Natural Product Sciences
27(4) : 240-244 (2021)
https://doi.org/10.20307/nps.2021.27.4.240

Chemical Constituents from *Aegle marmelos* Fruits

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Abstract – *Aegle marmelos* (Rutaceae) is a deciduous shrub or tree and typically known as bael throughout Southeast Asia and has been used as a medicinal plant and a food ingredient. In this study eight compounds were determined to be *O*-(3,3-dimethylallyl) halfordinol (**1**), (*R*)-aegeline (**2**), (*R*)-marmeline (**3**), imperatorin (**4**), xanthotoxol (**5**), valencic acid (**6**), vanillic acid (**7**) and rutin (**8**). The chemical structures of the isolates were elucidated through spectroscopic evidence including 1D, 2D NMR, ESI-Q-TOF-MS and optical rotation.
Keywords – *Aegle marmelos* fruits, Rutaceae, (3,3-dimethylallyl) halfordinol, (*R*)-aegeline, (*R*)-marmeline

Introduction

Aegle marmelos L. Corrêa is an aromatic medicinal plant belonging to the Rutaceae family and typically known as Bael throughout Southeast Asia such as India and Myanmar. For a long time, *A. marmelos* has been regarded as one of the most valuable medicinal plants in Indian ayurvedic system for treating dysentery, indigestion, edema and rheumatism and its fruits has been used as an ingredient of many food products such as drinks, cakes, jam, syrup, and pudding due to its flavor and fragrance.[1]

In terms of chemical constituents, many research papers have demonstrated that *A. marmelos* contains alkaloids, terpenoids, flavonoids, and coumarins such as imperatorin (= marmelosin), scopoletin and umbelliferone have been found to be the most abundant compounds in this plant.[2] Several studies on pharmacological action of *A. marmelos* have demonstrated that its roots, leaves, and stems possessed antinociceptive, antidiabetes, anticancer, and antiulcer activities.[3-6]

As part of ongoing chemical study on medicinal plants from Myanmar, we conducted chemical investigation on the acetone extract of *A. marmelos* fruits, which led to the isolation of eight compounds including alkaloids, coumarins, simple phenolics and a flavonoid glycoside. The chemical structures of isolates were elucidated using spectroscopic evidence such as 1D, 2D NMR, ESI-Q-TOF-MS and optical rotation.

Experimental

General experimental procedures – A Gilson preparative HPLC system (Gilson, WI, USA) was used to isolate compounds and it was composed of binary pumps, a UV detector, and a liquid handler. The preparative HPLC column was a Luna C18(2) column (21.2 × 250 mm I.D., 5 μm; Phenomenex, USA). The structures of the isolated compounds were elucidated by one-dimensional NMR (^{1}H NMR and ^{13}C NMR) and two-dimensional NMR experiments (HSQC, HMBC) using an AVANCE 500 spectrometer (Bruker, Karlsruhe, Germany). Optical rotation was recorded through a P-2000 polarimeter (Jasco, Tokyo, Japan). ESI-Q-TOF-MS experiment was conducted utilizing the 6460 Q-TOF-MS spectrometer (Agilent Technologies, CA, USA).

Plant material – Fruits of *A. marmelos* (L.) Corrêa were collected from Popa Mountain National Park in August 2013, and Khin Myo Htwe (Popa Mountain National Park) identified specimens of *A. marmelos.* A voucher specimen (#PopaAegle_M 082013) was deposited at the College of Pharmacy, the Catholic University of Korea.

Extraction and isolation – The dried fruits of *A. marmelos* (700 g) were ground into fine powder and extracted with acetone (60 min × 3 times). The solvent

Dedicated to Prof. Jinwoong Kim of the Seoul National University for his pioneering works on Pharmacognosy.

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was evaporated under reduced pressure to give an acetone extract (55 g). The acetone extract was suspended in H_2O and successively partitioned with organic solvents to give *n*-hexane (39 g), ethyl acetate (9 g) and water (7 g) extracts. The EtOAc soluble fraction (9 g) was subjected to a silica gel column chromatography (C.C.) [*n*-hexane-EtOAc (5:1→2:1, v/v), CH_2Cl_2-MeOH (20:1→10:1→5:1, v/v), and MeOH] to afforded 27 sub-fractions (E1-E27). The sub-fraction E1 (383 mg) was recrystallized using *n*-hexane-EtOAc (5:2, v/v) to give compound **4** (8.3 mg). The fractions E3-E5 (1.23 g) were pooled according to thin layer chromatography analysis and subjected to a Sephadex-LH20 C.C. with CH_2Cl_2-MeOH (1:5, v/v) to yield six sub-fractions (E3.1-E3.6). The subfraction E3.5 (133 mg) was purified by RP-HPLC eluted with MeCN-H_2O (80:20, v/v) to afford compound **5** (13 mg). The crystalline subfraction E3.3 (92 mg) was filtered using a paper filter to recover compound **1** (10.3 mg) from the solid residue. The subfraction E6 (841 mg) was subjected to a Sephadex-LH20 C.C. using MeOH as an eluent to yield 5 sub-fractions (E6.1-E6.5) and the subfraction E6.3 (208 mg) was rechromatographed on silica gel C.C eluted with $CHCl_3$-MeOH (50:1, v/v) to yield 11 sub-fractions (E6.3.1-E6.3.11). The subfraction E6.3.5 (84 mg) was purified by RP-HPLC eluted with MeCN-H_2O (75:25, v/v) to afford compound **2** (8.6 mg) and **3** (5.8 mg). The subfraction E6.3.10 (51 mg) was purified by an RP-HPLC eluted with MeOH-H_2O (80:20, v/v) to give compound **6** (10.5 mg). Fraction E13 (112 mg) was resolved by an RP-HPLC eluted with MeCN-H_2O (20:80→100:0, v/v) to yield compound **7** (1.4 mg).

The water fraction (7 g) was subjected to Diaion HP-20 C.C. eluted with H_2O (1.5 L), 50% MeOH (1.5 L), and MeOH (1 L) to yield H_2O (1.42 g), 50% MeOH (840 mg), and MeOH (300 mg). The 50% MeOH fraction (840 mg) was chromatographed on silica gel C.C. using CH_2Cl_2-MeOH (5:1→2.5:1→1:1, v/v) to yield 25 sub-fractions (W1-W25). The fractions W20-W25 (211.2 mg) were pooled and purified by RP-HPLC using MeOH-H_2O (10:90→100:0, v/v) mixture to yield compound **8** (3.5 mg).

***O*-(3,3-Dimethylallyl)-halfordinol (1)** – pale yellow solid; $C_{19}H_{18}N_2O_2$; ESI-Q-TOF-MS: *m/z* 307.1477 $[M+H]^+$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.24 (1H, brs, H-1), 8.61 (1H, brs, H-5), 8.32 (1H, dt, *J* = 8.1, 2.1 Hz, H-3), 7.61 (2H, brd, *J* = 8.8 Hz, H-2', 6'), 7.40 (1H, dd, *J* = 8.1, 4.8 Hz, H-4), 7.31 (1H, s, H-9), 6.95 (2H, brd, *J* = 8.8 Hz, H-3', 5'), 5.46 (1H, t, *J* = 6.75 Hz, H-2"), 4.52 (2H, d, *J* = 6.75 Hz, H-1"), 1.77 (3H, s, H-5"), 1.72 (3H, s, H-4"); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 159.6 (C-4'), 158.1 (C-7), 152.5 (C-10), 150.6 (C-5), 147.7 (C-1), 138.9 (C-3"), 133.7 (C-3), 126.1 (C-2', 6'), 124.0 (C-2, 4), 122.1 (C-9), 120.3 (C-1'), 119.3 (C-2"), 115.37 (C-3', 5'), 65.1 (C-1"), 26.0 (C-5"), 18.4 (C-4").

(*R*)-Aegeline (2) – white solid; $C_{18}H_{19}NO_3$; $[\alpha]^{25}_D$ = -19.11 (c 0.23, MeOH); ESI-Q-TOF-MS: *m/z* 320.1258 $[M+Na]^+$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.63 (1H, d, *J* = 15.5 Hz, H-7'), 7.47 (2H, dd, *J* = 3.0, 6.6 Hz, H-2', 6'), 7.34 (3H, o, H-3',4',5'), 7.30 (2H, d, *J* = 8.6 Hz, H-2", 6"), 6.87 (2H, d, *J* = 8.6 Hz, H-3", 5"), 6.37 (1H, d, *J* = 15.5 Hz, H-8'), 4.86 (1H, dd, *J* = 3.5, 8.4 Hz, H-2), 3.79 (4H, o, H-1b, 4"-OC<u>H</u>$_3$), 3.43 (1H, dd, *J* = 13.4, 8.4 Hz, H-1a); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 167.1 (C-9'), 159.3 (C-4"), 141.8 (C-7'), 134.6 (C-1'), 133.8 (C-1"), 129.8 (C-4'), 128.8 (C-3', 5'), 127.8 (C-2', 6'), 127.1 (C-2", 6"), 119.9 (C-8'), 113.9 (C-3", 5"), 73.4 (C-2), 55.3 (C-4"-O<u>C</u>H$_3$), 47.6 (C-1).

(*R*)-Marmeline (3) – colorless needles; $C_{22}H_{25}NO_3$; $[\alpha]^{25}_D$ = -14.04 (*c* 0.17, MeOH); ESI-Q-TOF-MS: *m/z* 374.1741 $[M+Na]^+$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.63 (1H, d, *J* = 15.6 Hz, H-7'), 7.47 (2H, dd, H-2', 6'), 7.34 (3H, o, H-3', 4', 5'), 7.28 (2H, d, *J* = 8.2 Hz, H-2", 6"), 6.88 (2H, d, *J* = 8.2 Hz, H-3", 5"), 6.38 (1H, d, *J* = 15.6 Hz, H-8'), 6.12 (1H, s, N<u>H</u>), 5.47 (1H, t, *J* = 6.8 Hz, H-2'"), 4.84 (1H, dd, *J* = 8.2, 3.3 Hz, H-2), 4.47 (2H, d, *J* = 6.8 Hz, H-1'"), 3.78 (1H, m, *J* = 13.0 Hz, H-1b), 3.43 (1H, m, *J* = 13.0 Hz, H-1a), 1.77 (3H, s, H-4'"), 1.72 (3H, s, H-5'") ; ^{13}C-NMR (125 MHz, $CDCl_3$): δ 167.1 (C-9'), 158.6 (C-4"), 141.7 (C-7'), 138.3 (C-3'"), 134.6 (C-1'), 133.7 (C-1"), 129.8 (C-4'), 128.8 (C-3', 5'), 127.8 (C-2', 6'), 127.0 (C-2", 6"), 120.0 (C-8'), 119.5 (C-2'"), 114.6 (C-3", 5"), 73.4 (C-2), 64.7 (C-1'"), 47.6 (C-1), 25.8 (C-4'"), 18.8 (C-5'").

Imperatorin (4) – colorless crystalline solid; $C_{16}H_{14}O_4$; ESI-Q-TOF-MS: *m/z* 271.0980 $[M+H]^+$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.74 (1H, d, *J* = 9.5 Hz, H-4), 7.67 (1H, d, *J* = 2.2 Hz, H-2'), 7.34 (1H, s, H-5), 6.79 (1H, d, *J* = 2.2 Hz, H-3'), 6.35 (1H, d, *J* = 9.5 Hz, H-3), 5.59 (1H, t, *J* = 7.2 Hz, H-2"), 4.98 (2H, d, *J* = 7.2 Hz, H-1"), 1.72 (3H, s, H-4"), 1.70 (3H, s, H-5"); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 160.5 (C-2), 148.6 (C-7), 146.6 (C-2'), 144.3 (C-4), 143.8 (C-8a), 139.7 (C-3"), 131.61 (C-8), 125.8 (C-6), 119.7 (C-2"), 116.4 (C-4a), 114.7 (C-3), 113.1 (C-5), 106.67 (C-3'), 70.1 (C-1"), 25.8 (C-4"), 18.1 (C-5").

Xanthotoxol (5) – white amorphous powder; $C_{11}H_6O_4$; ESI-Q-TOF-MS: *m/z* 203.0348 $[M+H]^+$; ^{1}H-NMR (500 MHz, CD_3OD): δ 8.00 (1H, d, *J* = 9.6 Hz, H-4), 7.84 (1H, d, *J* = 2.2 Hz, H-2'), 7.35 (1H, s, H-5), 6.90 (1H, d, *J* = 2.2 Hz, H-3'), 6.34 (1H, d, *J* = 9.6 Hz, H-3); ^{13}C-NMR (125 MHz, CD_3OD): δ 163.1 (C-2), 148.4 (C-7), 147.3 (C-2'), 147.2 (C-4), 141.2 (C-8a), 131.8 (C-8), 127.5 (C-

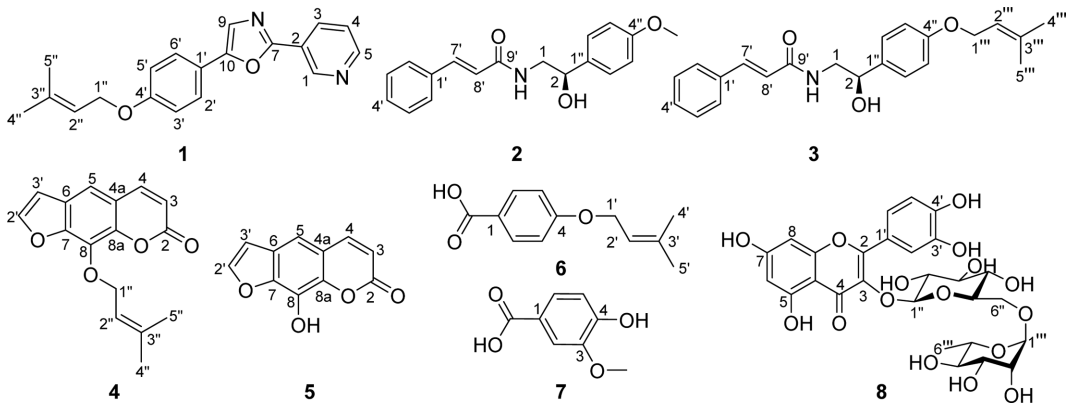

Fig. 1. Chemical structures of isolates from *Aegle marmelos.*

6), 117.9 (C-4a), 114.8 (C-3), 111.8 (C-5), 108.1 (C-3').

Valencic acid (6) – white solid; $C_{12}H_{14}O_3$; ESI-Q-TOF-MS: *m/z* 205.0866 $[M-H]^-$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.04 (2H, d, *J* = 8.4 Hz, H-2', 6'), 6.93 (2H, d, *J* = 8.4 Hz, H-3', 5'), 5.47 (1H, t, *J* = 6.8 Hz, H-2"), 4.56 (2H, d, *J* = 6.8 Hz, H-1"), 1.79 (3H, s, H-4"), 1.74 (3H, s, H-5"); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.9 (C=OOH), 163.3 (C-4), 139.0 (C-3'), 132.3 (C-2, 6), 121.5 (C-1), 118.8 (C-2'), 114.3 (C-3, 5), 65.0 (C-1'), 25.8 (C-4'), 18.2 (C-5').

Vanillic acid (7) – white-yellowish powder; $C_8H_8O_4$; ESI-Q-TOF-MS: *m/z* 167.0347 $[M-H]^-$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.69 (1H, dd, *J* = 8.3, 1.9 Hz, H-6), 7.57 (1H, d, *J* = 1.9 Hz, H-2), 6.95 (1H, d, *J* = 8.3 Hz, H-5), 3.94 (3H, s, H-3-OC$\underline{H}_3$); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 170.1 (C=OOH), 151.0 (C-4), 146.4 (C-3), 125.4 (C-6), 121.2 (C-1), 114.4 (C-5), 112.3 (C-2), 56.3 (C-3-O$\underline{C}H_3$).

Rutin (8) – yellow amorphous solid; $C_{27}H_{30}O_{16}$; ESI-Q-TOF-MS: *m/z* 611.1610 $[M+H]^+$; ^{1}H-NMR (500 MHz, CD_3OD): δ 7.67 (1H, d, *J* = 2.3 Hz, H-2'), 7.64 (1H, dd, *J* = 8.4, 2.3 Hz, H-6'), 6.88 (1H, d, *J* = 8.4 Hz, H-5'), 6.41 (1H, d, *J* = 2.1 Hz, H-8), 6.22 (1H, d, *J* = 2.1 Hz, H-6), 5.11 (1H, d, *J* = 7.7 Hz, H-1"), 4.52 (1H, d, *J* = 1.4 Hz, H-1'"), 1.12 (3H, d, *J* = 6.2 Hz, H-6'"); ^{13}C-NMR (125 MHz, CD_3OD): δ 179.6 (C-4), 166.2 (C-7), 163.2 (C-5), 159.5 (C-9), 158.7 (C-2), 150.0 (C-4'), 146.0 (C-3'), 135.8 (C-3), 123.7 (C-1'), 123.3 (C-6'), 117.8 (C-5'), 116.2 (C-2'), 105.8 (C-10), 104.8 (C-1"), 102.6 (C-1'"), 100.1 (C-6), 95.0 (C-8), 78.3 (C-3"), 77.4 (C-5"), 75.9 (C-2"), 74.1 (C-4"), 72.4 (C-3'"), 72.3 (C-2'"), 71.5 (C-4'"), 69.9 (C-5'"), 68.7 (C-6"), 18.0 (C-6'").

Results and Discussion

The chemical investigation on the acetone extract of *A. marmelos* fruits led to the isolation of eight compounds including three alkaloids (**1**–**3**), two coumarins (**4**, **5**), two simple phenolics (**6**, **7**), and a flavonoid glycoside (**8**). The chemical structures of **1**–**8** were identified to be *O*-(3,3-dimethylallyl)-halfordinol (**1**),[7-9] (*R*)-aegeline (**2**),[10,11] (*R*)-marmeline (**3**),[12-14] imperatorin (**4**),[15,16] xanthotoxol (**5**),[16] valencic acid (**6**),[17] vanillic acid (**7**)[18] and rutin (**8**)[19] (Fig. 1). Here, we describe the structure elucidation of compounds **1**–**3** only since compounds **4**–**8** were commonly found in several herbal medicines and nature while compounds **1**–**3** have been specifically found from *A. marmelos* and they have unique chemical structures.

Compound **1** was isolated as a pale yellow solid and it was inferred to be an alkaloid based on the molecular formula of $C_{19}H_{18}N_2O_2$ from the protonated ion peak at *m/z* 307.1477 $[M+H]^+$ in the ESI-Q-TOF-MS spectrum together with the positive reaction to the Dragendorff test. ^{1}H-NMR spectrum showed resonances typical to a 3-monosubstituted pyridine ring (**A**) at δ_H 9.24 (1H, brs, H-1), 8.61 (1H, brs, H-5), 8.32 (1H, dt, *J* = 8.1, 2.1 Hz, H-3) and 7.40 (1H, dd, *J* = 8.1, 4.8 Hz, H-4), an 1,4-disubstituted benzene ring (**C**) at δ_H 7.61 (2H, brd, *J* = 8.8 Hz, H-2', 6') and 6.95 (2H, brd, *J* = 8.8 Hz, H-3', 5'), and a 3,3-dimethylallyloxy group (**D**) at δ_H 1.77 (3H, s, H-5"), 1.72 (3H, s, H-4"), 5.46 (1H, t, *J* = 6.75 Hz, H-2"), and 4.52 (2H, d, *J* = 6.75 Hz, H-1"). In addition, an olefinic proton signal was observed at 7.31 (1H, s, H-9) and it was further identified to be derived from an 2,4-disubstituted oxazoline ring (**B**) using 2D-NMR experiments. The ^{13}C-NMR spectrum showed 16 carbon signals and proton/carbon pairs were determined by HSQC spectrum. HMBC experiment was utilized to determine the connectivities between four functional groups through correlation peaks at δ_H 9.24 (H-1) and 8.32 (H-3)/δ_C 158.1 (C-7) (**A**↔**B**), δ_H 7.31 (H-9)/δ_C 126.1 (C-2', 6') (**B**↔**C**) and δ_H 4.52 (H-1")/δ_C 115.4 (C-3', 5') (**C**↔**D**) (Fig. 2)

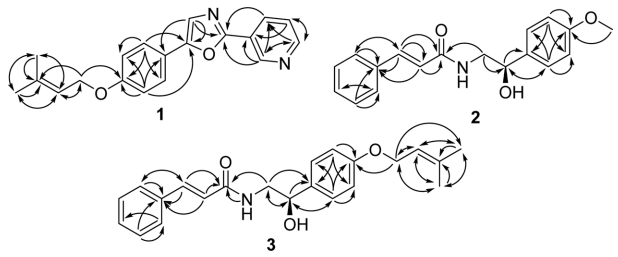

Fig. 2. HMBC correlations of compounds **1**–**3**.

(Fig. S1-S4). Based on the spectroscopic evidence and previously published literature, compound **1** was identified to be *O*-(3,3-dimethylallyl)-halfordinol[7-9] and it has been found from plants belong to Rutaceae family such as *Aegle marmelos*, *Aeglopsis chevalieri*, *Aeglopsis plumieri* and *Amyris brenesii,* and showed lipolytic and antiadipogenic effects on 3T3-L1 adipocytes and obesity induced mice.

In the previous references, the chemical structure of **1** was characterized according to only 1D NMR data and the way of structure numbering differed depending on the paper, while the chemical shift of each carbon and hydrogen were precisely specified using 1D and 2D NMR in the current study. It was found that some carbons were incorrectly characterized in the previous papers, which was corrected in this study (Fig. S1-S5).

Compound **2** showed a positive reaction to Dragendorff test and its molecular formula was determined to be $C_{18}H_{19}NO_3$ from the sodiated ion peak at *m/z* 320.1258 $[M+Na]^+$in the ESI-Q-TOF-MS spectrum. The ^{1}H-NMR experiment observed a 1,4-disubstituted benzene ring at δ_H 7.30 (2H, d, J = 8.6 Hz, H-2", 6") and 6.87 (2H, d, J = 8.6 Hz, H-3", 5"), a cinnamic amide at δ_H 7.63 (1H, d, J = 15.5 Hz, H-7'), 7.47 (2H, dd, J = 3.0, 6.6 Hz, H-2', 6'), 7.34 (3H, peak overlapped, H-3', 4', 5') and 6.37 (1H, d, J = 15.5 Hz, H-8'), a methylene group at δ_H 3.79 (1H, peak overlapped with a methoxy peak, H-1b), 3.43 (1H, dd, J = 13.4, 8.4 Hz, H-1a), a oxygenated methine proton at δ_H 4.86 (1H, dd, J = 3.5, 8.4 Hz, H-2) and a methoxy group (3H, peak overlapped with H-1b, 4"-OC$\underline{H}_3$). The ^{13}C-NMR spectrum showed 14 carbon signals including three symmetrical carbon signals. The hydrogen-carbon correlation was confirmed by HSQC spectrum and the whole structure of **2** was drawn using HMBC experiment as shown in Fig. 2. The absolute configuration at C-2 position was determined to be (*R*)-form by means of a negative optical rotation value at $[\alpha]^{25}_D$ = -19.11. Collectively, compound **2** was identified as (*R*)-aegeline.

Compound **3** showed a positive reaction to Dragendorff test and ESI-Q-TOF-MS displayed a sodiated ion peak at *m/z* 374.1741 $[M+Na]^+$ corresponding to a molecular formula of $C_{22}H_{25}NO_3$. The ^{1}H- and ^{13}C-NMR spectra were very close to compound **2** except that the methoxy group was replaced by a 3,3-dimethylallyloxy group [δ_H 1.77 (3H, s, H-4'")/δ_C 25.8 (C-4'"), δ_H 1.72 (3H, s, H-5'")/δ_C 18.2 (C-5'"), δ_H 5.47 (1H, t, J = 6.8 Hz, H-2'")/δ_C 119.5 (C-2'") and δ_H 4.47 (2H, d, J = 6.8 Hz, H-1'")/δ_C 64.7 (C-1")]. The HMBC correlation peak at δ_H 7.47 (2H, dd, H-2', 6')/δ_C 129.8 (C-4') confirmed that the 3,3-dimethylallyloxy group was linked at C-4" position (Fig. 2). The absolute configuration at C-2 position was determined to be *R*-form from a negative optical rotation value at $[\alpha]^{25}_D$ = -14.04. Therefore, compound **3** was elucidated to be (*R*)-marmeline.

In conclusion, eight compounds were characterized from the fruits of *A. marmelos* and three alkaloids, *O*-(3,3-dimethylallyl)-halfordinol, (*R*)-aegeline and (*R*)-marmeline were identified by spectroscopic evidence, which is good agreement with the previous literature. However, not much has been investigated on the biological effects of those alkaloids even though *A. marmelos* fruits have been used to food or cosmetic products in many countries. Therefore, various biological evaluations should be done for the safe use of *A. marmelos* fruits as natural medicines or dietary supplements.

Acknowledgements

This work was supported by the National Foundation of Korea (Grant No. 2018R1A6A1A03025108) and a research fund, 2021 of the Catholic University of Korea.

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Received November 18, 2021
Revised December 8, 2021
Accepted December 11, 2021