THREE NEW ENT-KAURANE DITERPENOIDS FROM THE SEEDS OF PHARBITIS NIL

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Abstract – Three new ent-kaurane diterpenoids, 7β, 16β, 17-trihydroxy ent-kauran 18-(6β)-olide (1), methyl 6β, 7β, 16β, 17-tetrahydroxy ent-kauran-18-oate (2) and 6β, 7β, 16β, 17-tetrahydroxy ent-kauran-18-oic acid (3), together with thirteen known compounds, were isolated from the seeds of Pharbitis nil (Convolvulaceae). The identification and structural elucidation of these compounds were based on 1D- and 2D-NMR spectral data analysis. The absolute configuration of 1 was determined by a convenient Mosher ester procedure carried out in NMR tube.

INTRODUCTION

Pharbitidis Semen, the seeds of 'morning-glory' Pharbitis nil Choisy (Convolvulaceae), has been used as a crude purgative drug in Korean traditional medicine. Previous phytochemical studies of this herb found that gibberellins and their glycosides were abundant secondary metabolites in this herb.1-4 Its major constituent is known to be an ether-insoluble resin glycoside with resinous purgative principles.5-7 Pharbitidis Semen has anti-gastric cancer and anti-fungal activities.8,9 In the course of our continuing search for potential lead compounds for drug development from Korean medicinal plant sources, we performed a phytochemical investigation of this herb. Column chromatographic purification of the CHCl₃-soluble fraction of the EtOH extract of this source led to the isolation of three new kaurane diterpenes (1-3), together with thirteen known compounds (4-16). The structures of known compounds were determined to be ethyl caffeate (4),10 p-coumaric acid ethyl ester (5),11 ferulic acid ethyl ester (6),12
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scopeletin (7), crenulatin (8), convulvinic acid (9), (12S, 13S) 12, 13-dihydroxyoctadec-9-cis-9-enoic acid (10), 9-oxoactadec-9-cis-12-enoic acid (11), 9-hydroxyoctadec-9-cis-12-enoic acid (12), (2R)-2-O-(9-oxoactadec-9-cis-12-enoxy) glycerol (13), (2R)-2-O-(9-hydroxyoctadec-9-cis-12-enoxy) glycerol (14), (9S, 10E, 12Z)-hydroxyoctadeca-10, 12-dienoic acid (15) and trilinolein (16) by comparing their spectroscopic data with those in the literatures. All the isolated known compounds (4-10, 10-16) except 9 were reported from this source for the first time.

RESULTS AND DISCUSSION

Compound 1 was obtained as a colorless gum, whose molecular formula was determined to be C_{26}H_{35}O_{5} from the [M + H]^+ peak at m/z 351.2173 (calcd. for C_{26}H_{35}O_{5}: 351.2172) in the high resolution-electron impact (HR-EI) MS spectrum. The IR spectrum indicated that 1 possessed hydroxyl (3413 cm^{-1}) and γ-lactone (1757 cm^{-1}) groups. The ^1H-NMR spectrum (Table 1) of 1 displayed signals for presence of two tertiary methyl groups at δ_{H}: 1.15 and 1.25 and one hydroxymethylene group at δ_{H}: 3.36 (d, J: 11.0 Hz) and 3.44 (d, J: 11.0 Hz), adjacent to the quaternary carbon. The ^13C-NMR and distortionless enhancement by polarization transfer (DEPT) experiments revealed that 1 displayed 20 carbon signals, composed of two methyls, eight methylenes, five methines, and five quaternary carbons. The ^13C-NMR resonances were similar to those of the related ent-kaurane γ-lactone diterpenes, ent-7β-hydroxykaurenolide, except for the replacement of double bond for C-16 and C-17 with hydroxylated carbons at δ_{C}: 80.4 ppm (C-16) and δ_{C}: 70.6 ppm (C-17) in 1, suggesting that 1 was to be ent-kaurane derivative. The ent-kaurane skeleton of 1 was also confirmed on the basis of the coupling constants (J_{5,6}: 11.5 Hz and J_{6,7}: 2.0 Hz) observed in the ^1H-NMR spectral data, NOESY correlations (H-6/H-20), and no NOESY correlations (H-5/H-6, H-5/H-20) (Figure 2). The HMBC spectrum confirmed the position of the two hydroxyl groups at C-16 and C-17; The signals of H-17 (δ_{H}: 3.36 and 3.44) correlated with C-13 (δ_{C}: 42.3), C-15 (δ_{C}: 49.5) and C-16 (δ_{C}: 80.4). The


Figure 1. The structures of the isolated compounds (1-3) from P. nil

\[ 1 \quad R = H \]
\[ 2 \quad R = \text{OMe} \]
\[ 3 \quad R = \text{OH} \]
γ-lactone function was located at C-4/C-6 from the HMBC correlations between H-19 (δH = 1.25) and C-18 (δC = 185.9), and H-5 (δH = 2.33) and C-18 (δC = 185.9) (Figure 2). And the signal of H-7 (δH = 3.80) correlated with C-6 (δC = 80.0), C-8 (δC = 51.9) and C-9 (δC = 55.8) in the HMBC experiment, allowing a hydroxyl group to be at C-7. The relative stereochemistry of I was assigned on the basis of the J values in the 1H-NMR spectrum and the NOESY experiment (Figure 2). The coupling constants of H-6 (dd, J5,6 = 11.5 Hz and J6,7 = 2.0 Hz) and H-7 (d, J6,7 = 2.0 Hz) observed in the 1H-NMR spectrum in I were very similar with those of H-6 (dd, J5,6 = 11.5 Hz and J6,7 = 2.5 Hz) and H-7 (d, J6,7 = 2.5 Hz) in 6β,7β-dihydroxykaurenoic acid.22 Thus, the configurations of H-6 and H-7 were determined to be α-orientation, and also the γ-lactone group to be β disposition. These configurations could be confirmed in the NOESY correlations between H-5/H-1α, H-5/H-3α, between H-6/H-20, between H-19/H-3eq, H-19/H-20 and between H-20/H-14α, which also suggested the α-orientation of CH1-19 and CH1-20 (Figure 2). In addition, a correlation between H-17/H-13 in the NOESY spectrum confirmed that the configuration of OH group at C-16 was β form. Thus, the structure of I was determined to be 7β, 16β, 17-trihydroxy ent-kauran 18-(6β)-olide. The absolute configuration of I was determined by a convenient Mosher ester procedure carried out in NMR tube.23 Analysis of the chemical shift differences between the (R)- and (S)-MTPA ester derivatives (1r and 1s, respectively) (δS - δR) of I (Figure 4) showed that the absolute stereostructures at C-7 and C-16 of I were to be R- and S-configuration, respectively.

Figure 2. Key HMBC (→) (a) and NOESY (↔) (b) correlations of I

Compound 2 was obtained as a colorless gum, whose molecular formula was determined to be C21H32O6 from the [M + Na]+ peak at m/z 405.2265 (calcd. for C21H31O6Na: 405.2253) in the positive-ion high resolution (HR)-FAB-MS spectrum. The IR spectrum indicated that 2 possessed hydroxyl (3421 cm⁻¹) and ester (1642 cm⁻¹) groups. The 1H- and 13C-NMR spectral data (Table 1) of 2 were very similar to those of 1, except for the presence of a methoxy group (δC = 52.8) at C-18 in 2. This suggested that C-4/C-6 γ-lactone function of 1 was broken into methylester functionality in 2. The position of the
methoxy group was also confirmed to be at C-18 from the HMBC correlation between methoxy proton \((\delta_H = 3.69)\) and C-18 \((\delta_C = 180.4)\), as shown in Figure 3. A correlation between H-19/OCH₃, H-19/H-20 in the NOESY spectrum confirmed that the methyl group at C-19 was \(\alpha\) form. In addition, the stereochemistry of 2 was assigned to be same as that of 1 on the basis of the NOESY experiment and the \(J\) values in the \(^1\)H-NMR spectrum (Figure 3). Thus, the structure of 2 was determined to be methyl \(6\beta, 7\beta, 16\beta, 17\)-tetrahydroxy \(\text{ent-kauran-18-oate}\). The compound 2 could be detected by TLC analysis in the 50% ethanol extract of the source, which implied that 2 was not an artifact.

![Figure 3. Key HMBC (\(\rightarrow\)) (a) and NOESY (\(\leftrightarrow\)) (b) correlations of 2]

Compound 3 was obtained as a colorless gum, whose molecular formula was determined to be C₂₀H₂₂O₆ from the \([M + Na]^+\) peak at m/z 391.2122 (calcd. for C₂₀H₂₂O₆Na: 391.2097) in the positive-ion high resolution (HR)-FAB-MS spectrum. The IR spectrum indicated that 3 possessed hydroxyl (3357 cm⁻¹) and ester (1661 cm⁻¹) groups. The \(^1\)H- and \(^1^3\)C-NMR spectral data (Table 1) of 3 were very similar to those of 2, except for the absence of a methoxy group at C-18 in 3. The stereochemistry of 3 was assigned to be same as that of 2 on the basis of the NOESY experiment and the \(J\) values in the \(^1\)H-NMR spectrum. Thus, the structure of 3 was determined to be \(6\beta, 7\beta, 16\beta, 17\)-tetrahydroxy \(\text{ent-kauran-18-oic acid}\).

The kaurenolides, diterpene lactones, are biosynthetically related to the gibberellin plant hormones.²⁴,²⁵ Michael et al.²⁶ reported that \(\text{ent-kaura-6, 16-dien-19-oic acid}\) was incorporated, after incubation with the mutant (B1-41a), into \(7\beta\)-hydroxykaurenolide via \(\text{ent-6}\beta, 7\alpha\)-dihydroxykaur-16-en-19-oic acid. Possible biosynthetic routes from \(\text{ent-kaura-6, 16-dien-19-oic acid}\) to \(7\beta\)-hydroxykaurenolide were also studied.²⁶ Thus, we assumed that the compounds 2 and 3 could be the precursors of 1.

**EXPERIMENTAL**

**General.** All melting points were determined on a Gallenkamp melting point apparatus and uncorrected.
Optical rotations were measured on a Jasco P-1020 polarimeter in MeOH. IR spectra were recorded on a Bruker IFS-66/S FT-IR spectrometer. EI and HR-EI mass spectra were recorded on a JEOL SX102 mass spectrometer. FAB and HR-FAB mass spectra were obtained on a JEOL JMS700 mass spectrometer. NMR spectra, including NOESY, DEPT and HMBC experiments, were recorded on a Varian UNITY INOVA 500 NMR spectrometer operating at 500 MHz (¹H) and 125 MHz (¹³C), respectively, with chemical shifts given in ppm (δ) using TMS as an internal standard. Preparative HPLC used a Gilson 306 pump with Shodex refractive index detector. Silica gel 60 (Merck, 70-230 mesh and 230-400 mesh) and RP-C₁₈ silica gel (Merck, 230-400 mesh) was used for column chromatography. Merck precoated Silica gel F₂₅₄ plates and RP-18 F₂₅₄, plates were used for TLC. Spots were detected on TLC under UV light or by heating after spraying with 10 % H₂SO₄ in C₂H₅OH (v/v). The packing material for molecular sieve column chromatography was Sephadex LH-20 (Pharmacia Co.). Low pressure liquid chromatography was carried out over a Merck Lichroprep Lobar®-A Si 60 (240×10 mm) or a Lichroprep Lobar®-A RP-18 (240×10 mm) column with a FMI QSY-0 pump (ISCO).

**Plant material.** The seeds of *P. nil* were purchased from Kyungdong herbal market, Seoul, Korea, in July 2006. A voucher specimen (SKKU 2006-7) was deposited in the herbarium of the College of Pharmacy, Sungkyunkwan University, Suwon, Korea.

**Extraction and isolation.** The dried seeds (10 kg) were extracted with 50% EtOH three times at rt. The resultant ethanolic extracts (1.4 kg) were suspended in distilled water (7.2 L) and then successively partitioned with *n*-hexane, CH₂Cl₂, EtOAc and *n*-BuOH, yielding 10 g, 7 g, 10 g and 550 g, respectively. The CH₂Cl₂ soluble fraction (7 g) was chromatographed on a RP-C₁₈ silica gel (230-400 mesh, 300 g), eluting with gradient solvent system of MeOH/H₂O (4:1, 9:1 and 1:0). According to TLC analysis, five crude fractions (fr. A - E) were collected. Fr. B (1.0 g) was chromatographed further on a RP-C₁₈ silica gel (230-400 mesh, 150 g), eluting with gradient solvent system of MeOH/H₂O (3:2, 4:1, 9:1 and 1:0) to

![Chemical structure](image-url)
give five subfractions (fr. B1 - B5). Fr. B1 (90 mg) was purified by silica gel Lobar®-A Si 60 (240×10mm) column (hexane/CHCl₃/EtOAc, 2:1:2) to afford 7 (5 mg) and 8 (6 mg) and was purified by preparative reversed-phase HPLC, using a solvent system of 30% MeCN to yield 3 (20 mg). Fr. B2 (550 mg) was chromatographed on a Sephadex LH-20 (150 g, Pharmacia Co.), using a solvent system of 100% MeOH, and purified by preparative reversed-phase HPLC, using a solvent system of 60% MeOH to yield 4 (50 mg). Fr. B3 (130 mg) was purified further by preparative reversed-phase HPLC, using a solvent system of 60% MeOH to obtain 1 (23 mg). Fr. B4 (60 mg) was purified by preparative reversed-phase HPLC, using a solvent system of 40% MeCN to obtain 2 (5 mg), 5 (14 mg) and 6 (20 mg), respectively.

Fr. C (400 mg) was chromatographed on a RP-C₁₈ silica gel (230-400 mesh, 100 g), eluting with a gradient solvent system of MeCN/H₂O (3:2, 4:1, 9:1 and 1:0) to give seven main fractions (fr. C1 - C7). Fr. C6 (70 mg) was purified by Lobar®-A RP-18 (240×10 mm) column (55% MeCN), and purified further by preparative reversed-phase HPLC, using a solvent system of 55% MeCN to obtain 10 (30 mg). Fr. C7 (30 mg) was chromatographed on a Sephadex LH-20 (150 g, Pharmacia Co.), using a solvent system of CH₂Cl₂/MeOH (1:1), to obtain 9 (8 mg). Fr. D (600 mg) was chromatographed on a Sephadex LH-20 (150 g, Pharmacia Co.), using a solvent system of 100% MeOH to give two main fractions (fr. D1 - D2), and Fr. D1 (400 mg) was rechromatographed on a RP-C₁₈ silica gel (230-400 mesh, 100 g), eluting with a gradient solvent system of MeCN/H₂O (7:3, 9:1 and 1:0) to give six subfractions (fr. D11 - D16). Fr. D11 (25 mg) was purified further by preparative HPLC, using a solvent system of n-hexane/EtOAc (2:1) to yield 15 (6 mg) and 16 (4 mg). Fr. D12 (65 mg) was purified further by preparative HPLC, using a solvent system of n-hexane/EtOAc (2:3) to obtain 14 (30 mg). Fr. D13 (40 mg) was purified further by preparative HPLC, using a solvent system of n-hexane/EtOAc (1:1) to obtain 13 (6 mg). Fr. D14 (200 mg) was purified further by preparative HPLC, using a solvent system of n-hexane/EtOAc (5:2) to yield 12 (40 mg). Finally, fr. D16 (50 mg) was purified by preparative HPLC, using a solvent system of n-hexane/EtOAc (5:2) to obtain 11 (30 mg).

7β, 16β, 17-Trihydroxy ent-kauran-18-(6β)-olide (1). colorless gum. [α]D²⁵ -20.2° (c 0.25, MeOH); IR (KBr) νmax cm⁻¹: 3413, 2935, 1757, 1463, 1182, 1095, 1009, 1616; EI-MS m/z (rel. int.) = 350 ([M]+, 2), 332 (10), 319 (35), 273 (28), 166 (28), 137 (28), 109 (100); HR-EI-MS m/z = 351.2173 [M + H]+ (calcd. for C₂₀H₃₆O₈: 351.2172); ¹H- and ¹³C-NMR: see Table 1.

Methyl 6β, 7β, 16β, 17-tetrahydroxy ent-kauran-18-oate (2). colorless gum. [α]D²⁵ -41.0° (c 0.15, MeOH); IR (KBr) νmax cm⁻¹: 3421, 1642, 1550, 1033, 668; Positive-ion HR-FAB-MS m/z = 405.2265 [M + Na]+ (calcd. for C₂₃H₃₄O₄Na: 405.2253); ¹H- and ¹³C-NMR: see Table 1.

Preparation Procedure. (S)-(++)-α-Me immediately MTPA chlor overnight, th were measured.

1. (500 MHz (1H, d, J = 1)
   (1H, m H-1; 2.096 (1H, r H-15b), 1.61
   (1H, m, H-9)

1r. (500 MHz (1H, dd, J = 1)
   (1H, m H-1; 2.080 (1H, r H-12b), 1.5
   (1H, m, H-9)

1s. (500 MHz (1H, dd, J = 1)
   (1H, m H-1; 2.070 (1H, r H-12b), 1.5
   (1H, m, H-9
6β, 7β, 16β, 17-Tetrahydroxy ent-kauran-18-oic acid (3). colorless gum. [α]_D^-25 = -58.6° (c 0.25, MeOH); IR (KBr) νmax cm⁻¹: 3357, 2948, 1661, 1453, 1033, 671; Positive-ion HR-FAB-MS m/z = 391.2122 [M + Na]^+ (calcd. for C_{20}H_{32}O_6Na: 391.2097); ¹H- and ¹³C-NMR: see Table 1.

**Preparation of the (R)- and (S)-MTPA Ester Derivatives of 1 by a Convenient Mosher Ester Procedure.** Compound 1 (0.6mg) in deuterated pyridine (1.0 mL) was transferred into clean NMR tube. (S)-(+)α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride (10 µL) was added into the NMR tube immediately under a N₂ gas stream, and then the NMR tube was shaken carefully to mix the sample and MTPA chloride evenly. The reaction NMR tube was permitted to stand at room temperature. After overnight, the reaction was completed to afford the (R)-MTPA ester derivative (1r) of 1. In manner described for 1r, (S)-MTPA ester derivative of 1 (1s) was obtained. The ¹H-NMR spectra of 1r and 1s were measured with the reaction NMR tubes directly.

1. (500 MHz, pyridine-d₅): δ 4.461 (1H, dd, J = 11.5, 2.0 Hz, H-6), 4.131 (1H, d, J = 2.0 Hz, H-7), 3.864 (1H, d, J = 11.0 Hz, H-17a), 3.799 (1H, d, J = 11.0 Hz, H-17b), 2.787 (1H, d, J = 11.5 Hz, H-5), 2.571 (1H, m H-13), 2.518 (1H, m, H-11a), 2.458 (1H, m, H-3a), 2.457 (1H, m, H-2a), 2.162 (1H, m, H-12a), 2.096 (1H, m, H-1a), 1.964 (1H, m, H-15a), 1.962 (1H, m, H-3b), 1.943 (1H, m, H-14a), 1.622 (1H, m, H-15b), 1.610 (1H, m, H-12b), 1.558 (1H, m, H-2b), 1.556 (1H, m, H-11b), 1.554 (1H, m, H-14b), 1.430 (1H, m, H-9), 1.299 (3H, s, H-19), 1.033 (3H, s, H-20), 0.825 (1H, m, H-1b).

1r. (500 MHz, pyridine-d₅): δ 5.833 (1H, d, J = 2.0 Hz, H-7), 4.703 (1H, d, J = 11.0 Hz, H-17a), 4.621 (1H, dd, J = 11.5, 2.0 Hz, H-6), 4.385 (1H, d, J = 11.0 Hz, H-17b), 2.763 (1H, d, J = 11.5 Hz, H-5), 2.423 (1H, m H-13), 2.410 (1H, m, H-11a), 2.273 (1H, m, H-3a), 2.272 (1H, m, H-2a), 2.104 (1H, m, H-12a), 2.080 (1H, m, H-1a), 1.994 (1H, m, H-3b), 1.957 (1H, m, H-15a), 1.934 (1H, m, H-14a), 1.584 (1H, m, H-12b), 1.572 (1H, m, H-15b), 1.548 (1H, m, H-2b), 1.546 (1H, m, H-11b), 1.496 (1H, m, H-14b), 1.380 (1H, m, H-9), 1.029 (3H, s, H-19), 1.018 (3H, s, H-20), 0.825 (1H, m, H-1b).

1s. (500 MHz, pyridine-d₅): δ 5.756 (1H, d, J = 2.0 Hz, H-7), 4.684 (1H, d, J = 11.0 Hz, H-17a), 4.420 (1H, dd, J = 11.5, 2.0 Hz, H-6), 4.478 (1H, d, J = 11.0 Hz, H-17b), 2.756 (1H, d, J = 11.5 Hz, H-5), 2.418 (1H, m H-13), 2.410 (1H, m, H-11a), 2.273 (1H, m, H-3a), 2.274 (1H, m, H-2a), 2.105 (1H, m, H-12a), 2.070 (1H, m, H-1a), 1.993 (1H, m, H-3b), 1.956 (1H, m, H-15a), 1.930 (1H, m, H-14a), 1.590 (1H, m, H-12b), 1.544 (1H, m, H-11b), 1.537 (1H, m, H-15b), 1.536 (1H, m, H-2b), 1.451 (1H, m, H-14b), 1.399 (1H, m, H-9), 1.001 (3H, s, H-19), 0.977 (3H, s, H-20), 0.825 (1H, m, H-1b).
Table 1. $^1$H- and $^{13}$C-NMR chemical shifts of 1-3 ($\delta$ in ppm, 500 MHz for $^1$H and 125 MHz for $^{13}$C, in CD$_2$OD)

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$^a$ Coupling constants ($J$ in Hz) are given in parentheses.

$^b$ Overlapped signals.