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Structure of a New Echinocystic Acid Bisdesmoside Isolated from *Codonopsis lanceolata* Roots and the Cytotoxic Activity of Prosapogenins

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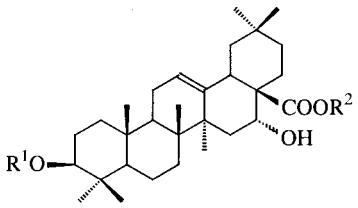
We isolated a new saponin named codonoposide (**1**) from the roots of *Codonopsis lanceolata* (Campanulaceae) and characterized it as 3-*O*-[β-D-xylopyranosyl(1-3)-β-D-glucuronopyranosyl]-3β,16α-dihydroxyolean-28-oic acid 28-*O*-[β-D-xylopyranosyl (1-3)-α-L-rhamnopyranosyl (1-2)-α-L-arabinopyranosyl] ester by chemical, physicochemical, and 2DNMR techniques. Complete hydrolysis of **1** produced a sapogenin (**1a**), and the partial hydrolysis and further isolation afforded two prosapogenins (**1b**, **1c**). The structures of **1a**, **1b**, and **1c** were found to be 3β,16α-dihydroxyolean-28-oic acid (echinocystic acid, **1a**), 3-*O*-β-D-glucuronopyranoside of **1a**, and 3-*O*-β-D-xylopyranosyl (1-3)-β-D-glucuronopyranoside of **1a**, respectively, on the basis of spectroscopic data. On MTT assay, **1a** showed marginal cytotoxic activity whereas **1b** exhibited more cytotoxicity than **1a**. However, the bisdesmosylsaponin **1** exhibited no cytotoxicity (IC_{50} > 0.3 mM against tested cell lines). This result indicated that glycoside linkage of glucuronic acid at C-3 enhances the cytotoxicity of sapogenin (**1a**), and additive glycosylation of xylose to **1b** strongly enhances the cytotoxicity of 3-*O*-monosaccharides (**1b**). Therefore, true forms of codonoposide for the cytotoxicity must be sapogenins or prosapogenins.

KEYWORDS: ***Codonopsis lanceolata*; Campanulaceae; saponin; codonoposide; cytotoxicity**

INTRODUCTION

The roots of *Codonopsis lanceolata* (Sieb et. Zucc.) Bentham et Hooker (Campanulaceae) have been used as an herbal drug to treat bronchitis, cough, spasm, and inflammation, and as a tonic crude drug and a vegetable (*1*). The related herbal drugs of Korea belonging to the Campanulaceae family include *Platycodon grandiflorum* A. De Candolle, *Codonopsis pilosula* (Franch) Nannf, and *Adenophora* species, which are taxonomically related and used for similar purposes (*2*). The roots of these plants mainly contain saponins which are assumed to be active principles. Shin et al. (*3*) reported the components of the essential oil obtained from the roots of *C. lanceolata*. Meanwhile, sterols and triterpenes have been isolated from *C. pilosula* (*4*).

We have studied structure−activity relationships on saponins (*5*, *6*). In the course of pursuing that relationship, we isolated a new saponin codonoposide from the roots of *C. lanceolata* as shown in **Figure 1**. Codonoposide itself and its hydrolysates, prosapogenins and a sapogenin, were tested in an MTT assay for the measurement of cytotoxicity.



1: R^1=β-D-xylopyranosyl (1-3)-β-D-glucuronopyranosyl
R^2=β-D-xylopyranosyl (1-3)-α-L-rhamnopyranosyl (1-2)-α-L-arabinopyranosyl

1a: R^1= R^2=H

1b: R^1=β-D-glucuronopyranosyl, R^2=H

1c: R^1=β-D-xylopyranosyl (1-3)-β-D-glucuronopyranosyl
R^2=H

Figure 1. Structure of codonoposide (**1**) isolated from *Codonopsis lanceolata* roots and its prosapogenins (**1b** and **1c**) and sapogenin (**1a**).

MATERIALS AND METHODS

General Experimental Procedures. Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected.

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Table 1. ^{13}C NMR Signals (ppm) of Codonoposide (**1**) Isolated from the Roots of *Codonopsis lanceolata* and Its Sapogenin (**1a**) and Prosapogenins (**1b** and **1c**) (125 MHz)

carbon	1	1a	1b	1c	carbon	1	1b	1c
1	39.3	41.0	38.6	38.9	sugar-3			
2	27.6	28.6	28.2	28.3	GlcU-1	106.5	107.9	106.6
3	89.4	80.1	90.7	91.4	2	75.5	76.7	75.3
4	40.5	41.3	40.3	40.7	3	87.5	79.7	87.9
5	56.4	57.9	57.4	57.9	4	69.4	74.8	69.4
6	18.0	18.5	18.5	19.0	5	75.7	77.6	77.1
7	32.4	33.0	32.6	32.8	6	172.4	172.6	172.7
8	39.9	40.1	40.3	40.7	Xyl-1	106.5		106.5
9	47.6	49.3	48.7	48.9	2	75.3		75.3
10	26.6	25.8	26.3	26.6	3	78.5		78.7
11	24.3	24.1	25.4	25.8	4	71.3		71.3
12	123.5	124.3	123.9	124.7	5	67.7		67.0
13	144.9	147.1	146.7	146.4				
14	42.5	42.4	42.9	43.2	sugar-28			
15	36.3	38.1	37.6	37.9	Ara-1	93.8		
16	74.2	76.7	76.3	76.3	2	75.8		
17	50.0	49.2	50.5	51.0	3	74.5		
18	41.7	43.4	43.6	43.8	4	69.9		
19	47.5	49.2	48.7	48.9	5	68.9		
20	31.3	31.9	31.5	31.8	Rha-1	101.1		
21	32.4	33.0	32.6	32.8	2	72.3		
22	33.7	34.6	34.9	35.2	3	83.8		
23	28.7	29.2	28.9	29.2	4	73.0		
24	18.7	17.6	19.1	19.1	5	66.2		
25	16.1[a]	16.9	17.2	17.6	6	19.0		
26	17.5[a]	18.5	19.1	19.1	Xyl-1	107.0		
27	25.3[b]	27.1	25.4	25.8	2	75.6		
28	176.3	181.9	181.6	181.6	3	78.5		
29	33.9	34.8	34.9	35.2	4	71.4		
30	24.4[b]	19.5	19.1	19.2	5	67.2		

[a,b] Values may be interchangeable in the column.

Optical rotations were measured on a JASCO DIP-360 digital polarimeter at 25 °C. IR spectra were recorded on a Hitachi 260-01 spectrometer in KBr disks. EIMS (ionization voltage 70 eV) and FABMS were measured with a JEOL JMS DX-300 spectrometer. ^{1}H- and ^{13}C NMR spectra were taken on a Bruker AM-500 spectrometer with TMS as an internal standard.

Plant Material and Extraction. *C. lanceolata* was collected in September 2000 at National Alpine Agricultural Experiment Station, Pyongchang, Korea. The roots of this plant were cut and dried, avoiding sunlight. The dried roots (2.0 kg) were extracted three times with MeOH under reflux. The MeOH extract was filtered and evaporated on a rotary evaporator under reduced pressure to give a viscous mass (390 g) of MeOH extract. This material was suspended in H_2O and partitioned with $CHCl_3$, EtOAc, and BuOH to give a $CHCl_3$-soluble fraction (65 g), EtOAc-soluble fraction (32 g), and a BuOH-soluble fraction (70 g) after being dried in vacuo.

Isolation of Codonoposide. A part of the BuOH-soluble fraction (10 g) was subjected to column chromatography on silica gel (280 g; Merck 7734, Darmstadt, Germany). The column was eluted with $CHCl_3$/MeOH/H_2O (65:35:10, lower phase) and a fraction over the retention volume of 950 mL−1420 mL. This fraction was filtered using Sephadex LH-20 column chromatography, and the fraction containing a major saponin was dried in vacuo. The combined residues were recrystallized in MeOH and resultantly yielded amorphous solid **1** (850 mg).

Codonoposide (**1**). Amorphous solid; mp 220 °C; $[\alpha]_D^{20}$−29.6°. IR (KBr): ν_{max} (cm^{-1}) = 3433 (OH), 2938 (CH), 1730 (C=O), 1078, 1042 (glycosidic C−O). ^{1}H NMR (500 MHz, pyridine-d_5): triterpene δ 0.82 (3H, s, H-24), 0.88 (3H, s, H-25), 1.03 (3H, s, H-29), 1.05 (3H, s, H-26), 1.15 (3H, s, H-30), 1.25 (3H, s, H-27), 1.77 (3H, s, H-23), 5.61 (1H, brs, H-12), sugar moieties δ 3.99 (1H, m, H-2‴), 3.89 (1H, m, H-3‴), 4.40 (1H, m, H-2″), 4.40 (1H, m, H-3′), 4.48 (1H, m, H-2′), 4.76 (1H, d, J = 7.0 Hz, H-1⁗), 5.07 (1H, d, J = 6.8 Hz, H-1″), 5.10 (1H, d, J = 7.4 Hz, H-1′), 5.12 (1H, brs, H-16), 5.58 (1H, brs, H-1‴), 1.66 (3H, d, J = 5.7 Hz, H-6⁗) 6.42 (1H, brs, H-1‴). ^{13}C NMR: **Table 1**. FABMS *m/z*: 1213 ([$C_{30}H_{90}O_{26}$+Na]$^+$).

Acid Hydrolysis of 1. Compound **1** (180 mg) was hydrolyzed in 5% HCl solution (MeOH−H_2O, 2:8) under reflux for 5 h. After cooling, the reaction mixture was partitioned with ethyl acetate (EtOAc) and washed with H_2O, and the EtOAc fraction was dehydrated with anhydrous sodium sulfate. The resulting EtOAc fraction was evaporated in vacuo and subjected to recrystallization from MeOH to give **1a** (sapogenin). After neutralization of the aqueous fraction with NH_4-OH, the fraction was evaporated in vacuo to give a residue. The resulting residue was applied to a TLC plate and developed with EtOAc/MeOH/H_2O/AcOH (13:6:3:3). The R_f values of the product were identical to those of D-glucuronic acid, D-xylose, L-arabinose, and L-rhamnose.

Echinocystic acid (**1a**): Amorphous solid, mp 306−309 °C, $[\alpha]_D^{19}$ +39° (c = 1.0, 95% EtOH). IR (KBr): ν_{max} (cm^{-1}) = 3500−3400 (OH) and 1685 (COOH). ^{1}H NMR (500 MHz, pyridine-d_5): 0.86 (3H, s, H-25), 0.90 (3H, s, H-26), 1.01 (3H, s, H-29), 1.07 (3H, s, H-30), 1.17 (3H, s, H-27), 1.22 (3H, s, H-24), 1.82 (3H, s, H-23), 3.44 (1H, dd, J = 4.2, 11.8 Hz, H-3), 3.58 (1H, dd, J = 4.2, 9.5 Hz, H-18), 5.24 (1H, brs, H-16), 5.65 (1H, t-like, H-12), 8.69 (1H, s, H-28). ^{13}C NMR (125 MHz, pyridine-d_5): **Table 1**. EIMS *m/z*: 472 (M^+, $C_{30}H_{48}O_4$), 264, 246.

Alkaline Hydrolysis of 1. A part (350 mg) of compound **1** was partially hydrolyzed in 3% NaOH (MeOH/H_2O, 2:8) under reflux for 50 min. After the reaction mixture cooled, it was acidified with the addition of 5% HCl. The resulting mixture was partitioned with EtOAc followed by dehydration with anhydrous sodium sulfate. This fraction was further chromatographed on silica gel column using the solvent $CHCl_3$/MeOH/H_2O (73:27:10, lower phase) to separate the two compounds from the mixture. The two corresponding fractions afforded **1b** and **1c** from the MeOH solutions, respectively. After neutralization of the aqueous layer with NH_4OH, the fraction was evaporated in vacuo to give a residue. The resulting residue was applied to a TLC plate and developed with EtOAc/MeOH/H_2O/AcOH (13:6:3:3). The R_f values of the product were identical to those of L-arabinose, L-rhamnose, and D-xylose.

1b: mp 223−225 °C. IR (KBr): ν_{max} (cm^{-1}) = 3408 (OH), 2949 (CH), 1694 (C=O), 1610, 1080, 1028 (glycosidic C−O). ^{1}H NMR (500 MHz, pyridine-d_5): δ 0.87 (3H, s, H-25), 0.96 (3H × 2, each s, H-26, H-30) 1.00 (3H, s, H-24), 1.06 (3H, s, H-29), 1.18 (3H, s, H-27), 1.76 (3H, s, H-23), 3.33 (1H, brs, H-3), 5.20 (1H, brs, H-16), 5.62 (1H, brs, H-12); D-glucuronic acid δ 4.98 (1H, d, J = 7.7 Hz, H-1′), 4.09 (1H, m, H-2′), 4.27 (1H, t, J = 8.8 Hz, H-3′), 4.46 (1H, m, J = 8.6 Hz, H-4′), 4.60 (1H, d, J = 9.7 Hz, H-5′). ^{13}C NMR (125 MHz, pyridine-d_5): **Table 1**.

1c: mp 267−270 °C. IR (KBr): ν_{max} (cm^{-1}) = 3400 (OH), 2948 (CH), 1704 (C=O), 1608, 1089, 1041 (glycosidic C−O). ^{1}H NMR (500 MHz, pyridine-d_5): δ 0.82 (3H, s, H-24), 0.87 (3H, s, H-25), 0.91 (3H, s, H-26), 1.03 (3H, s, H-30), 1.10 (3H, s, H-27), 1.27 (3H, s, H-29), 1.76 (3H, s, H-23), 3.33 (1H, dd-like, H-3), 5.18 (1H, brs, H-16), 5.58 (1H, brs, H-12); sugar moieties δ 5.07 (1H, d, J = 6.8 Hz, H-1′), 5.10 (1H, d, J = 7.4 Hz, H-1″). ^{13}C NMR (125 MHz): **Table 1**.

MTT Assay. The in vitro cytotoxicity tests against HL-60, U-937, and 3LL cell lines were performed essentially according to the method described previously (*7*). Cells were seeded into 96-well microtiter plates and incubated overnight. The test samples were dissolved in dimethyl sulfoxide (DMSO) and were added in serial dilution (the final DMSO concentrations in all assays did not exceeded 0.01%). At 24 h after seeding, 100 μL of new media or test compounds was added, and the plates were incubated for 48 h. Cells were washed once before adding 50 μL of FBS-free medium containing 5 mg/mL (MTT) concentration. After 4 h incubation at 37 °C, the medium was discarded, and formazan blue formed in the cells was extracted by adding 50 μL of DMSO. Optical density was measured at 540 nm.

RESULTS AND DISCUSSION

Compound **1** of an amorphous solid with mp 220 °C and $[\alpha]_D^{20}$−29.6°C showed a positive Liebermann−Burchard color reaction. The molecular weight of **1** was 1190 amu from the calculation of *m/z* 1213 ([M + Na]$^+$) shown on FABMS. The IR spectrum showed characteristic bands of OH, ester, and

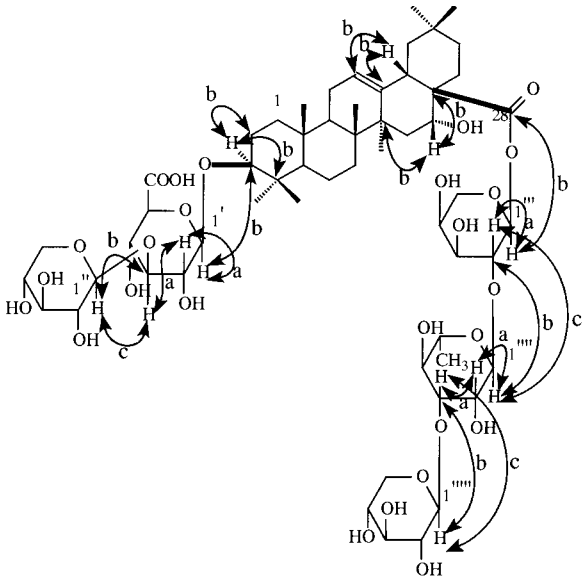

Figure 2. Structure of codonoposide (**1**) isolated from *C. lanceolata* and COSY (arrow a), HMBC (arrow b), and NOESY correlations (arrow c).

glycosidic C−O at 3033, 2938, 1730, and 1100−1000 cm^{-1}, respectively. Acid hydrolysis of **1** produced an aglycon **1a** and the sugar moieties were shown to be D-glucuronic acid, D-xylose, L-rhamnose, and L-arabinose on TLC. In the ^1H NMR spectrum, seven singlet methyl peaks at δ 0.86−1.82, a secondary carbon C-16 at δ 5.24, and an olefinic proton (H-12) at δ 5.65 indicated that it could be a Δ^{12}-16-hydroxyoleanene derivative. The physicochemical data of **1a** were in agreement with echinocystic acid that has been reported (*8*). Although Nagao et al. have isolated echinocystic acid glycosides from *Aster tataricus*, the sugar chain moieties do not involve a uronic acid. Alkaline hydrolysis produced the partial hydrolysates and sugars such as L-arabinose, D-rhamnose, and D-xylose which were shown on TLC. Silica gel column chromatography of the partial hydrolysates afforded **1b** and **1c**. The IR spectral bands of **1b** and **1c** near 1700 cm^{-1} indicated that the two compounds are the prosapogenins with no sugar moieties at C-28 position. The ^{13}C NMR spectrum of **1b** shown in **Table 1** indicated D-glucuronic acid attachment to echinocystic acid (**1a**) when compared to the literature data, and the corresponding chemical shifts in the ^1H NMR spectrum are shown in Materials and Methods. The sugar linkage configuration of D-glucuronic acid was found to be β from the scale of coupling constant of H-1′ (J = 7.7 Hz). Thus, **1b** is echinocystic acid 3-*O*-β-D-glucuronopyranoside. **1c** was revealed to be 3-*O*-β-D-xylopyranosyl (1-3)-β-D-glucuronopyranosyl echinocystic acid by ^1H-^1H COSY, ^1H-^{13}C COSY, and HMBC NMR spectra. As shown in **Table 1**, the terminal xylose was found by observing the chemical shifts (δ_C 106.5, 75.3, 78.7, 71.3, and 67.0). The anomeric proton of β-D-xylose of δ 5.07 (J = 7.4 Hz) was shown as coupled to $\delta_{C-3'}$ 87.9 of the inner sugar D-glucuronic acid on the HMBC NMR spectrum.

Compared with the ^1H and ^{13}C NMR assignments of **1a**, **1b**, and **1c** together with data in the literature, the 2DNMR spectral data strongly indicated the attachment of the most inner sugar L-arabinose, the termimal xylose, and the necessary middle L-rhamnose in a sugar chain at C-28 site. As the HMBC correlation was shown in **Figure 2**, the peak at δ 6.42 (brs) of the anomeric proton in most inner sugar (L-arabinose) at the C-28 site crossed the δ_C 176.3 (C-28) indicating a direct attachment of L-arabinose to C-28. A peak at δ 5.58 (1H, brs, H-1‴′) of L-rhamnose in the middle position of the C-28 sugar chain correlated with $\delta_{C-2'''}$ 75.8 of L-arabinose on the HMBC spectrum. Successive attachment of the terminal D-xylose to the L-rhamnose was identified by observing the correlation between δ_H 4.76 (1H, d, J = 7.0 Hz) of D-xylose and δ_C 83.8 of the middle L-rhamnose. Among the three sugars (L-arabinose, L-rhamnose, and D-xylose), only D-xylose showed the linkage configuration of β (J = 7.0 Hz), and the other two possess an α-configuration from the scale of the coupling constants (all broad singlets). The assignments of ^{13}C NMR shown in **Table 1** were fully aided by ^1H-^1H COSY, ^1H-^{13}C COSY, and HMBC spectral correlation. NOESY NMR correlations on **1** and the molecular formula ($C_{57}H_{90}O_{26}$, mw 1190) shown on FABMS confirmed the full structure of codonoposide as shown in **Figure 1**. Furthermore, the assigned ^{13}C NMR data on sugar chains of codonoposide were in agreement with the reported data of the 3-*O*-β-D-xylopyranosyl (1-3)-β-D-glucuronopyranosyl moiety in scoparianoside C (*9*) and the 28-*O*-β-D-xylopyranosyl (1-3)-α-L-rhamnopyranosyl (1-2)-α-L-arabinopyranosyl moiety in kalopanaxsaponin I (*10*), respectively. Therefore, the structure of **1** was determined as 3-*O*-[β-D-xylopyranosyl (1-3)-β-D-glucuronopyranosyl]-3β,16α-dihydroxyolean-28-oic acid 28-*O*-[β-D-xylopyranosyl (1-3)-α-L-rhamnopyranosyl (1-2)-α-L-arabinopyranosyl] ester. This is the first report from a natural source.

Table 2. Cytotoxic Activities of Codonoposide (**1**) and Its Sapogenin (**1a**) and Prosapogenins (**1b** and **1c**) against Tumor Cell Lines

	IC_{50} (mM)[a]		
treatment	U937	HL-60	3LL
1	>0.3	>0.3	>0.3
1a	>0.3	0.185	0.160
1b	0.159	0.061	0.107
1c	0.015	0.030	0.040

[a] The values are defined as the concentration which resulted in a 50% decrease in cell number. The values represent the means of three independent tests in each cell number.

We have previously reported the structure−cytotoxicity relationship of hederagenin glycosides isolated from *Kalopanax pictus* (*5*, *6*). Although a number of hederagenin glycosides are known, kalopanxsaponin A with the two sugar linkages is essential for the cytotoxic and antitumor activity. We acknowledge the linkage of sugar moieties are very important for the biological activities, and the kinds of sugar moieties are also important for the biological degradation in plants or in human intestinal bacteria. It should be emphasized also that linkages of enough sugars at C-28 site are essential for the noncytotoxicity, because Δ^{12}-oleanene 28 monosaccharides often show cytotoxicity (*11*). Compound **1** has a characteristic glucuronic acid as the inner sugar of the bisdesmoside at C-3 site. As shown in **Table 1**, **1** does not exhibit any cytotoxicity though it has the carboxyl in D-glucuronic acid. However, echinocystic acid (**1a**) and echinocystic acid 3-*O*-glucuronoside (**1b**) showed weak cytotoxicity (**Table 2**), and the latter is more potent than the former. This biological phenomenon is contrasted with the blocking effect of L-arabinose attachment on hederagenin cytotoxicity (*6*). Additional attachment of the second sugar, D-xylose, to **1b** increased the cytotoxicity. This result indicated that the most active moiety of codonoposide must be attributed to **1c**. It is also presumed that the enzymatic degradation of codonoposide is possibly a driving force for the cytotoxicity or antifungal effects. Furthermore, the prosapogenins (**1b** and **1c**) or a sapogenin (**1a**) could be active principles of the roots of *C. lanceolata*. Therefore, this result could contribute to the investigation of the biological significances of this saponin.

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