Terpenoids and Coumarins Isolated from the Fruits of *Poncirus trifoliata*

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Four new triterpenes, 21 α -methylmelianodiol (**1**), 21 β -methylmelianodiol (**2**), hispidol A 25-methyl ether (**3**) and hispidol B 25-methyl ether (**4**), and a new coumarin, isoschininallyl (5), were isolated from the fruits of *Poncirus trifoliata* RAFINESQUE, along with seventeen known compounds. The structures of the new compounds (**1**–**5**) were elucidated by interpretation of their spectroscopic data.

Key words *Poncirus trifoliata*; Rutaceae; triterpene; coumarin

The immature fruits of *Poncirus trifoliata* RAFINESQUE (Rutaceae), *Poncirus* Fructus, are well acknowledged as a traditional medicine in Eastern Asia, especially for treating allergic diseases. Previously, its crude extracts have exhibited anti-inflammatory, anti-bacterial and anti-mucin releasing activities,^{1–3} and several coumarin derivatives have been identified as potent antiplatelet constituents.⁴ Besides of coumarins, flavonoids, terpenoids and several essential oils have also been reported from this plant.^{5,6} In this study, five new compounds, 21 α -methylmelianodiol (**1**), 21 β -methylmelianodiol (**2**), hispidol A 25-Me ether (**3**), hispidol B 25-Me ether (**4**), and isoschininallyl (**5**), were isolated from the methanol extract of *Poncirus* Fructus, as well as seventeen known compounds, including three terpenoids, caryophyllene β -oxide, 21 α ,25-dimethylmelianodiol and 21 β ,25-dimethylmelianodiol; one steroid, β -sitosterol; nine coumarins, auraptene, isoimperatorin, bergapten, imperatorin, phellopterin, umbelliferone, isoschinilenol, scopoletin and heraclenol 3''-Me ether; two flavonoids, poncirin and naringin; and two phenolic compounds, bis(2-methylheptyl)-phthalate and avenalumic acid methyl ester.

Results and Discussion

Compound **1** was obtained as white powder. A molecular formula of C₃₁H₅₀O₅ was assigned to **1** on the basis of its HR-FAB-MS, ¹³C-NMR and DEPT spectral data. The ¹H-NMR spectrum of **1** (Table 1) displayed characteristic signals for seven tertiary methyl groups (CH₃-18, 19, 26, 27, 28, 29, 30), one methoxy group, three oxygenated methine protons (H-21, 23, 24), one olefinic proton (H-7), and several over-

lapping protons for aliphatic methines and methylenes. Consistent with the ¹H-NMR spectrum of compound **1**, its ¹³C-NMR spectrum (Table 1) exhibited signals for seven methyl groups, one methoxy group, eight methylenes, eight methines, and seven quaternary carbons. Based on the observed ¹³C-NMR chemical shifts, it was apparent that one saturated ketone (C-3), three oxygenated methine carbons (C-21, C-23, C-24) and one oxygenated quaternary carbon (C-25) were present in the molecule of **1**. All the above-mentioned NMR observation suggested that compound **1** is a triterpene possessing one methoxy group. The locations of five methyl groups were assigned at C-4, C-10, C-13, and C-14 on the basis of the following HMBC (Fig. 2) correlations: the proton signals of CH₃-28 and CH₃-29 with C-3, C-4, and C-5; CH₃-18 with C-12, C-13, C-14, and C-17; CH₃-19 with C-1, C-5, C-9, and C-10; CH₃-30 with C-7, C-8, C-9, and C-14. The downfield shift of two methyl groups at δ_H 1.24 and 1.27 suggested the presence of an oxygenated carbon at C-25. Additionally, the HMBC correlations of the proton signals of CH₃-26 and CH₃-27 at δ_H 1.24 and 1.27 with C-25 at δ_C 73.09 were observed. The presence of tetrahydrofuran ring in the side chain was assigned based on the observed correlations in its 2D NMR (¹H–¹H COSY, HMQC and HMBC) spectra. The HMBC correlation between a methoxy group at δ_H 3.31 and C-21 at δ_C 108.9 identified the attachment of a methoxy group at C-21. Its side chain possessing tetrahydrofuran ring in compound **1** was found to be similar to holstinone A,⁷ the 21-methoxy analogue of melianodiol.⁸ To determine the relative configuration at C-21 in compound **1**, NOE experiment was performed with irradiation at δ_H 3.31.

Fig. 1. Chemical Structures of Compounds **1**–**5**

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Table 1. ^1H - and ^{13}C -NMR Data for Compounds **1**–**4**^{a)}

Position	1 (CDCl_3)		2 (CDCl_3)		3 (pyridine- d_5)		4 (pyridine- d_5)	
	δ_{C}	δ_{H} (J in Hz)	δ_{C}	δ_{H} (J in Hz)	δ_{C}	δ_{H} (J in Hz)	δ_{C}	δ_{H} (J in Hz)
1	38.47		38.52		31.80		37.62	
2	35.06	2.23 m	35.08	2.25 m	26.49	1.82 m	28.62	1.85 m
		2.74 dt (14.4, 5.4)		2.75 dt (14.4, 5.4)		2.00 m		2.01 m
3	216.9		216.8		75.20	3.64 br s	78.32	3.45 t (8.1)
4	47.86		47.85		37.86		39.57	
5	52.32	1.70 m	52.41	1.71 m	44.80	2.18 m	51.15	1.45 m
6	24.32	2.07 m	24.35	2.05 m	24.27	2.00 m	24.43	2.02 m
7	118.1	5.27 br d (2.8)	118.1	5.28 br d (2.8)	118.4	5.29 br s	118.4	5.28 br s
8	145.5		145.6		146.3		146.1	
9	48.26	2.28 m	48.32	2.27 m	49.04	2.46 m	49.31	2.27 m
10	34.89		34.90		35.08		35.22	
11	17.74	1.56 m	17.71	1.55 m	18.30	1.56 m	18.43	1.52 m
12	31.48		31.08		34.27		34.37	
13	43.60		43.50		43.71		43.76	
14	50.94		50.76		51.45		51.46	
15	34.31		34.18		34.11		34.19	
16	27.38		27.31		28.72		28.81	
17	50.27	1.73 m	44.98	1.98 m	54.22	1.65 m	54.28	1.66 m
18	22.58	0.98 s	23.25	0.98 s	21.93	0.78 s	22.11	0.78 s
19	12.71	0.82 s	12.72	0.81 s	13.38	0.83 s	13.45	0.86 s
20	47.67	1.98 m	46.28	1.98 m	34.47	1.71 m	34.53	1.73 m
21	108.9	4.75 br s	104.9	4.71 br s	19.52	1.10 d (5.6)	19.62	1.12 d (5.8)
22	33.76	1.90 m	31.57	1.90 m	42.87	2.19 m	42.95	2.18 m
23	76.72	4.20 dt (2.9, 8.3)	78.85	4.40 dt (2.8, 8.4)	68.21	4.42 m	68.13	4.41 m
24	75.34	3.22 br s	76.52	3.31 br s	76.65	3.63 s	76.73	3.65 s
25	73.09		72.92		78.67		78.75	
26	26.33	1.24 s	26.30	1.22 s	22.48	1.39 s	22.58	1.41 s
27	26.43	1.27 s	26.38	1.24 s	20.73	1.41 s	20.82	1.43 s
28	21.55	1.09 s	21.53	1.09 s	22.11	0.94 s	15.58	1.09 s
29	24.46	1.01 s	24.48	1.01 s	28.65	1.14 s	28.32	1.15 s
30	27.26	0.99 s	27.41	1.00 s	27.44	0.99 s	27.47	0.98 s
MeO-21	55.62	3.31 s	55.17	3.31 s				
MeO-25					49.17	3.20 s	49.26	3.22 s

a) ^1H - and ^{13}C -NMR spectra were acquired at 250 and 63 MHz, respectively; TMS was used as internal standard; assignments were based on ^1H - ^1H COSY, HMQC, HMBC, and NOESY spectra.

Fig. 2. Selected HMBC Correlations of **1** and **2**

In NOE experiment, irradiation of the OMe-21 resonance at δ_{H} 3.31 gave an enhancement of the H-23 signal at δ_{H} 4.20 suggesting the relative configuration of a methoxy group at C-21 is α for **1**. The absolute configuration at C-24 for **1** was determined by comparison the NMR spectral data with limonoid melianodiols and limonoid 24-*epi*-melianodiols.⁸⁾ Based on the above spectral evidences, the structure of **1** was elucidated as 21 α -methylmelianodiols (21*R*,23*R*)-epoxy-24*S*-hydroxy-21 α -methoxytirucalla-7-en-3-one.

Compound **2** was isolated as a white powder. The molecular formula of $\text{C}_{31}\text{H}_{50}\text{O}_5$, the same as that of **1**, was determined for **2** by HR-FAB-MS, ^{13}C -NMR and DEPT spectral data. Both the ^1H - and ^{13}C -NMR spectroscopic data of compound **2** (Table 1) were closely comparable to those of **1**,

suggesting it is also a triterpene possessing one methoxy group. The gross structure of compound **2** was assigned as the same as that of compound **1** based on the observed correlations in its 2D NMR (^1H - ^1H COSY, HMQC and HMBC) spectra. The same correlations as that of **1** were observed in HMBC spectrum of **2** (Fig. 2). However, the signals for C-17 and C-21 were relatively upfield at δ_{C} 44.98 and 104.9, while the signal for C-23 was downfield at δ_{C} 78.85, suggesting γ -gauche effect of the oxygenated substituent on C-21 β .⁹⁾ Additionally, in contrast to compound **1**, an enhancement of the H-23 signal at δ_{H} 4.20 with irradiation of the OMe-21 resonance at δ_{H} 3.31 was not observed in its NOE experiment. Therefore, the relative configuration of the methoxy group at C-21 in compound **2** was assigned as a 21 β . Based on the above spectral evidences, the structure of **2** was elucidated as 21 β -methylmelianodiols (21*S*,23*R*)-epoxy-24*S*-hydroxy-21 β -methoxytirucalla-7-en-3-one.

Compounds **3** and **4** displayed very similar ^1H - and ^{13}C -NMR spectra, and the same molecular formula, $\text{C}_{31}\text{H}_{54}\text{O}_4$, as established for both substances based on their HR-FAB-MS, ^{13}C -NMR and DEPT spectral data. Their ^1H -NMR spectra exhibited the typical resonances for a seven tertiary methyl groups, one methoxy group, three oxygenated methine protons, and one olefinic proton, together with one secondary methyl group. These signals were characteristic of the tiru-

Fig. 3. Selected HMBC Correlations of **3** and **4**

call-7-ene triterpene skeleton with a 3-hydroxy group.¹⁰ The ¹H- and ¹³C-NMR spectroscopic data suggested that compounds **3** and **4** have the same gross structure, which was found to be similar to hispidol A and hispidol B,^{11,12} except for the presence of a new methoxy group at δ_{H} 3.20. The HMBC correlations of methoxy group with C-25 and two methyl groups, H-26 and H-27 with C-25 indicated the location of methoxy group is at C-25 (Fig. 3). Although compounds **3** and **4** have the same gross structure based on the interpretation of their NMR data, differences of NMR chemical shifts were observed in ring A, as well as the splitting pattern of H-3, suggesting compounds **3** and **4** were epimeric at C-3 (Table 1). While a broad singlet for H-3 signal at 3.64 was indicating the axial 3-OH in compound **3**, H-3 signal as a doublet of doublets at 3.45 ($J=11.0, 5.1$ Hz) was indicating equatorial 3-OH in compound **4**.¹³ Based on the above spectral evidences, the structures of **3** and **4** were elucidated as (3*R*,23*S*,24*R*)-25-methoxytirucalla-7-ene-3,23,24-triol and (3*S*,23*S*,24*R*)-25-methoxytirucalla-7-ene-3,23,24-triol, respectively.

Compound **5** was obtained as brown gum and its molecular formula, C₂₀H₂₄O₅, was established from HR-FAB-MS, ¹³C-NMR and DEPT spectral data. The UV absorptions at 348, 298 and 241 nm suggested a 7-oxygenated coumarin skeleton.¹⁴ In the ¹H-NMR spectrum of **5**, the characteristic signals of a 6,7-disubstituted coumarin were apparent, with doublets at δ_{H} 6.27 (1H, d, $J=9.5$ Hz, H-3) and 7.61 (1H, d, $J=9.5$ Hz, H-4), two aromatic signal at δ_{H} 6.82 (1H, s, H-5) and 6.79 (1H, s, H-8), and one methoxy signal at δ_{H} 3.88 (3H, s, OCH₃-6).¹⁵ The location of methoxy group was assigned to C-6 based on the HMBC correlation between a methoxyl signal at δ_{H} 3.88 and C-6 at δ_{C} 146.6 (Fig. 4). In addition, its ¹H-NMR spectrum showed eight more signals due to a terminal methylene proton (δ_{H} 4.90, 4.81), a methine proton (δ_{H} 4.02), three methylene protons (δ_{H} 4.67, 2.11, 1.66), one olefinic proton (δ_{H} 5.49), and two vinylic methyl protons (δ_{H} 1.75, 1.70). On the basis of the observed HMQC correlations, these signals were found to correspond to the ¹³C-NMR signals for the terpenyl side-chain, which is very similar to those of schininallyl.¹⁶ The HMBC correlation between H-1' at δ_{H} 4.67 and C-7 at δ_{C} 151.9 indicated the location of the terpenyl side-chain at C-7. Since the absolute configuration of analogue 7-(6*R*-hydroxy-3,7-dimethyl-2,7-octadienyl)oxy coumarin was determined as *R* and showed a positive optical rotation,¹⁷ whereas 7-(6*S*-hydroxy-3,7-dimethyl-2,7-octadienyl)oxy-8-methoxy coumarin displayed a negative value,¹⁶ the stereochemistry at C-6' of **5** was assigned as *S* configuration by its negative optical rotation. Thus, the structure of **5** was elucidated as 7-(6*S*-hydroxy-3,7-dimethyl-2,7-octadienyl)oxy-6-methoxy coumarin

Fig. 4. Selected HMBC Correlations of **5**

and named as isoschininallyl.

Other known compounds obtained in this study, 21 α ,25-dimethylmelianodiol,¹⁸ 21 β ,25-dimethylmelianodiol,¹⁸ caryophyllene β -oxide,¹⁹ β -sitosterol,²⁰ auroptene,²¹ isoimperatorin,²² bergapten,²³ imperatorin,²³ phellopterin,²⁴ umbelliferone,²⁴ isoschinilenol,²⁵ scopoletin,²⁶ heraclenol 3''-Me ether,^{27,28} poncirin,²⁹ naringin,³⁰ bis(2-methylheptyl)phthalate,³¹ and avenalumic acid methyl ester,³² were identified by comparing their physical and spectroscopic data with the published values.

Experimental

General Experimental Procedures Optical rotations were measured using a JASCO DIP-1000 (Tokyo, Japan) automatic digital polarimeter. FT-IR spectra were recorded on a JASCO FT-IR 300E spectrophotometer, and UV spectra on a JASCO V-550 spectrophotometer. The NMR spectra were recorded on Bruker 250 MHz (DMX 250) spectrometer using Bruker's standard pulse program, and chemical shifts were reported in ppm downfield from TMS. The HR-FAB mass spectra were recorded on JMS-700 mass spectrometer (JEOL, Japan). Column chromatography was carried out on Merck silica gel (70–230 mesh) and Merck Lichroprep RP-18 gel (40–63 μ m). TLC was performed on aluminum plates precoated with Kieselgel 60 F₂₅₄ (Merck). All other chemicals and solvents were analytical grade and used without further purification.

Plant Material Dried fruits of *Poncirus trifoliata* RAFINESQUE were purchased in September 2003 from a folk medicine market "Yak-ryong-si" in Daegu, South Korea.

Extraction and Isolation The dried fruits of *P. trifoliata* RAFINESQUE (10 kg) were extracted three times with 100% MeOH at room temperature for several days. The MeOH solution was concentrated under the reduced pressure to give a residue (500 g) and it was partitioned between H₂O and CH₂Cl₂. The CH₂Cl₂ extract (160 g) was loaded on a silica gel column (80 $\times$ 12 cm) and eluted with *n*-hexane/EtOAc (10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9, 0:10, each 4 l) in a gradient mode to give 10 fractions (PF1–10). The fraction PF7 (5.9 g) was chromatographed on a silica gel column (70 $\times$ 6 cm) and eluted with CH₂Cl₂/acetone (9:1, 8:2, 7:3, 6:4, 5:5, 3:7, each 4 l) to give 7 fractions (PF71–7). The fraction PF73 was rechromatographed on a silica gel column (50 $\times$ 3.5 cm) and eluted with *n*-hexane/EtOAc (4:6, 5:5, 6:4, 7:3, each 3 l) in a gradient mode to give 6 fractions PF731–6, the fraction PF732 was rechromatographed over a C-18 reverse-phase column (50 $\times$ 4 cm) eluting with MeOH/H₂O (4:6, 5:5, 6:4, 7:3, each 3 l) to afford **1** (20 mg) and **2** (5 mg), respectively. The fraction PF75 was rechromatographed on a silica gel column (50 $\times$ 3.5 cm) and eluted with *n*-hexane/EtOAc (4:6, 6:4, 8:3, each 3 l) in a gradient mode to give 4 fractions PF751–4, the fraction PF752 was rechromatographed over a C-18 reverse-phase column (50 $\times$ 3 cm) eluting with MeOH/H₂O (2:8, 4:6, 6:4, 7:3, each 3 l) to afford **3** (15 mg) and **4** (4 mg), respectively. The fraction PF9 (13.5 g) was chromatographed on a silica gel column (70 $\times$ 6 cm) and eluted with CH₂Cl₂/acetone (98:2, 96:4, 94:6, 92:8, 90:10, each 4 l) to give 5 fractions (PF91–5). The fraction PF92 was chromatographed on a silica gel column (60 $\times$ 5 cm) and eluted with *n*-hexane/EtOAc (95:5, 9:1, 8:2, 7:3, 6:4, each 4 l) in a gradient mode to give 5 fractions (PF921–5), the fraction PF923 was rechromatographed over a C-18 reverse-phase column (50 $\times$ 4 cm) eluting with MeOH/H₂O (2:8, 4:6, 6:4, each 3 l) to afford **5** (10 mg).

21 α -Methylmelianodiol (**1**): White powder; [α]_D¹⁸ –98.4° ($c=0.1$, CHCl₃); UV (CHCl₃) λ_{max} (log ϵ) 241 (2.99) nm; IR (KBr) ν_{max} 3505, 2953, 1707, 1468, 1386, 1099, 1037 cm^{–1}; ¹H-NMR (250 MHz, CDCl₃) and ¹³C-NMR (63 MHz, CDCl₃), see Table 1; HR-FAB-MS (positive ion mode) m/z : 503.3737 [M+H]⁺ (Calcd for C₃₁H₅₁O₅, 503.3738).

21 β -Methylmelianodiol (**2**): White powder; [α]_D¹⁸ –12.9° ($c=0.1$, CHCl₃); UV (CHCl₃) λ_{max} (log ϵ) 242 (3.01) nm; IR (KBr) ν_{max} 3444, 2952, 1707,

1467, 1385, 1093 cm^{-1} ; $^1\text{H-NMR}$ (250 MHz, CDCl_3) and $^{13}\text{C-NMR}$ (63 MHz, CDCl_3), see Table 1; HR-FAB-MS (positive ion mode) m/z : 503.3737 $[\text{M}+\text{H}]^+$ (Calcd for $\text{C}_{31}\text{H}_{51}\text{O}_5$, 503.3738).

Hispidol A 25-Me Ether (3): White powder; $[\alpha]_{\text{D}}^{18} -74.3^\circ$ ($c=0.1$, CHCl_3); UV (CHCl_3) λ_{max} (log ϵ) 241 (3.16) nm; IR (KBr) ν_{max} 3443, 2933, 1467, 1385, 1131, 1062 cm^{-1} ; $^1\text{H-NMR}$ (250 MHz, pyridine- d_5) and $^{13}\text{C-NMR}$ (63 MHz, pyridine- d_5), see Table 1; HR-FAB-MS (positive ion mode) m/z : 491.4100 $[\text{M}+\text{H}]^+$ (Calcd for $\text{C}_{31}\text{H}_{55}\text{O}_4$, 491.4102).

Hispidol B 25-Me Ether (4): White powder; $[\alpha]_{\text{D}}^{18} -65.5^\circ$ ($c=0.1$, CHCl_3); UV (CHCl_3) λ_{max} (log ϵ) 243 (3.20) nm; IR (KBr) ν_{max} 3414, 2951, 1467, 1384, 1152, 1070 cm^{-1} ; $^1\text{H-NMR}$ (250 MHz, pyridine- d_5) and $^{13}\text{C-NMR}$ (63 MHz, pyridine- d_5), see Table 1; HR-FAB-MS (positive ion mode) m/z : 491.4100 $[\text{M}+\text{H}]^+$ (Calcd for $\text{C}_{31}\text{H}_{55}\text{O}_4$, 491.4102).

Isoschininalylol (5): Brown gum; $[\alpha]_{\text{D}}^{18} -13.0^\circ$ ($c=0.1$, CHCl_3); UV (CHCl_3) λ_{max} (log ϵ) 348 (3.96), 298 (3.65), 241 (3.90) nm; IR (CHCl_3) ν_{max} 3425, 1700 cm^{-1} ; $^1\text{H-NMR}$ (250 MHz, CDCl_3) δ : 7.61 (1H, d, $J=9.5$ Hz, H-4), 6.82 (1H, s, H-5), 6.79 (1H, s, H-8), 6.27 (1H, d, $J=9.5$ Hz, H-3), 5.49 (1H, t, $J=6.4$ Hz, H-2'), 4.90 (1H, s, H-8a'), 4.81 (1H, s, H-8b'), 4.67 (2H, d, $J=6.4$ Hz, H-1'), 4.02 (1H, t, $J=6.5$ Hz, H-6'), 3.88 (3H, s, 6-OMe), 2.11 (2H, m, H-4'), 1.75 (3H, s, H-9'), 1.70 (3H, s, H-10'), 1.66 (2H, m, H-5'); $^{13}\text{C-NMR}$ (63 MHz, CDCl_3) δ : 161.5 (C-2), 151.9 (C-7), 149.8 (C-9), 147.2 (C-7'), 146.6 (C-6), 143.3 (C-4), 141.8 (C-3'), 118.6 (C-2'), 113.3 (C-3), 111.3 (C-10), 111.2 (C-8'), 107.9 (C-5), 101.1 (C-8), 75.37 (C-6'), 66.19 (C-1'), 56.30 (6-OMe), 35.40 (C-4'), 32.62 (C-5'), 17.52 (C-10') 17.00 (C-9'); HR-FAB-MS (positive ion mode) m/z : 345.1702 $[\text{M}+\text{H}]^+$ (Calcd for $\text{C}_{20}\text{H}_{25}\text{O}_5$, 345.1703).

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