Diterpene Glycosides from the Seeds of *Pharbitis nil*

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Six new *ent*-kaurane diterpene glycosides, pharbosides A−F (**1**−**6**), and a new *ent*-gibbane diterpene glycoside, pharboside G (**7**), together with three known *ent*-kaurane diterpenoids, 7β,16β,17-trihydroxy-*ent*-kauran-6α,19-olide (**8**), 6β,7β,16α,17-tetrahydroxy-*ent*-kauranoic acid (**9**), and 6β,7β,16β,17-tetrahydroxy-*ent*-kauranoic acid (**10**), were isolated from an ethanolic extract of the seeds of *Pharbitis nil*. The structures of the new compounds were determined by spectroscopic methods including 1D and 2D NMR analysis. The absolute configurations of the compounds were clarified by CD spectroscopic studies. Full NMR data assignments of the three known compounds (**8**−**10**) are reported. The isolated compounds were evaluated for their cytotoxic activities against four human cancer cell lines.

Pharbitis nil Choisy (Convolvulaceae) is a short-day plant that is distributed throughout Southeast Asia.[1] Pharbitidis Semen, the seeds of this plant, has been used as a purgative drug in folkloric medicine.[1] Previous phytochemical studies on the seeds and flowers of this plant have resulted in the isolation of resin glycosides,[2−4] gibberellins,[5−7] flavonoids, chlorogenic acid derivatives,[8] and anthocyanins.[9−11] Seeds of this plant are reported to show antitumor and antifungal activities.[12,13]

In a continuing search for bioactive constituents from Korean medicinal plant sources, we performed a phytochemical investigation of this herb, and we reported the isolation of three new *ent*-kaurane diterpenoids from the $CHCl_3$-soluble fraction of the EtOH extract.[14] In our continuing study on this herb, we have now isolated a further six new *ent*-kaurane diterpene glycosides, pharbosides A−F (**1**−**6**), a new *ent*-gibbane diterpene glycoside, pharboside G (**7**), and three known *ent*-kaurane diterpenoids (**8**−**10**) from the EtOAc-soluble and BuOH-soluble fractions of the ethanolic extract of *P. nil* seeds. The structures were determined using spectroscopic methods including 1D and 2D NMR. All the isolated diterpenoids were evaluated for their cytotoxic activities against four human cancer cell lines. Here we report the isolation, structural elucidation, and cytotoxicity of the isolated compounds.

Results and Discussion

Purification of the EtOH extract of dried seeds of *P. nil* by repeated column chromatography led to the isolation of six new *ent*-kaurane diterpene glycosides, pharbosides A−F (**1**−**6**), a new *ent*-gibbane diterpene glycoside, pharboside G (**7**), and three known *ent*-kaurane diterpenoids (**8**−**10**).

Pharboside A (**1**) was obtained as a colorless gum. The molecular formula was determined to be $C_{26}H_{40}O_8$ from the molecular ion peak $[M]^+$ at *m*/*z* 480.2706 (calcd for $C_{26}H_{40}O_8$: 480.2723) in the positive-ion HRFABMS. The IR spectrum indicated that **1** possesses hydroxy (3380 cm^{-1}), ester (1757 cm^{-1}), and C=C double bond (1664 cm^{-1}) functional groups. In the ^{13}C NMR (including DEPT) spectrum, a total of 26 carbon signals, composed of two methyls, eight methylenes, four methines, three quaternary carbons, one exocyclic double bond, and one carbonyl carbon, including six signals assignable to the glucose moiety (δ_C 95.8, 78.8, 78.7, 74.2, 71.2, 62.5),[15] were observed. On the basis of the NMR data and the spectroscopic pattern of diterpenes isolated from this source,[14] compound **1** was predicted to be an *ent*-kaurane diterpene glycoside. In particular, NMR data suggested that **1** was the glycoside of *ent*-7β-hydroxykaur-16-en-19-oic acid.[16,17] The diterpene skeleton was reconfirmed by the HMBC spectrum (Figure 1). In the ^1H NMR spectrum, the anomeric proton at δ_H 5.40 (1H, d, J = 8.0 Hz) suggested the presence of a β-glucopyranosyl moiety. The HMBC correlation between H-1′ (δ_H 5.40, 1H, d, J = 8.0 Hz) and C-19 (δ_C 178.7) and the NOESY correlation between H-1′ (δ_H 5.40, 1H, d, J = 8.0 Hz) and H_3-20 (δ_H 0.97, 3H, s) indicated that the β-glucopyranosyl moiety was located at C-19. Enzymatic hydrolysis of **1** afforded aglycone **1a** and D-glucose. The aglycone **1a** was identified by ^1H NMR and MS data.[16] The D-glucose was detected by TLC and identified by the sign of its specific rotation value. The configuration of **1** was the same as that of *ent*-7β-hydroxykaur-16-en-19-oic acid,[16,17] on the basis of its NMR data. The β-orientation of the OH group at C-7 was established by the NOESY experiment (Figure 2), in which correlation of H-7 with H-6a and H-14b was observed. Thus, the structure of **1** was determined to be β-D-glucopyranosyl-*ent*-7β-hydroxykaur-16-en-19-oate. The absolute configuration of **1** was determined by measuring the CD spectrum of **1a**. The CD spectrum of **1a** showed a negative (λ_{max} 212 nm) Cotton effect, which is similar to the negative (λ_{max} 216 nm) Cotton effect of *ent*-kaur-16-en-19-oic acid,[18] suggesting that compound **1** possessed the e*nt*-kaurane skeleton.

Pharboside B (**2**) was obtained as a colorless gum. The molecular formula was determined to be $C_{26}H_{40}O_8$ from the molecular ion peak $[M + H]^+$ at *m*/*z* 481.2836 (calcd for $C_{26}H_{41}O_8$: 481.2801) in the positive-ion HRFABMS. The IR, MS, and NMR data of compound **2** indicated that it was similar in structure to compound **1**. The only difference between **1** and **2** was the signal at C-7 in the NMR data [δ_H 3.53 (br s)/δ_C 78.1 in **1**; δ_H 3.43 (m)/δ_C 72.2 in **2**], implying that compounds **1** and **2** are stereoisomers at C-7.[17] This was confirmed by the NOESY correlations between H-7 and H-5, H-9, and H-15. Enzymatic hydrolysis of **2** afforded aglycone **2a** and D-glucose. The aglycone **2a** was identified by ^1H NMR and MS data.[19] Thus, we concluded that compound **2** is β-D-glucopyranosyl *ent*-7α-hydroxykaur-16-en-19-oate. The CD spectrum of **2** showed a negative (λ_{max} 202 nm) Cotton effect (λ_{max} 202 nm for **1**). Thus, compound **2** is an e*nt*-kaurane diterpenoid.

Pharboside C (**3**) was obtained as a colorless gum. The molecular formula was determined to be $C_{27}H_{44}O_{11}$ from the molecular ion peak $[M + H]^+$ at *m*/*z* 545.3001 (calcd for $C_{27}H_{45}O_{11}$: 545.2962) in the positive-ion HRFABMS. The IR spectrum indicated that **3** possesses hydroxy (3359 cm^{-1}) and ester (1726 cm^{-1}) functional groups. The ^1H and ^{13}C NMR and DEPT spectra indicated the presence of a glucopyranosyl moiety and three methyls, eight methylenes, five methines, four quaternary carbons, and one carbonyl carbon. Thus, on the basis of the NMR data, compound

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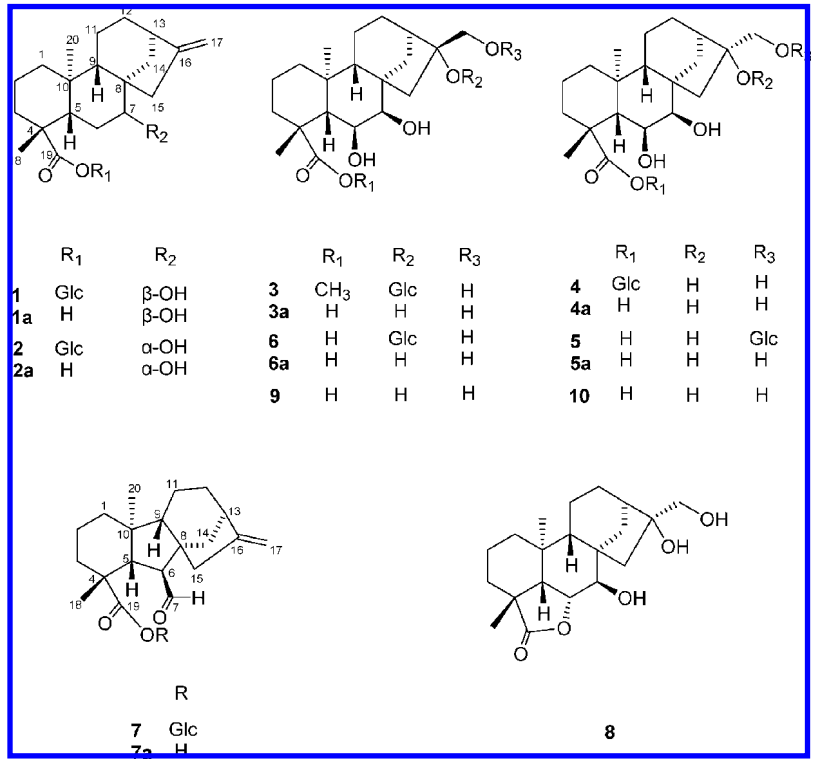

3 was also thought to be a diterpene glycoside. Comparison of the ^{1}H and ^{13}C NMR data of **3** with those of the known compound 6β,7β,16α,17-tetrahydroxy-*ent*-kauranoic acid (**9**) indicated that the only differences between **3** and **9** were the presence of a methoxy group at C-19 and glucose in **3**. The anomeric proton at δ_H 4.48 (1H, d, J = 7.5 Hz) in the ^{1}H NMR spectrum suggested the presence of a β-glucopyranosyl moiety, located at C-16 by the HMBC correlation between H-1′ (δ_H 4.48) and C-16 (δ_C 87.5). The HMBC correlation between the methoxy proton (δ_H 3.70, 3H, s) and C-19 implied that a methoxy group was present at C-19. In addition, the cross-peaks observed in the HMBC spectrum (Figure 1) from H-6 (δ_H 4.25, 1H, dd, J = 11.5, 2.5 Hz) to C-4, C-5, and C-8; from H-7 (δ_H 3.36, 1H, d, J = 2.5 Hz) to C-5, C-8, C-9, and C-15; and from H-17 (δ_H 3.39 and 3.60, 1H each, d, J = 12.0 Hz) to C-13, C-15, and C-16 reconfirmed the proposed structure of **3**. Enzymatic hydrolysis of **3** afforded D-glucose and aglycone **3a** (19-methyl ester of **9**). The aglycone **3a** was identified as methyl-*ent*-6β,7β,16α,17-tetrahydroxykauran-19-oate by NMR data analysis, including data from 2D NMR (DEPT, HMBC) and HRFABMS. The relative configuration of **3** was assigned on the basis of the J values in the ^{1}H NMR spectrum and the NOESY experiment (Figure 2). The coupling constants of H-6 (dd, $J_{5,6}$ = 11.5 Hz and $J_{6,7}$ = 2.5 Hz) and H-7 (d, $J_{6,7}$ = 2.5 Hz) observed in the ^{1}H NMR spectrum were the same as those of H-6 (dd, $J_{5,6}$ = 11.5 Hz and $J_{6,7}$ = 2.5 Hz) and H-7 (d, $J_{6,7}$ = 2.5 Hz) in 6β,7β-dihydroxykaurenoic acid.[20] Thus, H-6 and H-7 were determined to be in the α-orientation, which was reconfirmed by NOESY correlations between H-6 and H-7, H-12b, and H_3-20, and between H-7 and H-6, H-12b, and H-14b. In addition, the NOESY correlation between H-17 and H-15 confirmed that the OH group at C-16 was α-oriented. Thus, **3** was determined to be methyl-*ent*-6β,7β,16α,17-tetrahydroxykauran-19-oate-16-*O*-β-D-glucopyranoside. The CD spectrum of e*nt*-kaurane-type diterpenoids shows negative Cotton effects at 206−230 nm.[18] The CD spectrum of **3a** showed a negative (λ_{max} 225 nm) Cotton effect, which was similar to the negative (λ_{max} 226 nm) Cotton effect of **9** corresponding to *ent*-kauran-19-oic acid. Thus, the skeleton of **3** is an e*nt*-kaurane diterpenoid.

Pharboside D (**4**) was obtained as a colorless gum with the molecular formula $C_{26}H_{42}O_{11}$ based on the molecular ion peak $[M]^+$ at *m*/*z* 530.2712 (calcd for $C_{26}H_{42}O_{11}$: 530.2727) by positive-ion HRFABMS. The IR spectrum indicated that **4** possesses hydroxy (3360 cm^{-1}) and ester (1725 cm^{-1}) functional groups. The ^{13}C NMR and DEPT spectrum displayed signals indicating the presence of a hexose moiety and two methyls, eight methylenes, five methines, four quaternary carbons, and one carbonyl carbon. Comparison of the ^{1}H and ^{13}C NMR data of **4** with those of 6β,7β,16β,17-tetrahydroxy-*ent*-kauranoic acid (**10**) showed that the major difference between these compounds is the presence of a sugar moiety in **4**. The chemical shifts of H-1′ (C-1′) at δ_H 5.46 (δ_C 95.9) of glucopyranose are characteristic of an ester-linked sugar,[15] and the HMBC correlation between H-1′ (δ_H 5.46, 1H, d, J = 7.5 Hz) and C-19 (δ_C 178.9) confirmed that the sugar moiety is located at C-19. Enzymatic hydrolysis of **4** afforded D-glucose and aglycone **4a**, which was identified by comparison of the ^{1}H NMR and MS data with those of **10**.[21] The relative configuration of **4** was assigned to be the same as those of **3** on the basis of the NOESY experiment, except for the β-orientated OH group at C-16, which was confirmed by the NOESY correlation between H-17 and H-13. Thus, **4** was determined to be β-D-glucopyranosyl-*ent*-6β,7β,16β,17-tetrahydroxykauran-19-oate.

Pharboside E (**5**) possessed the same molecular formula as **4**, $C_{26}H_{42}O_{11}$, based on the molecular ion peak $[M]^+$ at *m*/*z* 530.2765 (calcd for $C_{26}H_{42}O_{11}$: 530.2727) in the HRFABMS. Detailed analyses of its IR and 1D and 2D NMR data indicated that **5** is an isomer of **4** that differs with respect to the position of a sugar moiety. The signal due to C-19 at δ_C 178.9 in **4** was shifted downfield to δ_C 185.8 in **5**, and the signal due to C-17 at δ_C 70.7 in **4** was shifted downfield to δ_C 78.8 in **5**. This information implied that the glucopyranosyl moiety was at C-17 in **5**, which was confirmed by the HMBC correlation between H-1′ (δ_H 4.31, 1H, d, J = 8.0 Hz) and C-17 (δ_C 78.8). Enzymatic hydrolysis of **5** yielded D-glucose and aglycone **5a** (same as **10**).[21] Thus, **5** was determined to be *ent*-6β,7β,16β,17-tetrahydroxykauran-19-oic acid-17-*O*-β-D-glucopyranoside.

The absolute configurations of **4** and **5** were assigned by measurement of the CD spectrum of **4a**. Its CD spectrum showed a negative (λ_{max} 226 nm) Cotton effect, similar to the CD spectrum of the e*nt*-kaurane diterpenoids that shows negative Cotton effects at 206−230 nm.[18]

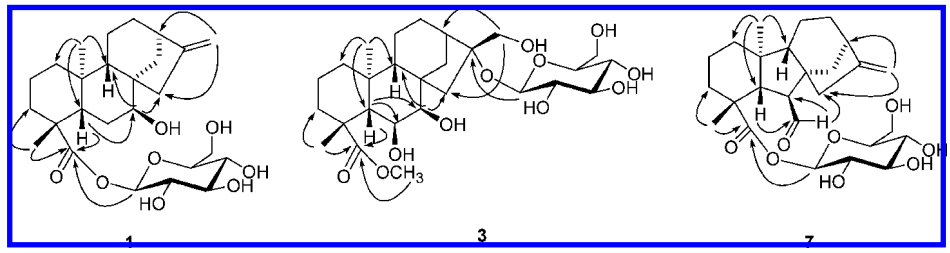

Figure 1. Key HMBC correlations of compounds **1**, **3**, and **7**.

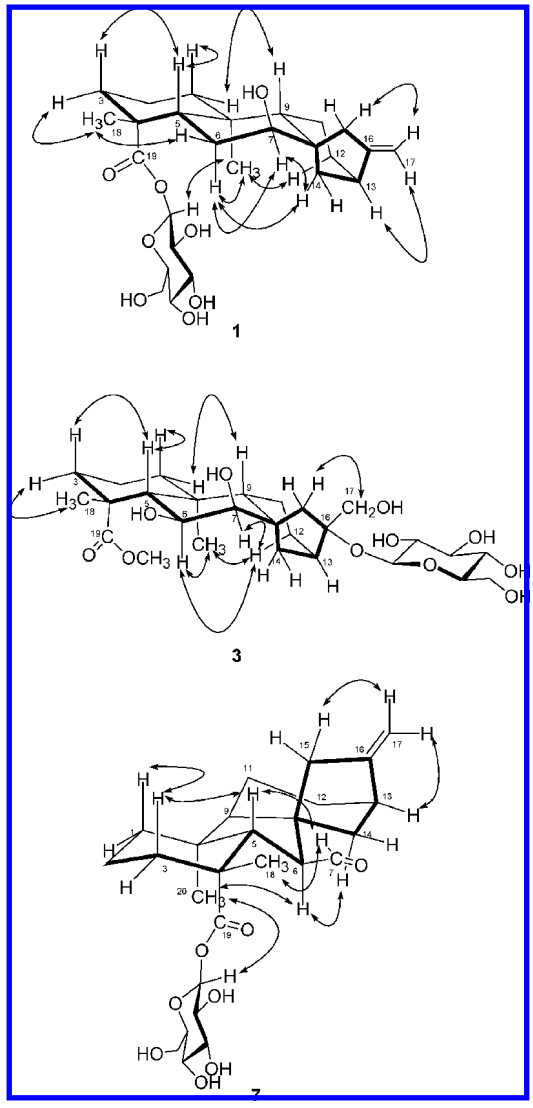

Figure 2. Key NOESY correlations of compounds **1**, **3**, and **7**.

Pharboside F (**6**) had the molecular formula $C_{26}H_{42}O_{11}$ (HRFABMS) from the molecular ion peak $[M + H]^+$ at *m/z* 531.2845 (calcd for $C_{26}H_{43}O_{11}$: 531.2805). The ^1H and ^{13}C NMR data showed that **6** was related to **3**, with the only major difference being the disappearance of the 19-methyl group in **6**. Enzymatic hydrolysis of **6** afforded D-glucose and aglycone **6a**. The structure of **6a** was identified by comparison of its ^1H NMR and MS data with those of **9**.[22] Moreover, the cross-peaks in the NOESY spectrum of **6** indicated that the corresponding substituents in **6** have the same orientations as those in **3**. Thus, **6** was determined to be *ent*-6β,7β,16α,17-tetrahydroxykauran-19-oic acid-16-*O*-β-D-glucopyranoside. Finally, we determined that compound **6** possesses the same absolute configuration as **3** on the basis of the CD spectrum of **6**, which showed a negative Cotton effect at 204 nm.

Pharboside G (**7**) was obtained as a colorless gum with the molecular formula $C_{26}H_{38}O_8$, based on the molecular ion peak $[M + Na]^+$ at *m/z* 501.2496 (calcd for $C_{26}H_{38}NaO_8$: 501.2464) in the HRFABMS. The IR spectrum indicated that **7** possesses a hydroxy group (3359 cm^{-1}), an ester (1725 cm^{-1}), and a C=C double bond (1635 cm^{-1}). In the ^{13}C NMR (including DEPT) spectrum, a total of 26 carbon signals, composed of two methyls, seven methylenes, four methines, three quaternary carbons, one exocyclic double bond, one carbonyl group, and one aldehyde group, including six signals assignable to the glucose moiety (δ_C 96.0, 78.9, 78.8, 74.0, 71.2, 62.5),[15] were observed. The NMR data were similar to those of the related gibberellins.[23] Besides the signals for the glucopyranosyl group, NMR data suggested that the aglycone of **7** is gibberellin A_{12}-7-aldehyde,[24,25] which was reconfirmed through analysis of the HMBC spectrum (Figure 1). In addition, the HMBC correlation between H-1′ (δ_H 5.38, 1H, d, J = 8.0 Hz) and C-19 (δ_C 177.4) and the NOESY correlation between H-1′ (δ_H 5.38, 1H, d, J = 8.0 Hz) and H_3-20 (δ_H 0.80, 3H, s) indicated that the β-glucopyranosyl moiety is located at C-19. Enzymatic hydrolysis of **7** afforded D-glucose and aglycone **7a**, as identified by ^1H NMR and MS data.[24,25] The relative configuration of **7** was established by the NOESY experiment (Figure 2). The NOESY correlations between H-6 and H-14b, H_3-20 and between H-7 and H-5, H_3-18 suggested that the aldehyde group (C-7) at C-6 was in the β-orientation. Thus, **7** was determined to be β-D-glucopyranosylgibberellin A_{12}-7-aldehyde-19-oate. The absolute configuration of **7** was determined by measuring the CD spectrum of **7a**. The CD spectrum of **7a** showed a negative (λ_{max} 218 nm) Cotton effect, which was identical to the negative Cotton effect of *ent*-gibberellins and their methyl esters at 220−230 nm.[26] The CD spectrum of **7** showed a negative (λ_{max} 208 nm) Cotton effect. This information indicated that compound **7** possessed the *ent*-gibberellin skeleton.

The known *ent*-kaurane diterpenoids 7β,16β,17-trihydroxy-*ent*-kauran-6α,19-olide (**8**),[27,28] 6β,7β,16α,17-tetrahydroxy-*ent*-kauranoic acid (**9**),[22] and 6β,7β,16β,17-tetrahydroxy-*ent*-kauranoic acid (**10**)[22] were identified by GC-MS and analysis of MS data. We performed full NMR data assignments of **8**−**10** by 2D NMR data (including DEPT, HMBC, and NOESY) because no published spectroscopic data of **8**−**10** were found. The absolute configurations of these compounds were confirmed by analysis of CD data.[18]

The cytotoxic activities of the isolated compounds (**1**−**10**) against A549, SK-OV-3, SK-MEL-2, and HCT15 human tumor cell lines were evaluated using the SRB assay *in vitro*. Compounds **4** and **5** exhibited moderate cytotoxic activity against A549, SK-OV-3, SK-MEL-2, and HCT15 cells (IC_{50} (**4**): 25.15, 28.73, 14.29, and 17.23 μM, and IC_{50} (**5**): 23.60, 13.77, 15.22, and 22.12 μM, respectively), while the other compounds showed little cytotoxicity against the tested cell lines (IC_{50} > 30 μM).

Experimental Section

General Experimental Procedures. Optical rotations were measured on a JASCO P-1020 polarimeter. CD spectra were measured on a JASCO J-715 spectropolarimeter. IR spectra were recorded on a Bruker IFS-66/S FT-IR spectrometer. NMR spectra were recorded on a Varian UNITY INOVA 500 NMR spectrometer operating at 500 MHz (^1H) and 125 MHz (^{13}C), respectively, with chemical shifts given in ppm (δ) using TMS as an internal standard. FAB and HR-FAB mass spectra

Table 1. ^{1}H NMR Data of Compounds **1**−**5** (methanol-d_4, 500 MHz, δ in ppm, J in Hz)[a]

H	1	2	3	4	5
1a	0.91, m	0.92, m	0.92, m	0.92, m	0.88, m
1b	1.40, m	1.43, m	1.78, m	1.77, m	1.82, m
2a	1.57, m	1.54, m	1.48, m	1.46, m	1.47, m
2b	1.94, m	1.95, m	2.16, m	2.13, m	2.13, m
3a	1.14, m	1.14, m	1.82, m	1.84, m	1.82, m
3b	1.28, m	1.31, m	1.99, m	1.97, m	1.99, m
5	1.78, d (11.5)	1.82, d (11.5)	1.81, d (11.5)	1.83, d (11.5)	1.84, d (11.5)
6a	1.91, m	1.94, m	4.25, dd (2.5, 11.5)	4.42, dd (2.0, 11.5)	4.26, dd (2.0, 11.5)
6b	2.20, m	2.12, m			
7	3.53, br s	3.43, m	3.36, d (2.5)	3.42, d (2.0)	3.39, d (2.0)
9	1.45, m	1.52, m	1.44, m	1.53, m	1.47, m
11a	1.16, m	1.15, m	1.51, m	1.50, m	1.50, m
11b	1.57, m	1.58, m	1.81, m	1.84, m	1.84, m
12a	1.43, m	1.43, m	1.48, m	1.48, m	1.49, m
12b	1.58, m	1.57, m	1.85, m	1.87, m	1.88, m
13	2.60, br s	2.64, br s	2.32, br s	2.08, br s	2.11, br s
14a	1.83, m	1.85, m	1.49, m	1.48, m	1.50, m
14b	2.18, m	2.15, m	1.84, m	1.80, m	1.84, m
15a	2.21, br s	2.28, br s	2.02, d (12.5)	1.89, d (12.5)	1.90, d (12.5)
15b			2.13, d (12.5)	2.16, d (12.5)	2.13, d (12.5)
17a	4.75, s	4.78, s	3.39, d (12.0)	3.40, d (11.0)	3.50, d (11.0)
17b	4.78, s	4.86, s	3.60, d (12.0)	3.47, d (11.0)	3.78, d (11.0)
18	1.20, s	1.50, s	1.43, s	1.48, s	1.37, s
20	0.97, s	1.01, s	0.89, s	1.01, s	1.07, s
OMe			3.70, s		
Glc-1′	5.40, d (8.0)	5.46, d (8.0)	4.48, d (7.5)	5.46, d (7.5)	4.31, d (8.0)
Glc-2′	3.35, m	3.35, m	3.35, m	3.35, m	3.35, m
Glc-3′	3.37, m	3.40, m	3.37, m	3.40, m	3.37, m
Glc-4′	3.39, m	3.42, m	3.39, m	3.42, m	3.39, m
Glc-5′	3.30, m	3.30, m	3.26, m	3.30, m	3.25, m
Glc-6′a	3.70, dd (3.5, 11.5)	3.72, dd (3.5, 11.5)	3.70, dd (3.5, 11.5)	3.72, dd (3.5, 11.5)	3.69, dd (3.5, 11.5)
Glc-6′b	3.83, br d (11.5)	3.83, dd (1.5, 11.5)	3.87, dd (1.5, 11.5)	3.84, dd (1.5, 11.5)	3.89, dd (1.5, 11.5)

[a] The assignments were based on DEPT, ^{1}H,^{1}H-COSY, and HMBC experiments.

were obtained on a JEOL JMS700 mass spectrometer. ESI mass spectra were obtained on a VG BIOTECH platform LC-mass spectrometer. Preparative HPLC was performed using a Gilson 306 pump with a Shodex refractive index detector and an Apollo Silica 5 μm column (250 × 22 mm) or Econosil RP-18 10 μm column (250 × 22 mm). Silica gel 60 (Merck Co., Germany, 70−230 mesh and 230−400 mesh) was used for column chromatography. TLC was performed using Merck precoated silica gel F_{254} plates and RP-18 F_{254s} plates. The packing material for molecular sieve column chromatography was Sephadex LH-20 (Pharmacia Co., Sweden). Low-pressure liquid chromatography was performed over 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 at Kyungdong herbal market, Seoul, Korea, in July 2006, and were identified by one of the authors (K.R.L.). 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 (3 × 4 L, each 3 days) at room temperature and filtered. The filtrate was evaporated *in vacuo* to obtain EtOH extracts (1.4 kg), which were suspended in distilled H_2O (7.2 L) and then successively partitioned with *n*-hexane, $CHCl_3$, EtOAc, and *n*-BuOH, yielding 10, 7, 10, and 550 g, respectively. The EtOAc-soluble fraction (10 g) was chromatographed on a silica gel (230−400 mesh, 300 g) column and eluted with $CHCl_3$−MeOH (10:1 → 1:1, gradient system) to yield five fractions (A−E). Fraction C (2.7 g) was chromatographed further on an RP-C_{18} silica gel (230−400 mesh, 150 g) column and eluted with MeOH−H_2O (3:2 → 1:0, gradient system) to give eight subfractions (C1−C8). Fraction C7 (1.5 g) was subjected to repeated column chromatography (including silica gel column, Sephadex LH-20) and purified by preparative reversed-phase HPLC using a solvent system of 60% MeCN to yield **7** (6 mg). Compounds **8** (6 mg) and **9** (5 mg) were obtained from fraction D (2.5 g) by separation of preparative reversed-phase HPLC, using a solvent system of 30% MeCN. Fraction E (3.0 g) was chromatographed further on an RP-C_{18} silica gel (230−400 mesh, 150 g) column and eluted with MeOH−H_2O (1:1 → 1:0, gradient system) to give 11 subfractions (E1−E11). Fractions E5 (80 mg), E10 (100 mg), and E11 (850 mg) were subjected to repeated column chromatography (including silica gel column, Sephadex LH-20, Lobar-A RP-18 column) and further purified by preparative reversed-phase HPLC (MeCN−H_2O, 2:3 or 1:4) to yield compounds **1** (7 mg) and **2** (4 mg) from fraction E10, **3** (50 mg) from fraction E11, and **10** (30 mg) from fraction E5. The BuOH-soluble fraction (50 g) was chromatographed on a DIAION HP-20 resin column using a gradient solvent system of 100% distilled H_2O and 100% MeOH to yield four fractions (F−I). Fraction G (7.0 g) was subjected to a silica gel (230−400 mesh, 150 g) column and eluted with $CHCl_3$−MeOH−H_2O (7:3:0.5) to give three subfractions (G1−G3). Fraction G2 (1.5 g) was chromatographed further on an RP-C_{18} silica gel (230−400 mesh, 50 g) column, eluted with MeOH−H_2O (1:1), and further purified by preparative reversed-phase HPLC, using a solvent system of 30% MeOH to obtain **4** (30 mg), **5** (4 mg), and **6** (7 mg).

Pharboside A (1): colorless gum; $[\alpha]^{25}_D$ −22.6 (*c* 0.18, MeOH); CD (MeOH) λ_{max} ($\Delta\epsilon$) 202 (−11.8) nm; IR (KBr) ν_{max} 3380, 2947, 2835, 1757, 1664, 1451, 1030, 699 cm^{-1}; ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 3; positive ESIMS *m/z* 983 [2 M + Na]$^+$; positive HRFABMS *m/z* 480.2706 [M]$^+$ (calcd for $C_{26}H_{40}O_8$, 480.2723).

Pharboside B (2): colorless gum; $[\alpha]^{25}_D$ +5.1 (*c* 0.10, MeOH); CD (MeOH) λ_{max} ($\Delta\epsilon$) 202 (−24.9) nm; IR (KBr) ν_{max} 3382, 2946, 2835, 1725, 1665, 1454, 1031, 699 cm^{-1}; ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 3; positive FABMS *m/z* 481 [M + H]$^+$; positive HRFABMS *m/z* 481.2836 [M + H]$^+$ (calcd for $C_{26}H_{41}O_8$, 481.2801).

Pharboside C (3): colorless gum; $[\alpha]^{25}_D$ −36.3 (*c* 0.25, MeOH); CD (MeOH) λ_{max} ($\Delta\epsilon$) 202 (−19.4) nm; IR (KBr) ν_{max} 3359, 2946, 2834, 1726, 1451, 1030, 699 cm^{-1}; ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 3; positive ESIMS *m/z* 1111 [2 M + Na]$^+$; positive HRFABMS *m/z* 545.3001 [M + H]$^+$ (calcd for $C_{27}H_{45}O_{11}$, 545.2962).

Pharboside D (4): colorless gum; $[\alpha]^{25}_D$ −104.5 (*c* 0.84, MeOH); CD (MeOH) λ_{max} ($\Delta\epsilon$) 223 (−40.6) nm; IR (KBr) ν_{max} 3360, 2946, 2835, 1725, 1451, 1030, 699 cm^{-1}; ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 3; positive FABMS *m/z* 530 [M]$^+$; positive HRFABMS *m/z* 530.2712 [M]$^+$ (calcd for $C_{26}H_{42}O_{11}$, 530.2727).

Pharboside E (5): colorless gum; $[\alpha]^{25}_D$ −10.5 (*c* 0.05, MeOH); CD (MeOH) λ_{max} ($\Delta\epsilon$) 222 (−7.95) nm; IR (KBr) ν_{max} 3358, 2946, 2834, 1451, 1030, 699 cm^{-1}; ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 3; positive FABMS *m/z* 530 [M]$^+$; positive HRFABMS *m/z* 530.2765 [M]$^+$ (calcd for $C_{26}H_{42}O_{11}$, 530.2727).

Table 2. ^{1}H NMR Data of Compounds **6**−**10** (methanol-d_4, 500 MHz, δ in ppm, J in Hz)[a]

H	6	7	8	9	10
1a	0.89, m	0.90, m	1.08, m	0.90, m	0.86, m
1b	1.83, m	1.42, m	1.60, m	1.83, m	1.69, m
2a	1.48, m	1.40, m	1.52, m	1.42, m	1.41, m
2b	2.14, m	1.74, m	1.57, m	2.09, m	2.12, m
3a	1.82, m	1.36, m	1.41, m	1.82, m	1.81, m
3b	1.99, m	2.07, m	2.02, m	1.99, m	1.97, m
5	1.84, d (11.5)	2.05, d (12.0)	1.87, d (6.5)	1.78, d (12.5)	1.84, d (11.5)
6	4.23, dd (2.0, 11.5)	3.38, dd (5.5, 12.0)	4.57, t (6.5)	4.26, dd (2.0, 11.5)	4.32, dd (2.0, 11.5)
7	3.39, d (2.0)	9.78, d (5.5)	4.17, d (6.5)	3.36, d (2.0)	3.47, d (2.0)
9	1.48, m	1.52, m	1.55, m	1.47, m	1.48, m
11a	1.51, m	1.40, m	1.53, m	1.51, m	1.53, m
11b	1.82, m	1.72, m	1.70, m	1.84, m	1.82, m
12a	1.48, m	1.41, m	1.41, m	1.49, m	1.45, m
12b	1.88, m	1.53, m	1.59, m	1.88, m	1.92, m
13	2.30, br s	2.50, t (1.5)	2.00, m	2.05, m	2.10, m
14a	1.49, m	1.87, m	1.02, m	1.46, m	1.49, m
14b	1.81, m	2.16, m	1.54, m	1.78, m	1.85, m
15a	1.95, d (12.5)	1.52, d (12.5)	1.60, d (12.5)	1.88, d (12.5)	1.92, d (12.5)
15b	2.14, d (12.5)	2.13, d (12.5)	2.11, d (12.5)	2.09, d (12.5)	2.12, d (12.5)
17a	3.39, d (12.0)	4.85, s	3.39, d (11.0)	3.39, d (11.0)	3.64, d (11.0)
17b	3.59, d (12.0)	4.93, s	3.44, d (11.0)	3.43, d (11.0)	
18	1.35, s	1.16, s	1.27, s	1.45, s	1.41, s
20	1.08, s	0.80, s	0.84, s	1.02, s	1.00, s
Glc-1′	4.50, d (8.0)	5.38, d (8.0)			
Glc-2′	3.35, m	3.35, m			
Glc-3′	3.37, m	3.37, m			
Glc-4′	3.39, m	3.39, m			
Glc-5′	3.25, m	3.25, m			
Glc-6′a	3.70, dd (3.5, 11.5)	3.69, dd (3.5, 11.5)			
Glc-6′b	3.87, dd (1.5, 11.5)	3.80, dd (1.5, 11.5)			

[a] The assignments were based on DEPT, ^{1}H,^{1}H-COSY, and HMBC experiments.

Table 3. ^{13}C NMR Data of Compounds **1**−**10** (methanol-d_4, 125 MHz, δ in ppm)

carbon	1	2	3	4	5	6	7	8	9	10
1	41.8 t	41.9 t	41.8 t	42.0 t	42.0 t	42.0 t	41.1 t	38.6 t	41.9 t	41.9 t
2	20.3 t	20.1 t	19.0 t	19.7 t	19.2 t	18.8 t	20.9 t	17.9 t	19.9 t	19.5 t
3	39.2 t	40.9 t	41.0 t	40.6 t	41.2 t	41.5 t	38.1 t	29.4 t	40.7 t	40.9 t
4	44.8 s	44.9 s	45.6 s	45.7 s	45.5 s	45.8 s	45.6 s	43.2 s	45.3 s	45.1 s
5	50.5 d	53.3 d	52.0 d	50.6 d	52.4 d	52.9 d	58.4 d	52.9 d	51.2 d	50.9 d
6	30.3 t	34.6 t	72.2 d	72.0 d	73.4 d	73.5 d	59.2 d	85.4 d	72.9 d	72.4 d
7	78.1 d	72.2 d	83.3 d	83.4 d	82.6 d	82.6 d	208.9 d	72.5 d	83.2 d	83.0 d
8	49.5 s	49.9 s	49.7 s	49.6 s	49.7 s	49.6 s	51.5 s	46.9 s	49.6 s	49.6 s
9	48.8 d	54.7 d	50.7 d	53.2 d	51.7 d	51.8 d	59.5 d	57.4 d	52.6 d	52.5 d
10	40.6 s	41.5 s	42.0 s	41.8 s	42.3 s	42.4 s	46.2 s	35.4 s	42.0 s	41.9 s
11	19.2 t	19.3 t	20.2 t	20.1 t	19.9 t	20.6 t	18.3 t	18.5 t	20.3 t	20.1 t
12	34.7 t	34.0 t	27.7 t	28.3 t	28.0 t	27.8 t	33.3 t	22.0 t	27.5 t	28.2 t
13	45.3 d	45.1 d	41.5 d	42.0 d	41.8 d	41.6 d	39.6 d	38.8 d	41.9 d	41.9 d
14	39.9 t	30.0 t	37.5 t	37.7 t	38.7 t	38.5 t	38.6 t	34.7 t	38.3 t	38.1 t
15	46.7 t	46.8 t	46.0 t	49.8 t	47.2 t	46.1 t	44.4 t	45.9 t	49.6 t	49.6 t
16	157.0 s	156.3 s	87.5 s	80.6 s	80.2 s	87.7 s	158.7 s	83.0 s	79.3 s	80.5 s
17	103.8 t	104.0 t	66.9 t	70.7 t	78.8 t	66.9 t	106.9 t	71.2 t	64.1 t	70.6 t
18	28.9 q	32.6 q	32.7 q	32.5 q	34.4 q	35.0 q	30.2 q	26.0 q	33.3 q	33.1 q
19	178.7 s	179.0 s	180.4 s	178.9 s	185.8 s	185.5 s	177.4 s	185.2 s	182.6 s	182.3 s
20	16.4 q	17.6 q	17.2 q	17.4 q	17.2 q	17.1 q	16.0 q	21.1 q	17.3 q	17.1 q
OMe			52.8 q							
Glc-1′	95.8 d	95.9 d	100.0 d	95.9 d	105.1 d	100.0 d	96.0 d			
Glc-2′	74.2 d	74.0 d	75.7 d	74.0 d	75.3 d	75.8 d	74.0 d			
Glc-3′	78.8 d	78.7 d	78.5 d	78.7 d	78.0 d	78.5 d	78.8 d			
Glc-4′	71.2 d	71.1 d	71.6 d	71.1 d	71.7 d	71.6 d	71.2 d			
Glc-5′	78.8 d	78.8 d	78.1 d	78.8 d	78.1 d	78.1 d	78.9 d			
Glc-6′	62.5 t	62.4 t	62.9 t	62.3 t	62.8 t	63.0 t	62.5 t			

Pharboside F (6): colorless gum; $[\alpha]^{25}_D$ −59.3 (*c* 0.21, MeOH); CD (MeOH) λ_{max} ($\Delta\epsilon$) 204 (−18.0) nm; IR (KBr) ν_{max} 3382, 2947, 2834, 1453, 1030, 699 cm^{-1}; ^{1}H NMR, see Table 2; ^{13}C NMR, see Table 3; positive FABMS *m/z* 531 $[M + H]^+$; positive HRFABMS *m/z* 531.2845 $[M + H]^+$ (calcd for $C_{26}H_{43}O_{11}$, 531.2805).

Pharboside G (7): colorless gum; $[\alpha]^{25}_D$ −33.5 (*c* 0.14, MeOH); CD (MeOH) λ_{max} ($\Delta\epsilon$) 208 (−26.7) nm; IR (KBr) ν_{max} 3359, 2946, 2834, 1725, 1635, 1451, 1020, 699 cm^{-1}; ^{1}H NMR, see Table 2; ^{13}C NMR, see Table 3; positive FABMS *m/z* 501 $[M + Na]^+$; positive HRFABMS *m/z* 501.2496 $[M + Na]^+$ (calcd for $C_{26}H_{38}NaO_8$, 501.2464).

7*β*,16*β*,17-Trihydroxy-*ent*-kauran-6α,19-olide (8): colorless gum; $[\alpha]^{25}_D$ +1.9 (*c* 0.27, MeOH); CD (MeOH) λ_{max} ($\Delta\epsilon$) 201 (−16.4), 208 (+24.1), 219 (+12.9) nm; IR (KBr) ν_{max} 3381, 2949, 1757, 1664, 1451, 1029, 699 cm^{-1}; ^{1}H NMR, see Table 2; ^{13}C NMR, see Table 3; positive FABMS *m/z* 351 $[M + H]^+$; positive HRFABMS *m/z* 351.2198 $[M + H]^+$ (calcd for $C_{20}H_{31}O_5$, 351.2172).

6*β*,7*β*,16α,17-Tetrahydroxy-*ent*-kauranoic acid (9): colorless gum; $[\alpha]^{25}_D$ −167.6 (*c* 0.80, MeOH); CD (MeOH) λ_{max} ($\Delta\epsilon$) 226 (−30.4) nm; IR (KBr) ν_{max} 3379, 2947, 2834, 1664, 1452, 1029, 669 cm^{-1}; ^{1}H NMR, see Table 2; ^{13}C NMR, see Table 3; positive FABMS *m/z* 391

$[M + Na]^+$; positive HRFABMS *m/z* 391.2122 $[M + Na]^+$ (calcd for $C_{20}H_{32}NaO_6$, 391.2097).

6β,7β,16β,17-Tetrahydroxy-*ent*-kauranoic acid (10): colorless gum; $[\alpha]^{25}_D$ −70.8 (*c* 0.25, MeOH); CD (MeOH) λ_{max} ($\Delta\epsilon$) 226 (−23.9) nm; IR (KBr) ν_{max} 3382, 2945, 2335, 1662, 1026, 699 cm^{-1}; ^1H NMR, see Table 2; ^{13}C NMR, see Table 3; positive FABMS *m/z* 369 $[M + H]^+$; positive HRFABMS *m/z* 369.2278 $[M + H]^+$ (calcd for $C_{20}H_{33}O_6$, 369.2277).

Enzymatic Hydrolysis of 1−7. A solution of each sample in H_2O (3 mL) was individually hydrolyzed with crude hesperidinase (20 mg, from *Aspergillus niger*, Sigma-Aldrich) at 37 °C for 72 h. Each reaction mixture was extracted with EtOAc (3 × 5 mL) to yield the individual EtOAc extract and H_2O phase after removing the solvents. The combined EtOAc layers from **1** (3 mg), **2** (1 mg), and **7** (2 mg) were chromatographed separately over silica gel Waters Sep-Pak Vac 6 cc ($CHCl_3$−MeOH, 30:1) to give aglycones **1a** (1 mg), **2a** (0.5 mg), and **7a** (1 mg), respectively. The combined EtOAc layers from **3** (10 mg), **4** (10 mg), **5** (1 mg), and **6** (2 mg) were chromatographed separately over silica gel Waters Sep-Pak Vac 6 CC ($CHCl_3$−MeOH, 5:1) to give aglycones **3a** (4 mg), **4a** (5 mg), **5a** (0.4 mg), and **6a** (1 mg), respectively. The aglycone of each compound was identified by ^1H NMR and MS data. In particular, aglycone **3a** was identified by NMR data analysis, including 2D NMR data (DEPT, HMBC), because no spectroscopic data of **3a** had been reported in the literature.

1a: colorless gum; $[\alpha]^{25}_D$ −15.0 (*c* 0.05, MeOH); CD (MeOH) λ_{max} ($\Delta\epsilon$) 212 (−19.8) nm; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.85 (1H, br s, H-17a), 4.82 (1H, br s, H-17b), 3.65 (1H, t, *J* = 3.0 Hz, H-7), 2.70 (1H, br s, H-13), 2.26 (2H, br s, H-15), 1.80 (1H, d, *J* = 11.5 Hz, H-5), 1.26 (3H, s, H-18), 0.98 (3H, s, H-20); positive FABMS *m/z* 319 $[M + H]^+$.

2a: colorless gum; $[\alpha]^{25}_D$ +2.2 (*c* 0.02, MeOH); ^1H NMR ($CDCl_3$, 500 MHz) δ 4.90 (1H, br s, H-17a), 4.85 (1H, br s, H-17b), 3.63 (1H, m, H-7), 2.75 (1H, br s, H-13), 2.21 (2H, br s, H-15), 1.79 (1H, d, *J* = 11.5 Hz, H-5), 1.27 (3H, s, H-18), 0.86 (3H, s, H-20); positive FABMS *m/z* 319 $[M + H]^+$.

Methyl-*ent*-6β,7β,16α,17-tetrahydroxykauran-19-oate (3a): colorless gum; $[\alpha]^{25}_D$ −30.5 (*c* 0.20, MeOH); CD (MeOH) λ_{max} ($\Delta\epsilon$) 225 (−43.4) nm; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.25 (1H, dd, *J* = 2.0, 11.5 Hz, H-6), 3.75 (3H, s, OMe), 3.50 (1H, d, *J* = 11.5 Hz, H-17a), 3.47 (1H, d, *J* = 1.5 Hz, H-7), 3.46 (1H, d, *J* = 11.5 Hz, H-17b), 2.15 (1H, d, *J* = 12.5 Hz, H-15a), 2.14 (1H, br s, H-13), 2.10 (1H, m, H-2a), 1.92 (1H, m, H-15b), 1.90 (1H, m, H-3a), 1.84 (1H, m, H-3b), 1.83 (1H, d, *J* = 11.5 Hz, H-5), 1.82 (1H, m, H-12a), 1.81 (1H, m, H-11a), 1.78 (1H, m, H-1a), 1.77 (1H, m, H-14a), 1.54 (1H, m, H-2b), 1.50 (1H, m, H-11b), 1.46 (1H, m, H-12b), 1.44 (1H, m, H-14b), 1.43 (3H, s, H-18), 1.35 (1H, m, H-9), 0.92 (1H, m, H-1b), 0.87 (3H, s, H-20); ^{13}C NMR (CD_3OD, 125 MHz) δ 180.4 (C-19), 82.3 (C-7), 79.2 (C-16), 70.9 (C-6), 65.0 (C-17), 53.1 (OCH_3-19), 52.1 (C-9), 50.6 (C-5), 49.1 (C-15), 48.4 (C-8), 45.8 (C-4), 41.9 (C-10), 41.8 (C-1), 40.6 (C-13), 39.7 (C-3), 36.7 (C-14), 31.4 (C-18), 29.5 (C-12), 20.1 (C-11), 18.9 (C-2), 18.3 (C-20); HMBC correlations for H-5 of C-4, C-6, C-7, and C-19, for H-7 of C-5, C-6, C-9, and C-15, for H-17 of C-13 and C-15, for H-18 of C-3 and C-19, for H-20 of C-1, C-5, and C-9, for 19-OCH_3 of C-19; positive FABMS *m/z* 383 $[M + H]^+$; positive HRFABMS *m/z* 383.2412 $[M + H]^+$ (calcd for $C_{21}H_{35}O_6$, 383.2434).

4a, **5a:** colorless gum; $[\alpha]^{25}_D$ −134.2 (*c* 0.25, MeOH); CD (MeOH) λ_{max} ($\Delta\epsilon$) 226 (−12.7) nm; ^1H NMR (CD_3OD, 500 MHz) δ 4.28 (1H, dd, *J* = 1.5, 11.5 Hz, H-6), 3.44 (1H, d, *J* = 11.5 Hz, H-17a), 3.38 (1H, d, *J* = 11.5 Hz, H-17b), 3.32 (1H, d, *J* = 1.5 Hz, H-7), 2.12 (1H, d, *J* = 12.5 Hz, H-15a), 2.09 (1H, br s, H-13), 1.93 (1H, d, *J* = 12.5 Hz, H-15b), 1.78 (1H, d, *J* = 11.5 Hz, H-5), 1.45 (3H, s, H-18), 1.02 (3H, s, H-20); positive FABMS *m/z* 391 $[M + Na]^+$.

6a: colorless gum; $[\alpha]^{25}_D$ −34.2 (*c* 0.05, MeOH); ^1H NMR ($CDCl_3$, 500 MHz) δ 4.26 (1H, dd, *J* = 1.5, 11.5 Hz, H-6), 3.44 (1H, d, *J* = 11.5 Hz, H-17a), 3.38 (1H, d, *J* = 11.5 Hz, H-17b), 3.33 (1H, d, *J* = 1.5 Hz, H-7), 2.18 (1H, d, *J* = 12.5 Hz, H-15a), 2.13 (1H, br s, H-13), 1.98 (1H, d, *J* = 12.5 Hz, H-15b), 1.79 (1H, d, *J* = 11.5 Hz, H-5), 1.35 (3H, s, H-18), 0.91 (3H, s, H-20); positive FABMS *m/z* 369 $[M + H]^+$.

7a: colorless gum; $[\alpha]^{25}_D$ −45.0 (*c* 0.05, MeOH); CD (MeOH) λ_{max} ($\Delta\epsilon$) 218 (−47.3) nm; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.79 (1H, d, *J* = 5.5 Hz, H-7), 4.96 (1H, s, H-17a), 4.85 (1H, s, H-17b), 3.25 (1H, dd, *J* = 5.5, 12.0 Hz, H-6), 2.56 (1H, t, *J* = 1.5 Hz, H-13), 2.18 (1H, d, *J* = 12.5 Hz, H-15a), 1.98 (1H, d, *J* = 11.5 Hz, H-5), 1.45 (1H, d, *J* = 12.5 Hz, H-15b), 1.27 (3H, s, H-18), 0.80 (3H, s, H-20); positive FABMS *m/z* 339 $[M + Na]^+$.

The aqueous phase of the hydrolysates of **1**−**7** were subjected separately to column chromatography over silica gel eluted with MeCN−H_2O (8:1) to yield glucose with positive specific rotation. The specific rotations of the sugar obtained from **1**−**7** ranged from +42.5 to +49.7; $[\alpha]^{25}_D$ +42.5 (*c* 0.05, H_2O) of **1**, $[\alpha]^{25}_D$ +44.6 (*c* 0.02, H_2O) of **2**, $[\alpha]^{25}_D$ +48.6 (*c* 0.20, H_2O) of **3**, $[\alpha]^{25}_D$ +47.8 (*c* 0.20, H_2O) of **4**, $[\alpha]^{25}_D$ +49.7 (*c* 0.02, H_2O) of **5**, $[\alpha]^{25}_D$ +46.1 (*c* 0.05, H_2O) of **6**, and $[\alpha]_D{}^{25}$ +45.6 (*c* 0.05, H_2O) of **7**. MeCN−H_2O (6:1) was used as the solvent system for TLC identification of glucose (R_f, 0.33).[29,30]

***In Vitro* Cytotoxicity Test.** A sulforhodamin B bioassay (SRB) was used to determine the cytotoxicity of each compound against four cultured human cancer cell lines.[31] The assays were performed at the Korea Research Institute of Chemical Technology. The cell lines used were A549 (non-small cell lung carcinoma), SK-OV-3 (ovary malignant ascites), SK-MEL-2 (skin melanoma), and HCT (colon adenocarcinoma). Doxorubicin was used as a positive control. The cytotoxicities of doxorubicin against A549, SK-OV-3, SK-MEL-2, and HCT cell lines were IC_{50} 0.007, 0.056, 0.117, and 0.164 μM, respectively.

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Supporting Information Available: 1D and 2D NMR data of **1** and **3**, 1D NMR data of **2** and **4**−**6**, and 1D, 2D NMR and MS data of **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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