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Trapanins A and B, Oligomeric Hydrolyzable Tannins from *Trapa japonica* FLEROV.

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Trapanin A (6), a trimeric hydrolyzable tannin, and trapanin B (7), a tetrameric hydrolyzable tannin, were isolated from the leaves of *Trapa japonica* (Trapaceae), and their structures were determined on the basis of spectroscopic and chemical data. The following tannins were also isolated from the leaves: cornusiin C (8) (trimer); cornusiin A (3), camptothin B (4) and cornusiin D (5) (dimer); gemin D (1), tellimagrandin I (2), pedunculagin, casuarictin and casuarinin (monomer).

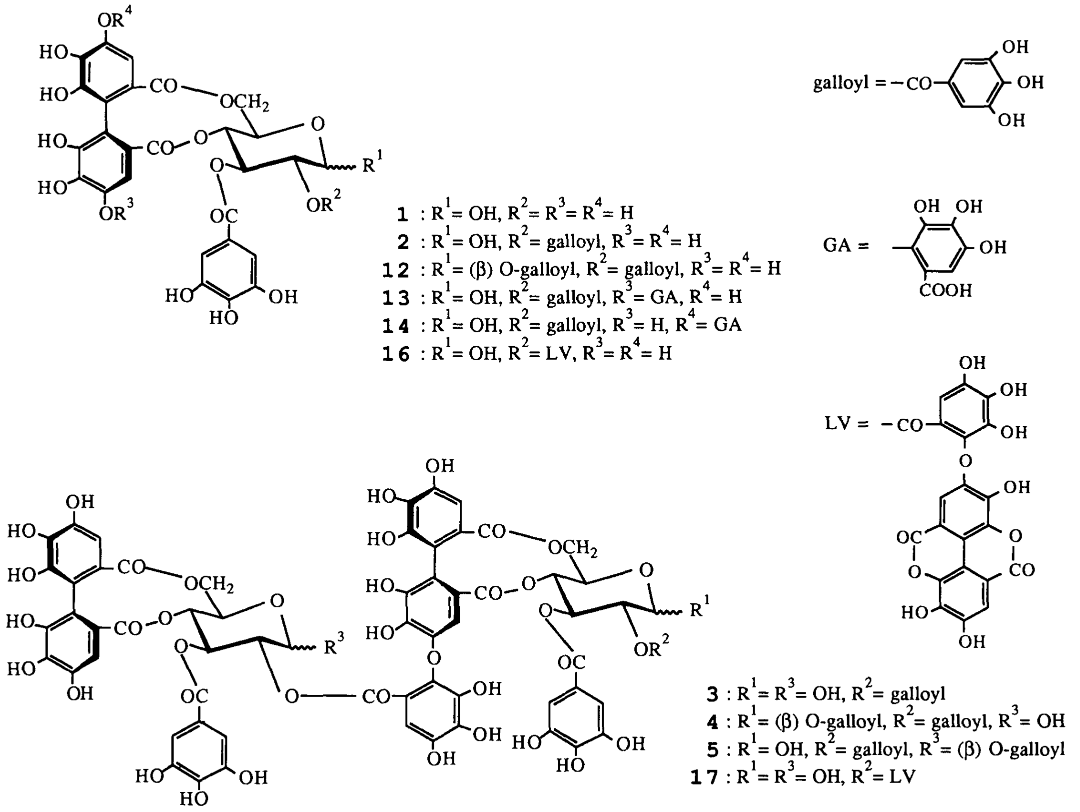
Keywords tannin; hydrolyzable tannin; trimeric hydrolyzable tannin; tetrameric hydrolyzable tannin; trapanin A; trapanin B; cornusiin C; camptothin B; *Trapa japonica*; Trapaceae

A large variety of oligomeric hydrolyzable tannins have been found in the plants of various families.[1] Among them, three dimeric hydrolyzable tannins, along with several monomeric tannins, were isolated from *Trapa bicornis* L. f. (Trapaceae).[2] We report here the isolation and structures of two new oligomeric hydrolyzable tannins, named trapanin A (trimer) and trapanin B (tetramer), from the leaves of *Trapa japonica* FLEROV. Nine other hydrolyzable tannins including four oligomeric tannins have also been islated from the leaves of this species.

Results and Discussion

Isolation of Tannins Concentrated filtrate obtained from the aqueous acetone homogenate of the leaves of *Trapa japonica* was extracted with Et_2O, EtOAc and *n*-BuOH, successively. The EtOAc extract was separated by column chromatography on Toyopearl HW-40 and on MCI gel CHP-20P, to give monomeric hydrolyzable tannins, gemin D (**1**),[3] tellimagrandin I (**2**),[4,5] pedunculagin,[5] casuarictin[5] and casuarinin,[5] and dimeric hydrolyzable tannins, cornusiin A (**3**),[6] camptothin B (**4**)[6,7] and cornusiin D (**5**).[8] The *n*-BuOH extract was also separated in a similar way, to afford trapanins A (**6**) and B (**7**), along with pedunculagin, **3**, and cornusiin C (**8**).[6]

Structure of Trapanin A Trapanin A (**6**) was obtained as an off-white powder. The fast-atom bombardment mass spectrum (FAB-MS) of this tannin showed the $[M+Na]^+$ ion at *m*/*z* 2529, indicating its molecular formula to be $C_{109}H_{78}O_{70}$. Quantitative analysis of constituent phenolic acids[6] in **6** was carried out by methylation followed by methanolysis, which afforded methyl tri-*O*-methylgallate (**9**), dimethyl hexamethoxydiphenate (**10**) and trimethyl octa-*O*-methylvaloneate (**11**) in a molar ratio of 5:1:2. Degradation of **6** with 1 M H_2SO_4 followed by gas liquid chromatography (GLC) analysis showed that the constituent sugar is glucose. Therefore, **6** consists of five galloyl



1 : R^1= OH, R^2= R^3= R^4= H
2 : R^1= OH, R^2= galloyl, R^3= R^4= H
12 : R^1= (β) O-galloyl, R^2= galloyl, R^3= R^4= H
13 : R^1= OH, R^2= galloyl, R^3= GA, R^4= H
14 : R^1= OH, R^2= galloyl, R^3= H, R^4= GA
16 : R^1= OH, R^2= LV, R^3= R^4= H

3 : R^1= R^3= OH, R^2= galloyl
4 : R^1= (β) O-galloyl, R^2= galloyl, R^3= OH
5 : R^1= OH, R^2= galloyl, R^3= (β) O-galloyl
17 : R^1= R^3= OH, R^2= LV

Chart 1

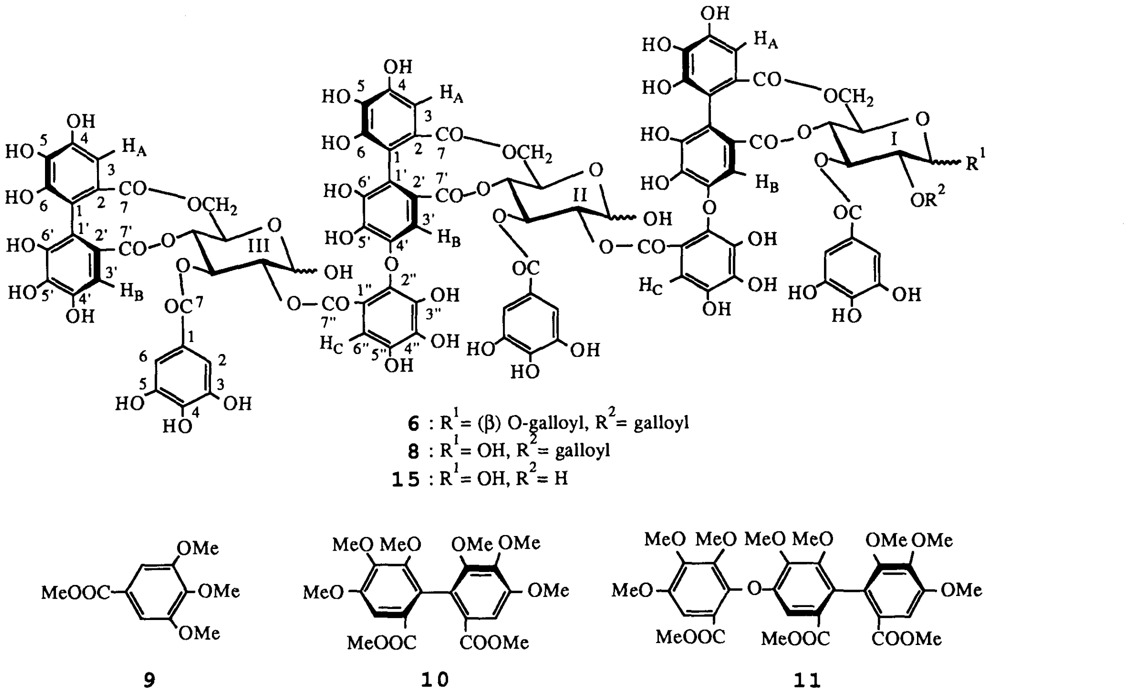


Chart 2

groups, a hexahydroxydiphenoyl (HHDP) group, two valoneoyl groups and three glucose cores. The circular dichroism (CD) spectrum of **6** showed a positive Cotton effect with large amplitude in the short-wavelength region ($[\theta]_{222}+4.5\times10^5$), indicating that all of the HHDP and valoneoyl groups in **6** have the *S*-conflguration.[6,9]

Although the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum of **6** (125.7 MHz, in acetone-d_6+D_2O) was complicated by anomerization of its glucose cores, the glucose carbon signals formed a pattern similar to that of the merged signals of glucose carbons of tellimagrandin II (**12**)[4,5] and **3** (Fig. 1). This similarity indicates[10] that the three HHDP moieties (an HHDP group and the HHDP moieties of two valoneoyl groups) are on O-4—O-6 of the three glucose cores, and seven galloyl moieties (five galloyl groups and the galloyl moieties of two valoneoyl groups) are on O-1 (*β*-configuration), O-2 and O-3 of one of the three glucose cores, and on O-2 and O-3 of the other two glucose cores.

Partial hydrolysis of **6** with tannase[11] afforded **8**, which consists of four galloyl groups, an HHDP group, two valoneoyl groups and three glucose cores.

These findings indicate that trapanin A has an additional galloyl group on one of the three anomeric centers of **8**.

The proton nuclear magnetic resonance (^{1}H-NMR) spectrum (500 MHz, in acetone-d_6+D_2O) of **6** showed signals of five galloyl groups, an HHDP group and two valoneoyl groups as follows: δ 7.12—6.96 (galloy × 3, valoneoyl $H_C\times2$), 6.91—6.80 (galloyl × 2), 6.65—6.60 (valoneoyl $H_A\times2$, HHDP H_A), 6.50—6.48 (HHDP H_B), 6.24—6.16, 6.08—6.07 (valoneoyl $H_B\times2$). The H-1 signals of the glucose core whose anomeric center is acylated, were at δ 6.16 and 6.14 (each d, $J=7.5$ Hz). These chemical shifts are comparable with the shifts of the corresponding proton of **4** (δ 6.23 and 6.18),[6,7] and are remarkably different from that of **5** (δ 5.66).[8] As for the upfield shift of the H-1 signal of **5**, relative to the corresponding signal of **12** (δ 6.17), this is attributable to the anisotropic effect of the adjacent valoneoyl group.[8] Therefore, galloylated O-1 is that in the glucose core I of **6**.

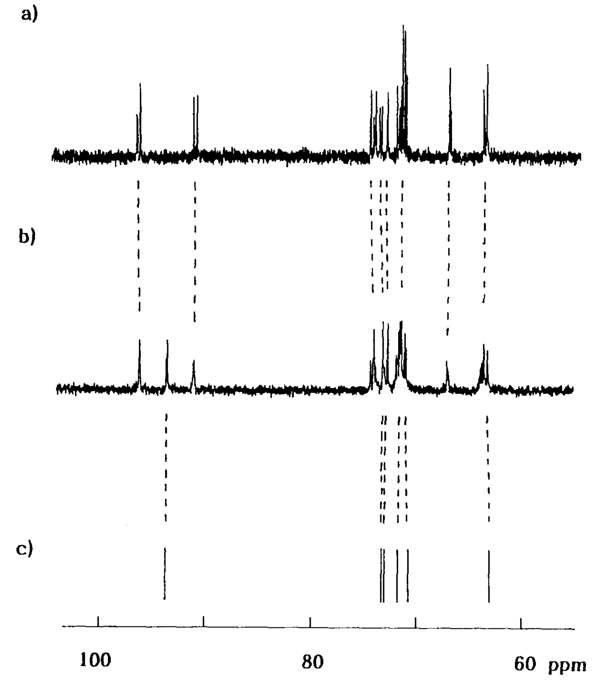
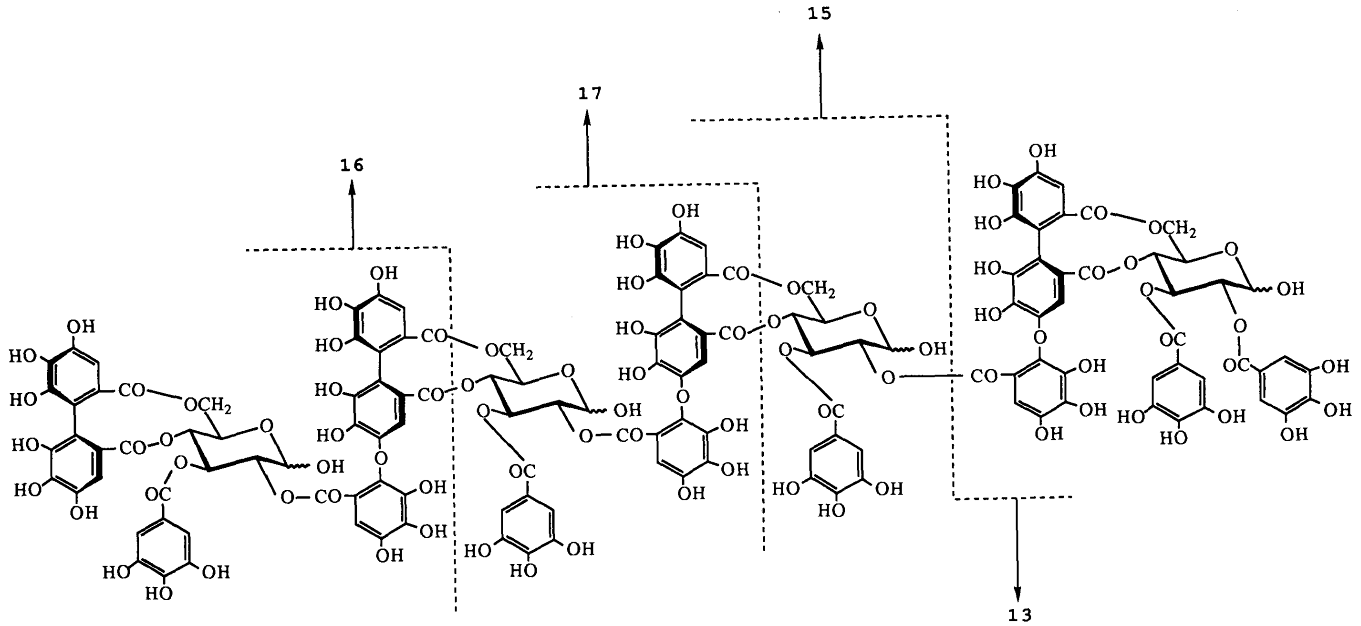


Fig. 1. Comparison of the ^{13}C Chemical Shifts of Glucose Carbons of a) Cornusiin A (**3**) (in Acetone-d_6+D_2O),[6] b) Trapanin A (**6**) (in Acetone-d_6+D_2O) and c) Tellimagrandin II (**12**) (in Acetone-d_6)[10a]

On the other hand, the H-1 signals of the *β*-glucose cores whose anomeric centers are unacylated, were at δ 4.73, 4.61, 4.48 and 4.46 (each d, $J=8$ Hz) in the ^{1}H-NMR spectrum of **6**. These remarkable upfield shifts, relative to the corresponding H-1 signal of **2** (δ 5.13), indicate the absence



7

Chart 3

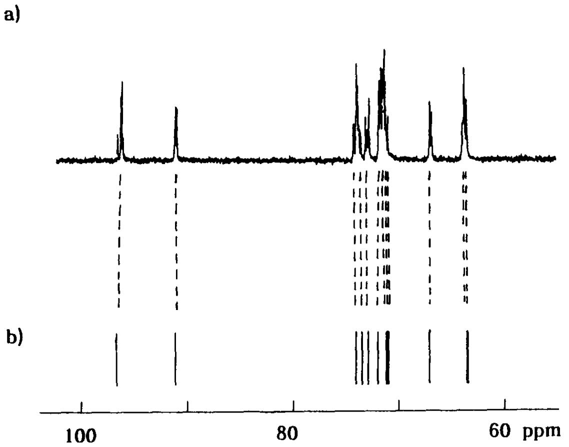


Fig. 2. Comparison of the ^{13}C Chemical Shifts of Glucose Carbons of a) Trapanin B (7) (in Acetone-d_6 + D_2O) and b) Tellimagrandin I (2) (in Acetone-d_6)[10b)]

of a galloyl groups on the anomeric centers adjacent to valoneoyl groups (glucose cores II and III, see formula **6**) in the molecule.

Based on these findings, structure **6** was assigned for trapanin A.

Structure of Trapanin B Trapanin B (**7**) was obtained as an off-white powder. High-performance GPC (gel-permeation chromatography)[6)] of **7** revealed that this tannin has a molecular weight *ca.* 4 times that of **2**. Treatment of **7** with diluted sulfuric acid, followed by GLC analysis, proved that the constituent sugar is glucose. Quantitative analysis of constituent phenolic acids[6)] of **7** revealed the presence of galloyl, HHDP and valoneoyl groups in a ratio of 5 : 1 : 3 in the molecule. A positive Cotton effect of large amplitude in the short-wavelength region ($[\theta]_{220}$ $+5.6 \times 10^5$) indicates the *S*-configuration of all of the HHDP and valoneoyl groups in **7**.

The signal pattern of the glucose carbons in the ^{13}C-NMR spectrum of **7** is analogous to that of **2** (Fig. 2), and is practically indistinguishable form that of **8**.

These findings indicate that **7** consists of five galloyl groups, an HHDP group, three (*S*)-valoneoyl groups and four glucose cores, and that the eight galloyl moieties (including the galloyl moieties of valoneoyl groups) are on O-2 and O-3 of four glucose cores, and the four HHDP moieties (including the HHDP moieties of valoneoyl groups) are O-4—O-6 of the four glucose cores. Therefore, **7** is a tetramer of **2**.

The ^1H-NMR spectrum (500 MHz, in acetone-d_6 + D_2O) of **7** showed the signals of five galloyl groups, an HHDP group and three valoneoyl groups as follows: δ 7.11—6.94 (galloyl × 3, valoneoyl $H_C \times 3$), 6.91—6.79 (galloyl × 2), 6.65—6.60 (valoneoyl $H_A \times 3$, HHDP H_A), 6.50—6.47 (HHDP H_B), 6.23—6.07 (valoneoyl $H_B \times 3$). The chemical shifts of the three H_A and three H_B prorons of the valoneoyl groups are similar to those of the corresponding valoneoyl protons of isorugosin B (**13**),[12)] rather than those of rugosin B (**14**).[12,13)] The orientation[6,12)] of the three valoneoyl groups in **7** is hence the same as that in **13**.

Partial hydrolysis of **7** afforded **13** and cornusiin F (**15**),[8)] together with cornusiin B (**16**)[6)] and **17**[6)] (Chart 3). The structure **7** was thus assigned for trapanin B.

Among the tannins hitherto isolated from the plants of Trapaceae,[2)] **1**—**5** and **8** were also isolated from a species of Cornaceae (*Cornus officinalis*),[6,8)] and **1**—**4** and **8** were isolated from a species of Nyssaceae (*Camptotheca acuminata*).[6,7)] The monomeric hydrolyzable tannins, **1** and **2**, are widely distributed in plants.[14)] However, the co-occurrence of the oligomeric hydrolyzable tannins, **3**, **4**, and **8**, which should be produced through more complex metabolic pathways, in these three plant families suggests that these families may have some phylogenetic correlation[8,15)] with each other.

Experimental

Ultraviolet (UV) and infrared (IR) spectra were recorded on a Hitachi 200-10 spectrophotometer and a JASCO A-102 spectrometer, respectively. FAB-MS were recorded on a JEOL GMS-HX100 spectrometer. Optical rotations were measured on a JASCO DIP-4 polarimeter. CD spectra were recorded on a JASCO J-500 machine equipped with a DP-501 data processor. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian VXR-500 instrument (500 MHz for ^{1}H-NMR and 126 MHz for ^{13}C-NMR), and chemical shifts are given in δ values (ppm) based on those of the methyl group of acetone-d_6 (δ_H 2.04; δ_C 29.8). Normal-phase high-performance liquid chromatography (HPLC) was performed on (A) a Merck Superspher Si 60 column (4 × 125 mm), at a flow rate of 1.5 ml/min, and also on (B) a Superspher Si60 column (4 × 250 mm), at a flow rate of 1.2 ml/min. Solvent systems used were (N1) *n*-hexane–EtOAc (2 : 1, by volume), (N2) *n*-hexane–MeOH–tetrahydrofuran (THF)–HCOOH (60 : 45 : 15 : 1) containing oxalic acid (500 mg/l), (N3) *n*-hexane–MeOH–THF–HCOOH (55 : 33 : 11 : 1) containing oxalic acid (450 mg/l) and (N4) *n*-hexane–MeOH–THF–HCOOH (47 : 39 : 13 : 1) containing oxalic acid (450 mg/l). Gradient elution was performed using a Shimadzu LC-9A pump, and the solvent profile was programmed as follows: 0—25 min, 0—50% (N4) in (N3); 25—35 min, 50—100% (N4) in (N3); 35—80 min 100% (N4). Reversed-phase HPLC was conducted on (C) a Merck LiChrospher RP-18 column (4 × 250 mm) in an oven at 40 °C, at a flow rate of 1.0 ml/min. Solvent systems used were (R1) 0.01 M H_3PO_4–0.01 M KH_2PO_4–EtOH–EtOAc (8 : 8 : 3 : 1), (R2) 0.01 M H_3PO_4–0.01 M KH_2PO_4–acetonitrile (9 : 9 : 2) and (R3) 0.01 M H_3PO_4–0.01 M KH_2PO_4–acetonitrile (11 : 11 : 3). The eluate was monitored with a Shimadzu SPD-6A UV spectrophotometric detector set at 280 nm. GLC was performed on a Hitachi 163 gas chromatograph equipped with a G-250 column (corresponding to OV-17; 1.2 mm × 40 m, CITI, Tokyo). The injection temperature and column temperature were set at 200 and 170 °C, respectively.

Isolation of Tannins from *Trapa japonica* Dried leaves (1.5 kg) of *Trapa japonica*, which were collected in October, 1987, at the Herbal Garden of Okayama University, were homogenized in 70% acetone, and the concentrated filtrate from the homogenate was successively extracted with Et_2O, EtOAc and *n*-BuOH. The solvent of each solution was evaporated off. A portion (9.8 g) of the EtOAc extract (59.5 g) was chromatographed over Toyopeal HW-40 (coarse grade) (2.2 × 38 cm) with 70% EtOH (fr. 1—5) and then with 70% acetone (fr. 6). Fraction 2 (684 mg) was further separated on MCI-gel CHP-20P with increasing concentrations of MeOH in water, to give **1** (24.2 mg) and **2** (3.0 mg). Fraction 3 (1.04 g) was further purified on MCI-gel CHP-20P and on Toyopearl HW-40 (superfine and fine grades), to give **3** (11.0 mg), casuarictin (9.0 mg), **4** (4.0 mg) and **5** (3.7 mg). Fraction 4 (1.21 g) was purified on MCI-gel CHP-20P, to give pedunculagin (76.8 mg) and casuarinin (25.9 mg). A part (45.4 g) of the *n*-BuOH extract (50.8 g) was chromatographed over Toyopearl HW-40 (coarse grade) (6 × 40 cm) with 70% EtOH, and then with 70% EtOH–70% acetone (9 : 1). The 70% EtOH eluate afforded pedunculagin (668 mg) and **3** (2.31 g). The eluate with 70% EtOH–70% acetone (9 : 1) afforded **8** (3.73 g), a mixture containing **6** (1.10 g), and another mixture containing **7** (1.74 g). The latter two were further purified on Toyopeal HW-40 (fine grade) and on MCI-gel CHP-20P, to give **6** (52.5 mg) and **7** (63.0 mg).

Trapanin A (6) An off-white powder, $[\alpha]_D^{20}$ +25° (c=0.3, MeOH). *Anal.* Calcd for $C_{109}H_{78}O_{70} \cdot 14H_2O$: C, 47.43; H, 3.87. Found: C, 47.28; H, 3.63. FAB-MS *m/z*: 2529 ($[M+Na]^+$). UV λ_{max}^{MeOH} nm (log ε): 218 (5.31), 274 (4.96). IR ν_{max}^{KBr} cm^{-1}: 1720 (ester carbonyl), 1610. CD (MeOH) $[\theta]_{222}$: $+4.5 \times 10^5$, $[\theta]_{240}$: $+1.0 \times 10^5$, $[\theta]_{259}$: -1.9×10^5, $[\theta]_{283}$: $+1.7 \times 10^5$. ^{1}H-NMR: See text. ^{13}C-NMR (acetone-d_6 + D_2O) δ: 63.2—64.0 [glc$_I$ (glucose I) C-6; glc$_{II,III}$ (glucose II, III) C-6 (α) (α-anomer) and C-6 (β) (β-anomer)], 66.8—67.0 [glc$_{II,III}$ C-5(α)], 70.9—71.9 [glc$_I$ C-4 and C-2; glc$_{II,III}$ C-3 (α), C-4 (α), C-4 (β) and C-5 (β)], 72.7, 73.0—73.1 [glc$_I$ C-5 and C-3; glc$_{II,III}$ C-2(α)], 73.8—74.3 [glc$_{II,III}$ C-3(β) and C-2 (β)], 90.9—91.1 [glc$_{II,III}$ C-1 (α)], 93.5, 93.6 (glc$_I$ C-1), 96.1—96.2 [glc$_{II,III}$ C-1 (β)], 104.2—106.0 (valoneoyl C-3′), 107.7—108.1 (HHDP C-3 and C-3′; valoneoyl C-3), 110.0—110.8 (galloyl C-2 and C-6; valoneoyl C-6″), 113.2—117.2 (HHDP C-1 C-1′; valoneoyl C-1, C-1′ and C-1″), 119.6—120.6 (galloyl C-1), 125.5—126.5 (HHDP C-2 and C-2′; valoneoyl C-2 and C-2′), 136.2—137.6 (HHDP C-5 and C-5′; valoneoyl C-2″, C-5 and C-5′), 138.9—140.6 (galloyl C-4; valoneoyl C-3″ and C-4″), 143.1—143.3 (valoneoyl C-5″), 144.3—146.1 (galloyl C-3 and C-5; HHDP C-4, C-4′, C-6 and C-6′; valoneoyl C-4, C-6 and C-6′), 146.5, 146.5, 147.5 (valoneoyl C-4′), 164.6—168.7 (galloyl C-7; HHDP C-7 and C-7′; valoneoyl C-7, C-7′ and C-7″).

Trapanin B (7) An off-white powder, $[\alpha]_D^{20}$ +16° (c=0.3, MeOH). *Anal.* Calcd for $C_{136}H_{98}O_{88} \cdot 16H_2O$: C, 47.64; H, 3.82. Found: C, 47.48; H, 3.63. UV λ_{max}^{MeOH} nm (log ε): 218 (5.36), 273 (5.09). IR ν_{max}^{KBr} cm^{-1}: 1730 (ester carbonyl), 1620. CD (MeOH) $[\theta]_{220}$: $+5.6 \times 10^5$, $[\theta]_{259}$: -3.3×10^5, $[\theta]_{285}$: $+2.5 \times 10^5$. ^{1}H-NMR: See text. ^{13}C-NMR (acetone-d_6 + D_2O) δ: 63.4—63.9 [glc C-6 (α) and C-6 (β)], 66.8—67.0 [glc C-5(α)], 71.0—71.8 [glc C-3 (α), C-4 (α), C-4 (β) and C-5 (β)], 72.8—73.1 [glc C-2 (α)], 73.6—74.3 [glc C-3 (β) and C-2 (β)], 90.9—91.1 [glc C-1 (α)], 96.0—96.4 [glc C-1(β)], 104.7—105.7 (valoneoyl C-3′), 107.7—108.1 (HHDP C-3 and C-3′; valoneoyl C-3), 109.9—110.8 (galloyl C-2 and C-6; valoneoyl C-6″), 113.6—117.6 (HHDP C-1 and C-1′; valoneoyl C-1, C-1′ and C-1″), 120.3—120.9 (galloyl C-1), 125.6—126.5 (HHDP C-2 and C-2′; valoneoyl C-2 and C-2′), 136.0—137.6 (HHDP C-5 and C-5′; valoneoyl C-2″, C-5 and C-5′), 138.9—139.1 (galloyl C-4), 140.1—140.5 (valoneoyl C-3″ and C-4″), 143.0—143.3 (valoneoyl C-5″), 144.3—145.9 (galloyl C-3 and C-5; HHDP C-4, C-4′, C-6 and C-6′; valoneoyl C-4, C-6 and C-6′), 146.5—147.5 (valoneoyl C-4′), 164.6—168.7 (galloyl C-7; HHDP C-7 and C-7′; valoneoyl C-7, C-7′ and C-7″).

Quantitative Analysis of the Constituent Phenolic Acids of 6 and 7 Ethereal diazomethane (0.5 ml) was added to an EtOH solution (0.5 ml) of **6** (1 mg), and the mixture was left to stand for 30 min. Then, the solvent was evaporated off, and the residue was treated with 0.2% NaOMe in MeOH (5 ml) overnight. The solution was acidified with 10% HCl, the solvent was evaporated off, and the residue was further treated with an excess of ethereal diazomethane for 30 min. Then, the solvent was evaporated off, and the residue was analyzed by HPLC [column (A), solvent (N1)], which showed the presence of **9**, **10** and **11** in a molar ratio of 5 : 1 : 2. An analogous treatment of **7** gave **9**, **10** and **11** in a molar ratio of 5 : 1 : 3.

Degradation of 6 and 7 A suspension of **6** (2 mg) in 1 M H_2SO_4 (0.1 ml) was heated in a sealed tube in a boiling-water bath for 4 h. The reaction mixture was neutralized with Dia-ion SA-20AP, then the solvent was evaporated off, and the residue was trimethylsilylated and analyzed by GLC, which showed the presence of glucose. An analogous treatment of **7** also showed the presence of glucose in the molecule.

Partial Hydrolysis of 6 with Tannase Tannase was added to an aquous solution of **6** (27 mg), and the mixture was kept at 37 °C for 1.5 h. The enzyme reaction was stopped by adding EtOH, and the solvent was evaporated off. Then, the residue was chromatographed over Toyopearl HW-40 (fine grade) with 70% EtOH–70% acetone (9 : 1), to afford **8** (9.6 mg).

Molecular Weight Analysis of 7 The molecular weight of **7** was analyzed by high-performance GPC [column, Shimadzu HSG-15 (7.9 mm × 50 cm); oven temperature, 40°C; developer, THF], with **8** (trimer), **3** (dimer) and **2** (monomer) as standards. The retention time (t_R, in min) of each tannin was plotted against the logarithm of its molecular weight (MW), to show a linear relationship expressed by the following equation:

$$\log \mathrm{MW} = -0.49 \times t_R + 8.53$$

Partial Hydrolysis of 7 An aqueous solution (1 ml) of **7** (1 mg) in a sealed tube was heated in a boiling-water bath for 30 min. The reaction mixture was passed through an Analytichem BondElute C18 cartridge, and adsorbed materials were eluted with increasing concentrations of MeOH in water (20% → 40% → 60%). The eluate with 40% MeOH was analyzed by HPLC [column (B) with solvent (N2) or solvent (N3)–(N4) (gradient); column (C) with solvent (R1), (R2) of (R3)], to show the presence of **13**[16] [t_R 8.4 and 9.1 min (N2); 13.4 and 13.5 min (N3)–(N4); 3.4 and 4.7 min (R1); 5.0 and 9.9 min (R2); 4.0 and 6.3 min (R3)], **15**[16] [t_R 30.0 min (N2); 39.5 min (N3)–(N4); 3.4 and 4.0 min (R1); 5.0, 5.8 and 7.4 min (R2); 3.7, 4.2 and 4.8 min (R3)], **16**[16] [t_R 8.6 and 9.1 min (N2); 12.9 and 13.5 min (N3)–(N4); 4.4 and 5.3 min (R1); 11.4 and 12.6 min (R2); 7.0 and 7.4 min (R3)] and **17**[16] [t_R 17.3 min (N2); 26 min (N3)–(N4); 6.4 and 8.4 min (R1); 13.9 and 19.5 min (R2); 9.8 and 13.0 min (R3)].

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