New Iridoid Glucosides from *Harpagophytum procumbens* DC.

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Three new iridoid glucosides, 8-*O*-(*p*-coumaroyl)-harpagide, 6′-*O*-(*p*-coumaroyl)-procumbide and procumboside, have been isolated from the roots of *Harpagophytum procumbens* DC., together with three known iridoid glucosides, harpagide, harpagoside, and procumbide. Procumboside is a novel iridoid glucoside having an ether linkage between C-3 and C-6.

Keywords——*Harpagophytum procumbens* DC.; Pedaliaceae; iridoid glucoside; 8-*O*-(*p*-coumaroyl)-harpagide; 6′-*O*-(*p*-coumaroyl)-procumbide; procumboside

Harpagophytum procumbens DC. (Pedaliaceae) is native to the southwestern part of Africa, and its dried roots are used for the treatment of rheumatism as a folk medicine in Europe. Chemical investigation of this plant has been done by several research groups[1] and the isolation of three iridoid glucosides (harpagide (**1**), harpagoside (**2**),[2] and procumbide (**5**)[3]) was reported. In the course of our search for biologically active substances from this crude drug, we isolated three new iridoid glucosides. This paper describes the structure elucidation of these new iridoid glucosides.

The MeOH extract of dried roots of *H. procumbens* was separated into the AcOEt-soluble part and the H_2O-soluble one (see Experimental). The latter was further fractionated by a combination of charcoal chromatography, silica gel chromatography, and preparative layer chromatography (PLC), giving a new iridoid, named procumboside (**8**), and 8-*O*-(*p*-coumaroyl)-harpagide (**3**) along with known iridoid glucosides (**1**, **2**, and **5**). The former portion was also purified by silica gel chromatography and PLC to give 6′-*O*-(*p*-coumaroyl)-procumbide (**6**).

8-*O*-(*p*-Coumaroyl)-harpagide (3)

The glucoside (**3**) was obtained as a hygroscopic white powder, $C_{24}H_{30}O_{12} \cdot 1/2H_2O$, $[\alpha]_D$ $-30.5°$ (MeOH). It showed ultraviolet (UV) absorptions at 313 and 224 nm (log ε 4.17 and 3.97), and characteristic infrared (IR) bands at 1680 and 1630 cm^{-1} (conjugated ester), and 1600 and 1510 cm^{-1} (phenyl group), along with a strong hydroxyl band (3350 cm^{-1}). The ^{1}H-nuclear magnetic resonance (NMR) spectrum (200 MHz) of **3** showed signals due to *cis*-olefinic protons at δ 6.49 and 5.04 (each d, $J = 6.5$ Hz), ABX type protons (–CH$_2$–CH–OH) at δ 2.08 (dd, $J = 15$ and 4.0 Hz), 2.28 (d, $J = 15$ Hz), and 3.88 (d, $J = 4.0$ Hz), besides two singlets at δ 2.95 (9-H) and 6.18 (1-H) and other signals arising from a glucose moiety. This pattern is very similar to that of **1**, but the methyl signal (δ 1.50) appeared downfield (0.23 ppm) relative to the corresponding signal of **1**. In addition, two pairs of doublets due to *trans*-olefinic protons and aromatic protons were observed at δ 6.40 and 7.65 (each 1H, $J = 16$ Hz), and at δ 6.94 and 7.58 (each 2H, $J = 8.5$ Hz), respectively, which are suggestive of a *p*-coumaroyl grouping. Acetylation of **3** gave the hexaacetate (**4**), whose ^{1}H-NMR spectrum showed signals due to five aliphatic acetoxyl groups (δ 2.02—2.15), an aromatic acetoxyl group (δ 2.34), and a hydroxyl proton (δ 3.0, disappeared on treatment with D_2O).
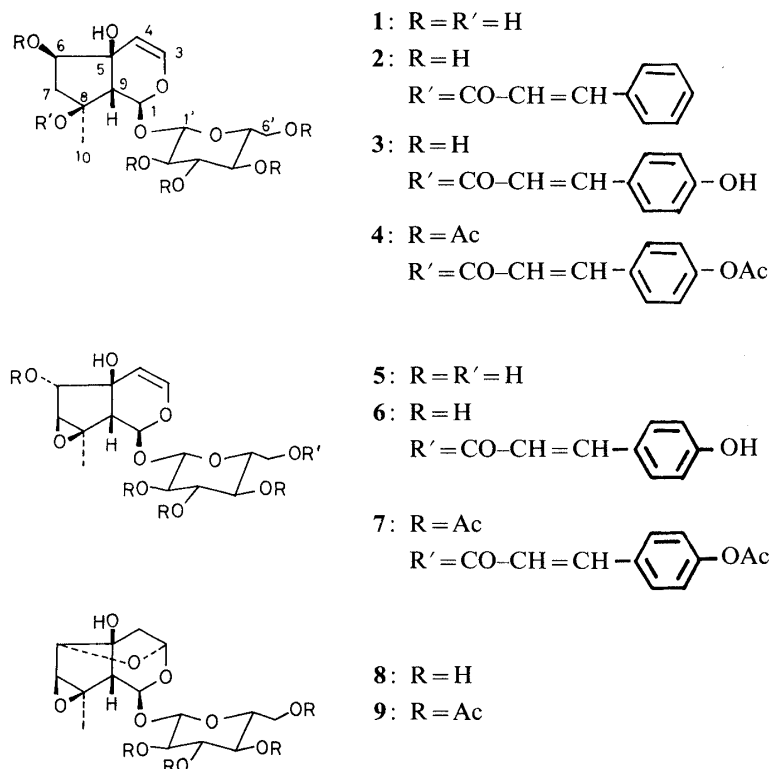
Chart 1

The above data indicated that **3** might be the 8-*p*-coumaroyl ester of **1**, and this was further supported by comparison of the ^{13}C-NMR spectra of **1** and **3**. In the case of **3**, nine signals arising from the *p*-coumaroyl group were observed, and the signal of C-8 was shifted downfield by 10.3 ppm, whereas those of C-7, C-9, and C-10 were shifted upfield by 0.9— 4.0 ppm as shown in Table I. This behavior in ^{13}C-NMR spectra is quite parallel with that observed with some iridoid glucosides.[4] Finally, alkaline hydrolysis of **3** afforded **1** together with *p*-coumaric acid. Thus, the structure of this glucoside (**3**) was established.

6′-*O*-(*p*-Coumaroyl)-procumbide (6)

The glucoside (**6**) was obtained as a hygroscopic white powder, $C_{24}H_{28}O_{12} \cdot 1/2H_2O$, $[\alpha]_D$ −58.2° (MeOH). It showed UV absorptions at 313 and 228 nm (log ε 4.36 and 4.10), and IR bands due to hydroxyl groups (3300 cm^{-1}), conjugated ester (1680 and 1630 cm^{-1}), and a phenyl group (1600 and 1510 cm^{-1}). The ^{1}H-NMR spectrum of **6** showed a pattern closely similar to that of procumbide (**5**) except for signals of the 6′-methylene protons (δ 4.46, dd, $J = 12$ and 4.5 Hz; δ 4.60, d, $J = 12$ Hz) and those assignable to a *p*-coumaroyl group. These spectral data suggested that the 6′-hydroxyl group of the sugar moiety in **6** is acylated, and this view was supported by comparison of the ^{13}C-NMR spectra of **5** and **6**. Namely, C-6′ of **6** resonated downfield (1.2 ppm), whereas the signal of C-5′ was shifted upfield (2.8 ppm).

Acetylation of **6** afforded the pentaacetate (**7**), whose ^{1}H-NMR spectrum showed singlets due to four aliphatic acetoxyls (δ 2.02—2.08), an aromatic one (δ 2.31), and a hydroxyl proton (δ 3.3, disappeared on treatment with D_2O). Furthermore, alkaline hydrolysis of **6** yielded **5**. The glucoside was thus determined to be 6′-*O*-(*p*-coumaroyl)-procumbide (**6**).

Procumboside (8)

Procumboside (**8**) was obtained as a hygroscopic white powder, $C_{15}H_{22}O_{10} \cdot 1/2H_2O$, $[\alpha]_D$ −112° (MeOH). It showed no characteristic UV absorption, but had a strong IR band at

TABLE I. ^{13}C-NMR Data (in CD$_3$OD)

Carbon	(1)	(3)	(5)	(6)	(8)
1	93.1 (d)	94.6 (d)	95.6 (d)	96.1 (d)	93.4 (d)[a]
3	142.5 (d)	143.9 (d)	144.1 (d)	144.1 (d)	101.8 (d)[a]
4	108.2 (d)	106.7 (d)	104.4 (d)	104.2 (d)	37.4 (dd)
5	72.5 (s)	73.3 (s)	80.0 (s)	80.1 (s)	81.8 (s)
6	77.4 (d)[a]	77.5 (d)[a]	77.8 (d)	77.6 (d)	85.3 (d)
7	47.1 (t)	46.2 (t)	65.8 (d)	65.8 (d)	64.9 (d)
8	78.1 (s)	88.4 (s)	66.8 (s)	66.9 (s)	66.1 (s)
9	59.5 (d)	55.5 (d)	53.0 (d)	52.9 (d)	58.9 (d)
10	24.9 (q)	22.7 (q)	17.7 (q)	17.6 (q)	15.4 (q)
1′	99.3 (d)	99.9 (d)	99.6 (d)	100.0 (d)	98.5 (d)[a]
2′	74.3 (d)	74.4 (d)	74.8 (d)	74.7 (d)	74.6 (d)
3′	78.1 (d)	78.0 (d)	78.4 (d)	78.1 (d)	78.3 (d)
4′	71.6 (d)	71.6 (d)	71.7 (d)	71.5 (d)	71.6 (d)
5′	78.1 (d)[a]	78.0 (d)[a]	77.8 (d)	75.6 (d)	78.1 (d)
6′	62.7 (t)	62.8 (t)	63.0 (t)	64.2 (t)	62.6 (t)
1″		127.0 (s)		127.0 (s)	
2″		131.0 (d)		131.2 (d)	
3″		116.7 (d)		116.8 (d)	
4″		161.1 (s)		161.2 (s)	
5″		116.7 (d)		116.8 (d)	
6″		131.0 (d)		131.2 (d)	
α		146.5 (d)		146.8 (d)	
β		116.3 (d)		114.9 (d)	
C=O		169.3 (s)		169.0 (s)	

a) Assignments may be interchanged in each column.

3300 cm^{-1}.

On acetylation, **8** gave the tetraacetate (**9**), which showed ^{1}H-NMR signals due to four acetoxyl groups (δ 2.0—2.09) and a hydroxyl group (δ 2.6). In the field desorption mass spectrum (FD-MS), **8** and **9** exhibited quasi-molecular ion $(M^+ + 1)$ peaks at m/z 363 and 531, respectively, and a characteristic peak at m/z 183, corresponding to the aglycone moiety.

Inspection of the ^{13}C-NMR spectrum of **8** led us to suppose that the compound might be a monoterpene glucoside (Table I). In the ^{1}H-NMR spectrum (Fig. 1), however, no olefinic proton signals due to a dihydropyran ring, which is characteristic of usual iridoid glucosides, were observed and instead, it showed signals comprising an AMX system at δ 2.09 (dd, $J = 12$ and 3.5 Hz), 2.96 (d, $J = 12$ Hz), and 5.48 (d, $J = 3.5$ Hz), whose coupling patterns suggested the presence of the partial structure (A) (Chart 2). The presence of the partial structure (B) was also postulated in view of the positive epoxide test[5] and the NMR signals at δ 1.55 (3H, s), 4.20 (1H, s), and 3.76 (1H, s) which are assignable to a methyl group and hydrogens at the 6- and 7-positions, respectively. It is noteworthy here that in the ^{13}C-NMR spectrum of **8**, the signal of C-6 was shifted downfield (7.5 ppm) relative to the corresponding signal of **5** and signals assignable to three acetalic carbons were observed at 101.8, 93.4, and 98.5 ppm. These data suggested that the compound might be an iridoid glucoside having an ether linkage between C-3 and C-6. The proposed structure (**8**) imposes a rigid conformation, as illustrated in Fig. 2, in which the juncture between the cyclopentane and the tetrahydropyran rings must be *cis*, and the latter ring must be in a boat form. Thus, the dihedral angles between the 1- and 9-, 3- and 4β-, and 6- and 7-protons should be nearly 90°. In fact, the coupling patterns of these protons in ^{1}H-NMR spectrum are consistent with this conformation. Furthermore, the 20% nuclear Overhauser effect (NOE) observed between the 1-proton and the 8-methyl group supports the structure (**8**).
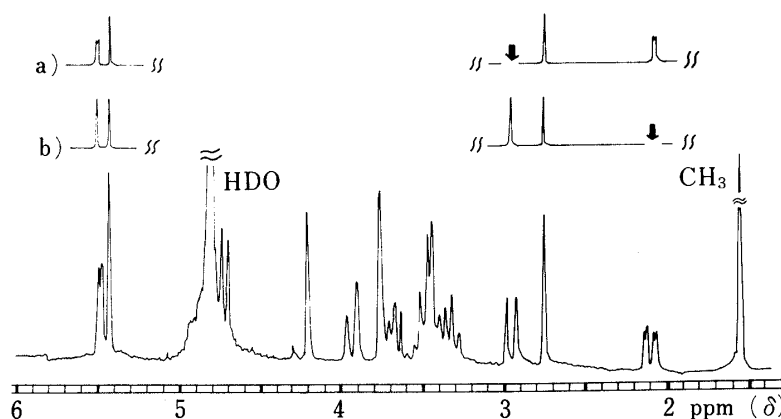
Fig. 1.   200 MHz ^{1}H-NMR Spectrum of Procumboside (8) in D_2O
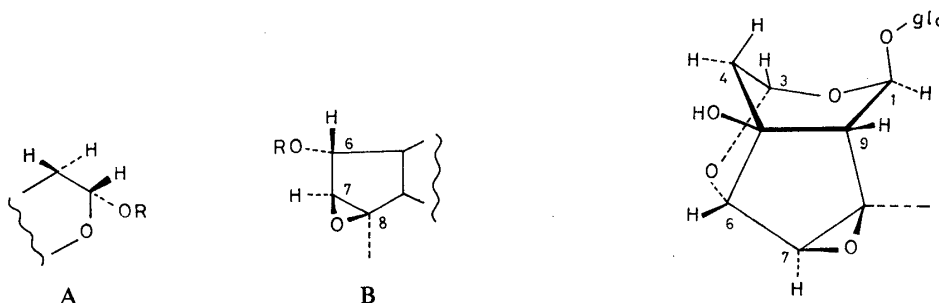
a), b): decoupling experiments.

Chart 2

Fig. 2

Procumboside (8)[6] is the first example of an iridoid glucoside having an ether linkage between C-3 and C-6.

Experimental

Melting points were determined with a Kofler-type apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-4 automatic polarimeter. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Associates XL-200 spectrometer. As the internal standard, tetramethylsilane (TMS) was used in $CDCl_3$ and CD_3OD, while sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) was used in D_2O. Mass spectrum (MS) measurements were done on a JEOL JMS-D 300 spectrometer. Column chromatography was carried out using activated charcoal (Wako) or silica gel (Mallinckrodt). Unless otherwise stated, the columns were eluted with MeOH–$CHCl_3$ mixtures of increasing MeOH content, and the solutions were concentrated in vacuo. For thin layer chromatography (TLC), Kieselgel 60 F_{254} (Merck) was used and spots were detected by spraying the plates with an anisaldehyde–H_2SO_4 reagent or by exposing them to I_2 vapor. For PLC, Kieselgel 60 PF_{254} (Merck) was employed and the plates were examined under UV light or exposed to I_2 vapor. Extraction of substances from the silica gel was done with MeOH–$CHCl_3$ mixture or MeOH.

Isolation of Iridoid Glucosides from *H. procumbens* DC.——Dried roots (1.5 kg) of *H. procumbens* from South-West Africa were extracted with ether (3.5 l × 2) at room temperature and the ether solution was concentrated to give a residue (7.2 g). Then the plant material was extracted with boiling MeOH (3 l × 4) and the MeOH extracts were concentrated in vacuo. The residue was diluted with water (1 l) and extracted with AcOEt (400 ml × 3). The combined AcOEt layer was washed with water, dried (MgSO₄), and concentrated in vacuo, giving an amorphous residue (8.36 g) (F-I). The H_2O layer was transferred to a charcoal (300 g) column, which was eluted successively with H_2O (10 l), H_2O–MeOH (1 : 1) (15 l) (F-II), H_2O–MeOH (3 : 7) (9 l) (F-III), and MeOH (30 l) (F-IV). Concentration of F-II, F-III, and F-IV gave amorphous residues (7.24 g, 2.51 g, and 12.07 g, respectively).

F-I was subjected to silica gel (400 g) column chromatography. The MeOH–$CHCl_3$ (1 : 9) eluate was concentrated to give a residue (3.15 g), which was subjected to PLC with MeOH–$CHCl_3$ (1 : 4) as the eluent. The less polar band gave harpagoside (2) (1.50 g) as a white powder, whereas the more polar one afforded 6′-*O*-(*p*-coumaroyl)-procumbide (6) (47 mg) as a hygroscopic white powder.

F-II was also chromatographed on a silica gel (250 g) column. The eluate with MeOH–CHCl$_3$ (1:4) was concentrated to give a mixture (920 mg), and the eluates with MeOH–CHCl$_3$ (3:7 and 1:1) were combined and concentrated to afford harpagide (1) (820 mg) as a white powder. The former mixture was separated by repeated chromatography on silica gel and the less polar fraction eluted with MeOH–CHCl$_3$ (15:85) gave procumboside (8) (42 mg) as a hygroscopic white powder, whereas the more polar one (MeOH–CHCl$_3$; 2:8) afforded procumbide (5) (300 mg) as colorless plates, mp 191—192°C (from MeOH).

F-IV was purified by silica gel (600 g) column chromatography in a manner similar to that described above and the MeOH–CHCl$_3$ (1:9) eluate provided harpagoside (2) (6.94 g). On the other hand, the MeOH–CHCl$_3$ (15:85) eluate was a mixture (1.30 g), which was further separated by PLC with MeOH–CHCl$_3$ (2:8) to give an additional crop of 2 (459 mg) and 8-O-(p-coumaroyl)-harpagide (3) (276 mg), hygroscopic white powder.

8-O-(p-Coumaroyl)-harpagide (3): $[\alpha]_D^{22}$ $-30.5°$ ($c = 1.09$, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3350, 1680, 1630, 1600, 1510. UV λ_{max}^{MeOH} nm (log ε): 313 (4.17), 224 (3.97). ^{1}H-NMR (D$_2$O) δ: 1.50 (3H, s, CH$_3$), 2.08 (1H, dd, $J = 15$ Hz, 4.0 Hz, 7-H), 2.28 (1H, d, $J = 15$ Hz, 7-H), 2.95 (1H, s, 9-H), 3.88 (1H, d, $J = 4.0$ Hz, 6-H), 5.04 (1H, d, $J = 6.5$ Hz, 4-H), 6.18 (1H, br s, 1-H), 6.49 (1H, d, $J = 6.5$ Hz, 3-H), 6.40 and 7.65 (each 1H, d, $J = 16$ Hz, olefinic H), 6.94 and 7.58 (each 2H, d, $J = 8.5$ Hz, aromatic H). Anal. Calcd for C$_{24}$H$_{30}$O$_{12}$·1/2H$_2$O: C, 55.27; H, 6.38. Found: C, 55.31; H, 6.25.

6'-O-(p-Coumaroyl)-procumbide (6): $[\alpha]_D^{22}$ $-58.2°$ ($c = 0.78$, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3300, 1680, 1630, 1600, 1510. UV λ_{max}^{MeOH} nm (log ε): 313 (4.36), 228 (4.10). ^{1}H-NMR (D$_2$O) δ: 1.43 (3H, s, CH$_3$), 2.34 (1H, d, $J = 8.0$ Hz, 9-H), 3.38 (1H, s, 7-H), 3.93 (1H, s, 6-H), 4.46 and 4.60 (1H, dd, $J = 12$, 4.5 Hz and 1H, d, $J = 12$ Hz; 6'-H$_2$), 4.93 (1H, d, $J = 6.5$ Hz, 4-H), 5.30 (1H, d, $J = 8.0$ Hz, 1-H), 6.53 (1H, d, $J = 6.5$ Hz, 3-H), 6.44 and 7.72 (each 1H, d, $J = 16$ Hz, olefinic H), 6.95 and 7.59 (each 2H, d, $J = 8.5$ Hz, aromatic H). Anal. Calcd for C$_{24}$H$_{28}$O$_{12}$·1/2H$_2$O: C, 55.70; H, 5.65. Found: C, 55.31; H, 5.44.

Procumboside (8): $[\alpha]_D^{22}$ $-112°$ ($c = 0.64$, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3300. ^{1}H-NMR (D$_2$O) δ: 1.55 (3H, s, CH$_3$), 2.09 (1H, dd, $J = 12$, 3.5 Hz, 4α-H), 2.76 (1H, s, 9-H), 2.96 (1H, d, $J = 12$ Hz, 4β-H), 3.76 (1H, s, 7-H), 4.20 (1H, s, 6-H), 4.75 (1H, d, $J = 8.0$ Hz, 1'-H), 5.43 (1H, s, 1-H), 5.48 (1H, d, $J = 3.5$ Hz, 3-H). FD-MS m/z: 363 (M$^+$ + 1), 183. Anal. Calcd for C$_{15}$H$_{22}$O$_{10}$·1/2H$_2$O: C, 48.52; H, 6.24. Found: C, 48.59; H, 6.22.

Acetylation of 8-O-(p-Coumaroyl)-harpagide (3)——The glucoside (3) (16 mg) was acetylated with Ac$_2$O–pyridine (each 0.2 ml) for 3 h at room temperature. The reaction mixture was worked up in the usual way and the product was purified by PLC with MeOH–CHCl$_3$ (5:95) as the eluent. The product obtained from the major band was recrystallized from EtOH to give the hexaacetate (4) (11 mg) as colorless needles, mp 199.5—200.5 °C. $[\alpha]_D^{22}$ $-61.2°$ ($c = 0.73$, CHCl$_3$). IR ν_{max}^{KBr} cm^{-1}: 1740, 1700, 1640, 1220. UV λ_{max}^{MeOH} nm (log ε): 281 (4.38). ^{1}H-NMR (CDCl$_3$) δ: 1.51 (3H, s, CH$_3$), 2.02, 2.04, 2.05, 2.08, and 2.15 (each 3H, s, aliphatic AcO), 2.34 (3H, s, aromatic AcO), 3.0 (1H, s, OH), 3.15 (1H, br s, 9-H), 4.86 (1H, d, $J = 8.0$ Hz, 1'-H), 6.16 (1H, br s, 1-H), 6.35 (1H, d, $J = 6.5$ Hz, 3-H), 6.35 and 7.63 (each 1H, d, $J = 16$ Hz, olefinic H), 7.16 and 7.55 (each 2H, d, $J = 8.5$ Hz, aromatic H). Anal. Calcd for C$_{36}$H$_{42}$O$_{18}$: C, 56.69; H, 5.55. Found: C, 56.57; H, 5.61.

Alkaline Hydrolysis of 8-O-(p-Coumaroyl)-harpagide (3)——Three drops of 0.1 N NaOH were added to a solution of 3 (20 mg) in MeOH (3 ml). The mixture was refluxed for 1 h, then diluted with H$_2$O, neutralized with dil. HCl, and extracted with CHCl$_3$. The CHCl$_3$ layer was concentrated and methylated with CH$_2$N$_2$ to give a methyl ester, which was identified as methyl p-coumarate by direct gas chromatography (GC) comparison (2% Thermon-3000 column, 2 m × 3 mm i.d. glass tube) with an authentic sample. The H$_2$O layer was concentrated and subjected to PLC with MeOH—CHCl$_3$ (3:7) as the eluent. The major band gave harpagide (1) (7.3 mg), $[\alpha]_D^{22}$ $-151°$ ($c = 0.7$, MeOH). This identification was confirmed by comparison of the TLC behavior and ^{1}H-NMR spectrum of the product with those of an authentic sample (1).

Acetylation of 6'-O-(p-Coumaroyl)-procumbide (6)——The glucoside (6) (5.0 mg) was acetylated with Ac$_2$O–pyridine (each 0.1 ml) for 3 h at room temperature. The product was purified by PLC with MeOH–CHCl$_3$ (5:95) as the eluent. The residue obtained from the major band was recrystallized from EtOH to afford the pentaacetate (7) (4.0 mg) as colorless plates, mp 78.5—80.0 °C. $[\alpha]_D^{22}$ $-86°$ ($c = 0.30$, MeOH). UV λ_{max}^{MeOH} nm (log ε): 283 (4.17). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750, 1220. ^{1}H-NMR (CDCl$_3$) δ: 1.50 (3H, s, CH$_3$), 2.02, 2.05, 2.06, and 2.08 (each 3H, s, aliphatic AcO), 2.31 (3H, s, aromatic AcO), 3.3 (1H, s, OH), 3.36 (1H, s, 7-H), 4.85 (1H, d, $J = 6.5$ Hz, 4-H), 4.99 (1H, d, $J = 8.0$ Hz, 1'-H), 6.38 (1H, d, $J = 6.5$ Hz, 3-H), 6.40 and 7.70 (each 1H, d, $J = 16$ Hz, olefinic H), 7.13 and 7.56 (each 2H, d, $J = 8.5$ Hz, aromatic H). FD-MS m/z: 741 (M$^+$ + 23), 719 (M$^+$ + 1), 676 (M$^+$ − 42).

Alkaline Hydrolysis of 6'-O-(p-Coumaroyl)-procumbide (6)——One drop of 1 N NaOH was added to a solution of 6 (3 mg) in MeOH (2 ml), and the reaction mixture was allowed to stand for 3 h at room temperature, then neutralized with Amberlite IR-120 (H$^+$). The solvent was removed in $vacuo$ and the residue was purified by PLC with MeOH–CHCl$_3$ (3:7) as the eluent. The major band gave 5 (1.2 mg), $[\alpha]_D^{23}$ $-72°$ ($c = 0.1$, MeOH), which was proved to be identical with procumbide (5) by comparisons of TLC behavior and ^{1}H-NMR spectra.

Acetylation of Procumboside (8)——The glucoside (8) (10 mg) was acetylated with Ac$_2$O–pyridine (each 0.2 ml) in the usual way. The product was purified by silica gel (2 g) column chromatography. CHCl$_3$ (30 ml) was applied first, then elution with MeOH–CHCl$_3$ (5:95) (30 ml) gave the tetraacetate (9) (10 mg) as a hygroscopic white powder. $[\alpha]_D^{22}$ $-75.8°$ ($c = 0.36$, CHCl$_3$). IR ν_{max}^{KBr} cm^{-1}: 1750, 1220. ^{1}H-NMR (CDCl$_3$) δ: 1.57 (3H, s, CH$_3$), 2.01, 2.03, 2.05, and 2.09 (each 3H, s, AcO), 2.56 (1H, d, $J = 12$ Hz, 4β-H), 2.62 (1H, s, OH), 2.67 (1H, s, 9-H), 3.64 (1H, s, 7-H), 4.07

(1H, s, 6-H), 4.89 (1H, d, $J = 8.0$ Hz, 1′-H), 5.25 (1H, s, 1-H), 5.34 (1H, d, $J = 3.5$ Hz, 3-H). FD-MS m/z: 531 (M$^+$ + 1), 331, 183. *Anal.* Calcd for $C_{23}H_{30}O_{14}$: C, 52.08; H, 5.70. Found: C, 51.84; H, 5.75.

References and Notes

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