosyl unit were observed. In addition, the correlation of H–C(2‴) of the rhamnopyranosyl unit with C=O of the syringyl group indicated that the syringyl group was linked at C(2‴) of the rhamnopyranosyl unit. In the ^{13}C-NMR spectrum of **9**, signals attributed to C(1‴), C(2‴), and C(3‴) of the rhamnose residue were shifted by −3.0, +2.2, and −1.8 ppm, respectively, compared to those of rutin (**2**), supporting the position of the syringyl moiety at C(2‴) of the terminal rhamnose moiety [23].

From these data, the structure of compound **9** was established as quercetin 3-*O*-(2‴-syringyl)-α-L-rhamnopyranosyl(1 → 6)-β-D-glucopyranoside. Although various acylated flavonol glycosides are found widely in the plant kingdom [24], syringates such as **9** are quite rare, and, to our knowledge, compound **9** is the first example of a natural flavonol glycoside syringated at HO–C(2) of the rhamnose of the rutinose residue. Quercetin 3-(3‴-syringylrobinobioside), heternoside, was isolated for the first time as a natural flavonol glycoside syringated from the same genus, *L. heterophyllus* [22]. The known labdane diterpene and six flavonoids were identified as leosibirinone A (**4**) [13], and nicotiflorin (**1**) [12], rutin (**2**) [12], genkwanin (**5**), tiliroside (**6**), cosmoiin (**7**), and isoquercitrin (**8**) [12], respectively, by comparing their physical properties and spectral data with those reported in the literature.

Experimental Part

General. TLC: silica gel GF_{254} pre-coated plates (*Merck*) and $RP\text{-}18_{254S}$ (*Merck*). Column chromatography (CC): silica gel (SiO_2; *Merck*) and *LiChroprep RP-18* (40–63 μm, *Merck*). Optical rotations: *JASCO P-1020* digital polarimeter. UV Spectra: *Hitachi JP/U3010* spectrophotometer; λ_{max} (log ε) in nm. IR Spectra: *JASCO FT/IR5300* spectrometer, KBr pellet; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Bruker Avance 500* spectrometer or *Bruker Avance 400* instruments; δ in ppm with TMS as internal standard, *J* in Hz. EI-MS: *Hewlett Packard 5989B.* HR-FAB-MS: *JEOL JMS-700 MStation.*

Plant Material. The aerial parts of *Leonurus japonicus* were collected in Youngcheon, Kyungbuk Province, Korea, in June, 2008, and identified by Prof. *KiHwan Bae*, College of Pharmacy, Chungnam National University. A voucher specimen (No. NPRI-208-02) has been deposited with the Herbarium of Natural Products Research Institute.

Extraction and Isolation. The dried, powdered aerial parts of *L. japonicus* (2.7 kg) were extracted with MeOH (5 × 3 h each) at 70–80°, and then filtered. The combined MeOH extracts were evaporated to dryness under reduced pressure. The crude extract (310.2 g) was dissolved in H_2O (3 l), and extracted with hexane, AcOEt, and BuOH, successively. The BuOH-soluble fraction (53.5 g) was subjected to CC (SiO_2; CH_2Cl_2/MeOH/H_2O 14 : 2 : 1 (4 l) and 52 : 28 : 8 (5 l)) to afford ten fractions, *Frs. A–J*, according to TLC. *Frs. D* (1.3 g) and *G* (10.1 g) were resubmitted to CC (SiO_2; step gradient of AcOEt saturated with H_2O/MeOH 100 : 1 to 50 : 50 in 5% steps, 100%) to yield **1** (15 mg) and **2** (134 mg), resp. The AcOEt-soluble fraction (69.3 g) was subjected to CC (SiO_2; CH_2Cl_2/MeOH/H_2O 70 : 1 : 5 (5 l) and 52 : 28 : 8 (8 l)) to afford 14 fractions, *Frs. A–N*, according to TLC. *Fr. B* (1.8 g) was subjected to CC (SiO_2; linear hexane/AcOEt gradient 10 : 1 to 1 : 10 in 10% steps) to afford subfractions B_1–B_{20}, of which *Subfr.* B_5 was recrystallized from MeOH to yield **3** (2 mg). The *Subfr.* B_6 (98 mg) was separated by CC (SiO_2; CH_2Cl_2/MeOH/H_2O 70 : 1 : 5) to afford *Subfr.* $B_{6(13)}$ (6 mg), which was further purified by CC (SiO_2; linear hexane/AcOEt gradient 10 : 3 to 10 : 8 in 50% steps) to yield **4** (2 mg). *Fr. C* (1.0 g) was subjected to CC (SiO_2; linear hexane/AcOEt gradient 10 : 1 to 1 : 10 in 10% steps) to afford *Subfr.* C_6, which was recrystallized from MeOH to yield **5** (4 mg). *Frs. J* (1.0 g) and *L* (8.4 g) were separated by CC (SiO_2; AcOEt sat. with H_2O/MeOH step gradient 100 : 1 to 50 : 50 in 5% steps) to yield **6** (13 mg) and **7** (2 mg) from *Fr. J* and **8** (5 mg), and *Subfr.* L_7 from *Fr. L*, resp. *Subfr.* L_7 (300 mg) was further purified on an *RP-18* column with 50% MeOH to give **9** (22 mg).

*3α-Acetoxy-15-*O*-methylleopersin C* (= rel-*(2″*R,*3″*R,*3‴*R,*4a″*S,*5*S,*5′*R,*6″*R,*8a″*S*)-Dodecahydro-3″-hydroxy-5-methoxy-2″,5″,5‴,8a″-tetramethyl-4″-oxo-2″*H*-dispiro[furan-3,2′-furan-5′,1‴-naphthalen]-6″-yl Acetate*; **3**). White needles. $[\alpha]_D^{28} = -9.6$ ($c = 0.50$, MeOH). IR: 3465 (OH), 2937, 1732 (ester), 1710 (C=O), 1614, 1466, 1372, 1242 (acetate), 1104, 1036. ^{1}H- and ^{13}C-NMR: *Table 1.* EI-MS: 424 (3, M^+), 406 (5, $[M - H_2O]^+$), 393 (1, $[M - MeO]^+$), 364 (1, $[M - AcOH]^+$), 347 (3, $[M - H_2O - AcOH]^+$), 213 (100), 123 (71), 95 (32), 81 (43), 69 (33). HR-FAB-MS (pos.): 425.2525 ($[M + H]^+$, $C_{23}H_{37}O_7^+$; calc. 425.2539).

2‴-Syringylrutin (= *2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-4-oxo-4*H*-chromen-3-yl 6-*O*-{6-Deoxy-2-*O*-[(4-hydroxy-3,5-dimethoxyphenyl)carbonyl]-α-*L*-mannopyranosyl}-β-*D*-glucopyranoside*; **9**). Yel-

low needles. $[\alpha]_D^{28} = -43.9$ ($c = 0.20$, MeOH). UV (MeOH): 260 (sh, 4.49), 266 (4.49), 293 (sh, 4.29), 360 (4.30). UV (MeONa): 272 (4.49), 327 (sh, 4.47), 400 (4.35). ($AlCl_3$): 275 (4.59), 429 (4.33). UV ($AlCl_3$/HCl): 272 (4.54), 294 (sh, 4.28), 362 (sh, 4.19), 402 (4.27). UV (AcONa): 271 (4.52), 327 (sh, 4.33), 386 (4.32). UV (AcONa + H_3BO_3): 263 (4.57), 295 (sh, 4.26), 379 (4.35). IR: 3397 (OH), 1652 (α,β-unsat. C=O), 1608, 1513 (arom. C=C), 1457, 1360, 1209, 1115, 1067 (glycosidic C–O). ^{1}H- and ^{13}C-NMR: *Table 2*. FAB-MS (pos.): 813 ($[M+Na]^+$), 791 ($[M+H]^+$). HR-FAB-MS (pos.): 791.2012 ($[M+H]^+$, $C_{36}H_{39}O_{20}^+$; calc. 791.2035).

Alkaline Hydrolysis of **9**. A soln. of **9** (5 mg) in 0.1% MeONa/MeOH (1 ml) was stirred at r.t. for 1 h. The mixture was neutralized with *Dowex HCR-S* (H^+ form), and the residue was removed by filtration. After removal of the solvent under a N_2 stream, the residue was chromatographed on an *RP-18* column with 10% and then 50% MeOH to give *rutin* (**2**), which was identified by direct comparison with an authentic sample.

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