Tannins and Related Compounds. LXXVI.[1] Isolation and Characterization of Cercidinins A and B and Cuspinin, Unusual 2,3-(*R*)-Hexahydroxydiphenoyl Glucoses from *Cercidiphyllum japonicum* and *Castanopsis cuspidata* var. *sieboldii*

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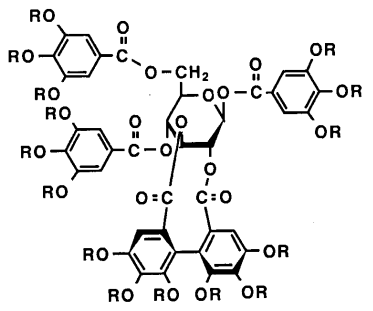
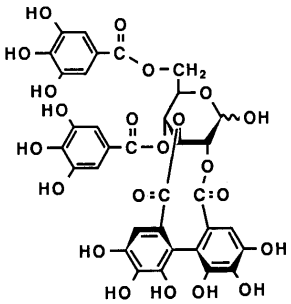
Cercidinins A (1) and B (2) and cuspinin (3), unusual ellagitannins having an *R*-hexahydroxydiphenoyl ester group at the glucose 2,3-positions, have been isolated from the bark of *Cercidiphyllum japonicum* (Cercidiphyllaceae) and the leaves of *Castanopsis cuspidata* var. *sieboldii* (Fagaceae). On the basis of chemical and spectroscopic evidence, their structures were established as 1,4,6-tri-*O*-galloyl-2,3-(*R*)-hexahydroxydiphencoyl-β-D-glucose (1), 4,6-di-*O*-galloyl-2,3-(*R*)-hexahydroxydiphenoyl-D-glucose (2) and 1-*O*-galloyl-2,3-(*R*);4,6-(*S*)-hexahydroxydiphenoyl-β-D-glucose (3). The co-occurrence of 3 with the atropisomeric *S*-hexahydroxydiphenoyl derivative suggests the non-specificity of the enzyme which converts gallic acid to hexahydroxydiphenoic acid.

Keywords *Cercidiphyllum japonicum*; Cercidiphyllaceae; *Castanopsis cuspidata* var. *sieboldii*; Fagaceae; cercidinin A; cercidinin B; cuspinin; ellagitannin; 2,3-(*R*)-hexahydroxydiphenoyl glucose; atropisomerism

The 3,3′,4,4′,5,5′-hexahydroxydiphenoyl group, the acid ester component of ellagitannins, has been shown to be derived biosynthetically by an oxidative carbon-to-carbon coupling of two appropriately positioned gallic acid ester groups attached to a polyalcohol (usually D-glucopyranose) moiety.[2,3] Because of the restricted rotation about the biphenyl bond, atropisomerism exists in this hexahydroxydiphenoyl group. The chirality of the biphenyl bond was formerly regarded as being enantiospecific, depending upon the positions of attachment of the ester group in the polyalcohol moiety. For instance, when the hexahydroxydiphenoyl ester group is located at the 2,3- or 4,6-positions of glucose, the chirality is invariably in the *S*-series, whereas 2,4- or 3,6-substituted tannins possess *R*-configuration.[3,4] In the preceding paper, we have, however, isolated a series of exceptional 3,6-(*S*)-hexahydroxydiphenoyl glucoses from the rhizomes of *Nuphar japonicum*.[1] We now wish to report on the isolation and structural determination of another series of unusual ellagitannins, cercidinins A (**1**) and B (**2**) and cuspinin (**3**), which do not fall into the above categories.



1 : R=H
1a: R=Me



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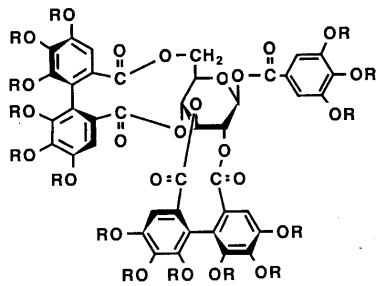


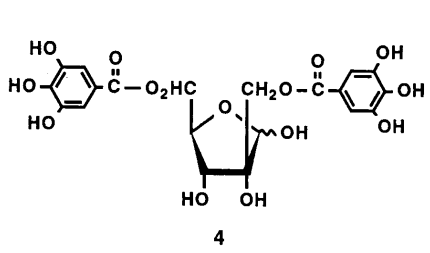
3 : R=H
3a: R=Me

Cercidinins A (**1**) and B (**2**) were isolated from the aqueous acetone extract of the fresh bark of *Cercidiphyllum japonicum* SIEB. *et* ZUCC. (Cercidiphyllaceae) by a combination of Sephadex LH-20 and various reversed-phase (Fuji-gel ODS G3, MCI-gel CHP 20P and Bondapak C_{18}/Porasil B) chromatographies. Other constituent tannins isolated from this plant material were identified as hamamelitannin (**4**),[5,6] 3-*O*-galloyl hamamelitannin (**5**),[6] 1,2,3,6-tetra- (**6**) and 1,2,3,4,6-penta-*O*-galloyl-β-D-glucoses (**7**),[7] corilagin (**8**),[8] geraniin (**9**)[9] and elaeocarpusin (**10**).[10]

Cercidinins A (**1**) and B (**2**) were characterized as ellagitannins by their color reactions with ferric chloride (dark blue) and sodium nitrite–acetic acid (reddish brown).[11] The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **1** revealed the presence of three galloyl groups [δ 7.15 (2H) and 7.10 (4H), each s] and one hexahydroxydiphenoyl group (δ 6.70 and 6.46, each 1H, s). The fairly lowfield shifts of aliphatic signals, including an anomeric doublet, suggested that all the hydroxyl groups in the sugar moiety are acylated.

Acid hydrolysis of **1** yielded glucose, together with gallic acid and ellagic acid, while alkaline methanolysis of the pentadecamethyl ether (**1a**), prepared by ordinary phenol methylation, produced methyl trimethoxybenzoate (**11**) and dimethyl hexamethoxydiphenoate (**12**) in a molar ratio of 3:1. The specific optical rotation measurement [+27.1° ($CHCl_3$)] of **12** unequivocally established the atropisomerism of the biphenyl bond to be in the *R*-series.[12] In the ^{1}H-NMR spectrum of **1a**, large coupling constants (see Experimental) of the glucose H-1—H-6 signals clearly indicated that the glucopyranose ring adopts typical $^4C_1$ conformation.

When carried out enzymatic hydrolysis with tannase, **1** yielded, together with gallic acid, a hydrolysate (**13**) whose ^{1}H-NMR spectrum showed signals due to a hexahydroxydiphenoyl group (δ 6.72 and 6.58, each 1H, s) and no galloyl peak. The complex signal patterns in the sugar region implied that **13** is a mixture of α- and β-anomers, and this was also supported by carbon-13 nuclear magnetic res-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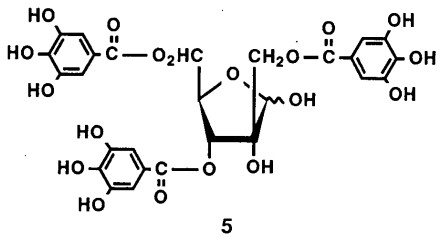
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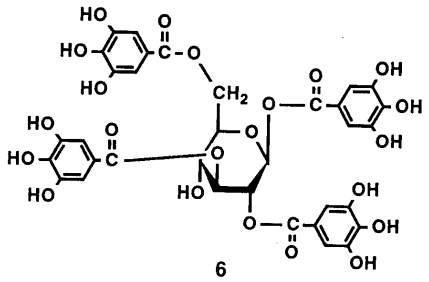
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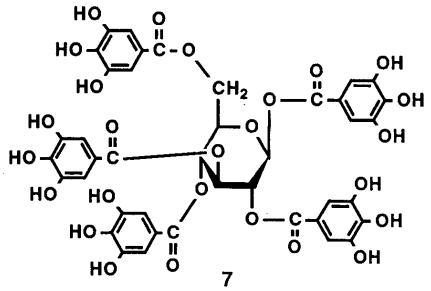
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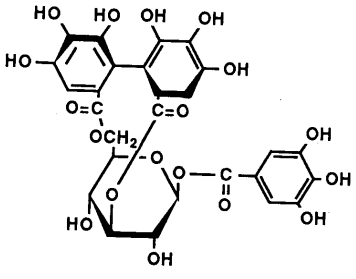
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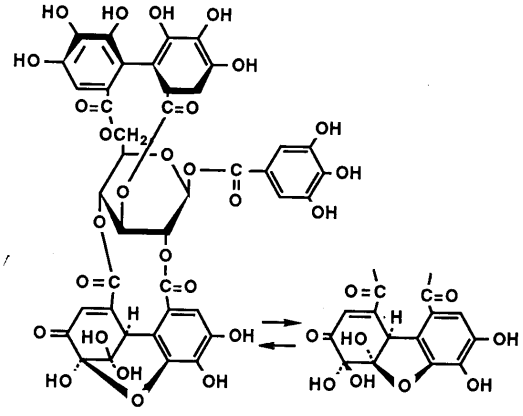
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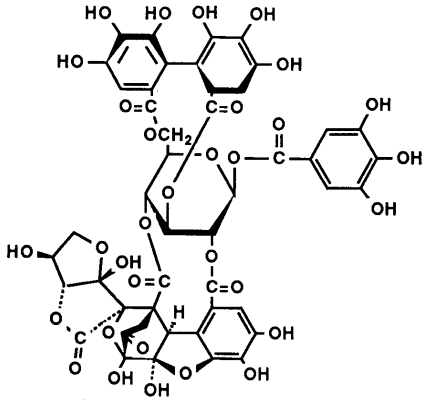
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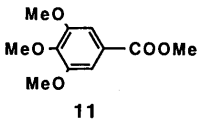
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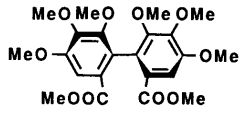
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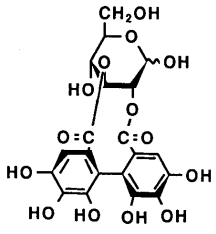
12' (racemic)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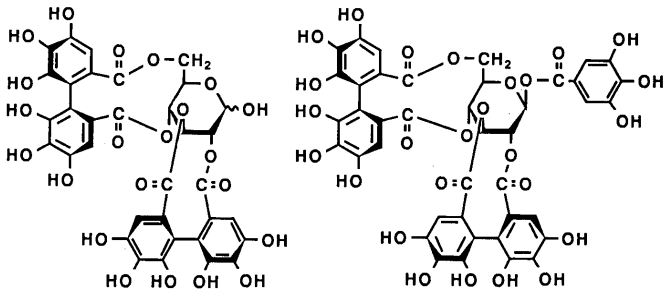
onance (^{13}C-NMR) spectroscopy showing a duplicated sugar signal pattern (twelve peaks). Furthermore, since it is obvious from the upfield shift (-1.1 ppm) of the glucose C-6 signal on hydrolysis that the acyl group is absent at the C-6 position, the hexahydroxydiphenoyl group is located at either the 2,3- or the 3,4-positions. Final structural confirmation was obtained by comparison of the ^{1}H-NMR spectra of **13** and 2,3-(*S*)-hexahydroxydiphenoyl glucose,[13] which showed the same signal patterns in both aliphatic and aromatic regions.

Since the configuration of the anomeric center could be concluded to be β on the basis of the large coupling constant value ($J=8$ Hz) of the above-mentioned H-1 signal, cercidinin A was characterized as 1,4,6-tri-*O*-galloyl-2,3-(*R*)-hexahydroxydiphenoyl-β-D-glucose (**1**).

The ^{1}H-NMR spectrum of cercidinin B (**2**) showed the presence of two galloyl groups (δ 7.15, 4H, s) and one hexahydroxydiphenoyl group (δ 6.44 and 6.68, each 1H, s). The aliphatic signal pattern was similar to that of **1**, differing only in the upfield shift (-0.6 ppm) of the sugar H-1 signal, suggesting the absence of an acyl group at the anomeric position. Furthermore, the small coupling constant ($J=4$ Hz) of this anomeric signal, as well as the absence of signals arising from a β-anomer, indicated that the α-glucopyranose form with $^4C_1$ conformation predominates in **2**.

Tannase hydrolysis of **2** selectively cleaved the ester bond of the galloyl group to yield a hydrolysate, which was found to be identical with **13** by physical and ^{1}H-NMR comparisons, thus establishing the structure of **2** as 4,6-di-*O*-galloyl-2,3-(*R*)-hexahydroxydiphenoyl-D-glucose.

Cuspinin (**3**) was isolated from the fresh leaves of *Castanopsis cuspidata* var. *sieboldii* NAKAI (Fagaceae) by chromatographic procedures similar to those described above. The field-desorption mass spectrum (FD-MS) exhibited a prominent $(M)^+$ peak at *m/z* 936, two mass units less than that found in the case of **1**. The ^{1}H-NMR spectrum showed the presence of one galloyl group (δ 7.26, 2H, s) and two hexahydroxydiphenoyl groups (δ 6.60, 6.72, 6.80 and 7.12, each 1H, s), together with sugar signals



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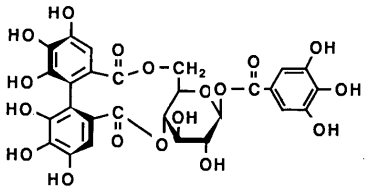

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analogous to those of **1**.

Alkaline methanolysis of the pentadecamethyl ether (**3a**) liberated compounds **11** and **12'** and glucose. On the other hand, hydrolysis of **3** with tannase yielded gallic acid and a partial hydrolysate (**14**). The ^{1}H-NMR spectrum of **14** revealed hexahydroxydiphenoyl signals (δ 6.63, 6.67, 6.75 and 6.79, 4H in total, each s) and was complicated owing to the presence of α- and β-anomers, indicating that the galloyl group is located at the anomeric position. Based on these findings, **3** was considered to be 1-*O*-galloyl-2,3;4,6-bis-hexahydroxydiphenoyl-β-D-glucose. The ^{1}H- and ^{13}C-NMR spectra of **3**, however, did not coincide with those of the most commonly occurring 1-*O*-galloyl-2,3;4,6-bis-(*S*)-hexahydroxydiphenoyl-β-D-glucose (**15**).[3] This discrepancy was rationalized by specific optical rotation measurement of **12'**, which showed it to be completely racemic and therefore to consist of equimolar proportions of *R*- and *S*-forms.

The specific allocation of the enantiomeric hexahydroxydiphenoyl groups could be successfully achieved by treatment of **3** with hot water to give 1-*O*-galloyl-4,6-(*S*)-hexahydroxydiphenoyl-β-D-glucose (**16**)[14] in considerable yield. Thus, it is evident that the glucose 2,3-positions are occupied by an *R*-hexahydroxydiphenoyl group, and therefore cuspinin was characterized as 1-*O*-galloyl-2,3-(*R*);4,6-(*S*)-hexahydroxydiphenoyl-β-D-gluose (**3**).

The above-mentioned compound **15** also occurs in *C. cuspidata* var. *sieboldii*, although cuspinin (**3**) predominates. The co-existence of these compounds in the same plant material implies that the biosynthetic conversion of gallic acid into hexahydroxydiphenoic acid is not enantiospecific, at least in the glucose 2,3-positions.

Experimental

The instruments and chromatographic conditions used throughout this work were essentially the same as described in the preceding paper.[1]

Isolation of Tannins from *Cercidiphyllum japonicum* The fresh bark (7.1 kg) of *C. japonicum* was chopped into small pieces, and extracted three times with 80% aqueous acetone at room temperature. The acetone was removed by evaporation under reduced pressure, and the resulting insoluble material was filtered off. The filtrate was applied to a Sephadex LH-20 column. Elution with water containing increasing proportions of methanol and finally with a mixture of water–acetone (1 : 1) afforded five fractions; frs. I (120 g), II (364 g), III (125 g), IV (29 g) and V (39 g). Fr. I contained compounds negative to ferric chloride, and was not examined further. Fr. II, consisting of lower-molecular-weight tannins, was rechromatographed over Sephadex LH-20 with ethanol to give two further fractions. Chromatography of the first fraction over Fuji-gel ODS G3 with water containing increasing amounts of methanol yielded hamamelitannin (**4**) (12.4 g). The second fraction was rechromatographed over MCI-gel CHP 20P with 30% aqueous methanol to afford 3-*O*-galloyl hamamelitannin (**5**) (464 mg) and corilagin (**8**) (3.31 g). Fr. III was subjected to Sephadex LH-20 chromatography with ethanol to yield geraniin (**9**) (8.2 g) and elaeocarpusin (**10**) (619 mg). Fr. IV was repeatedly chromatographed over Fuji-gel ODS G3 and Bondapak C_{18}/Porasil B with a mixture of water and methanol to give cercidinin B (**2**) (917 mg) and 1,2,3,6-tetra-*O*-galloyl-β-D-glucose (**6**) (2.04 g). Rechromatography of fr. V over MCI-gel CHP 20P with water containing increasing proportions of methanol gave crude cercidinin A (**1**) and 1,2,3,4,6-penta-*O*-galloyl-β-D-glucose (**7**), each of which was purified by Sephadex LH-20 chromatography with 80% aqueous methanol to furnish pure samples of **1** (970 mg) and **7** (3.32 g).

Cercidinin A (1) An off-white amorphous powder, $[\alpha]_D^{22}$ −71.6° (c = 1.0, acetone). *Anal.* Calcd for $C_{41}H_{30}O_{26}\cdot 3H_2O$: C, 49.70; H, 3.66. Found: C, 49.76; H, 3.71. FAB-MS m/z: 961 $(M+Na)^+$. ^{1}H-NMR (acetone-d_6) ppm: 4.4—4.7 (3H in total, H-5,6), 5.4—5.8 (3H in total, H-2,3,4), 6.28 (1H, d, J=8 Hz, H-1), 6.46, 6.70 (each 1H, s, HHDP[15]-H), 7.10 (4H, s, galloyl H), 7.15 (2H, s, galloyl H). ^{13}C-NMR (acetone-d_6+D_2O) ppm: 62.5 (C-6), 70.6 (C-4), 72.6 (2C, C-2,3), 77.0 (C-5), 93.5 (C-1), 107.4 (HHDP C-6,6'), 110.1 (galloyl C-2,6), 114.7 (HHDP C-2,2'), 119.1, 119.7, 120.6 (galloyl C-1), 125.7 (HHDP C-1,1'), 136.5 (HHDP C-4,4'), 139.2, 139.7, 140.1 (galloyl C-4), 144.4, 145.3, 145.9 (galloyl C-3,5 and HHDP C-3,3',5,5'), 165.4, 166.4, 167.0, 169.1, 169.5 (–COO–).

Acid Hydrolysis of 1 A solution of **1** (5 mg) in 1 N sulfuric acid (1 ml) was heated on a boiling water bath for 4 h. After cooling, the reaction mixture was extracted with ethyl acetate, and examination of the ethyl acetate layer by thin-layer chromatography (TLC) [silica gel, benzene–ethyl formate–formic acid (2 : 7 : 1)] revealed the presence of gallic acid and ellagic acid. The aqueous layer was neutralized with barium carbonate, and analyzed by cellulose TLC [*n*-butanol–pyridine–water (6 : 4 : 3)] to detect glucose.

Methylation of 1 A mixture of **1** (198 mg), dimethyl sulfate (1.5 ml) and anhydrous potassium carbonate (2.0 g) in dry acetone (20 ml) was heated under reflux for 40 min. After removal of the inorganic salts by filtration, the filtrate was applied to a column of silica gel. Elution with benzene containing increasing amounts of acetone yielded the pentadecamethyl ether (**1a**) as a white amorphous powder (190 mg), $[\alpha]_D^{21}$ −11.6° (c=0.9, $CHCl_3$). *Anal.* Calcd for $C_{56}H_{60}O_{26}$: C, 58.53; H, 5.26. Found: C, 57.96; H, 5.28. ^{1}H-NMR ($CDCl_3$) ppm: 3.65—3.94 (OMe), 4.40 (1H, m, H-5), 4.49 (1H, dd, J=6, 13 Hz, H-6), 4.83 (1H, dd, J=2, 13 Hz, H-6), 5.41 (1H, t, J=8 Hz, H-2), 5.60 (1H, t, J=8 Hz, H-4), 5.74 (1H, t, J=8 Hz, H-3), 6.06 (1H, d, J=8 Hz, H-1), 6.60, 6.64 (each 1H, s, HMDP[15]-H), 7.20, 7.27, 7.32 (each 2H, s, TMB[15]-H).

Alkaline Methanolysis of 1a A solution of **1a** (94 mg) in 2% methanolic sodium methoxide (5 ml) was left standing overnight at room temperature. The reaction mixture was treated with Amberlite IR-120B (H^+ form), and was separated by silica gel chromatography with benzene–acetone (19 : 1) to give methyl trimethoxybenzoate (**11**) (31 mg), colorless needles, mp 81 °C, and dimethyl hexamethoxydiphenoate (**12**) (17 mg), colorless syrup, $[\alpha]_D^{22}$ +27.1° ($CHCl_3$).

Tannase Hydrolysis of 1 A solution of **1** (94 mg) in water (5 ml) was shaken with tannase at room temperature for 30 min. After evaporation of the solvent, the residue was treated with ethanol. The ethanol-soluble portion was subjected to Sephadex LH-20 chromatography, and elution with ethanol furnished gallic acid (39 mg) and the hydrolysate (**13**) as an off-white amorphous powder (38 mg), $[\alpha]_D^{22}$ +12.9° (c=1.0, MeOH). *Anal.* Calcd for $C_{20}H_{18}O_{16}\cdot 2H_2O$: C, 46.33; H, 4.27. Found: C, 46.34; H, 4.28. ^{1}H-NMR (acetone-d_6) ppm: 3.6—5.5 (glucose H), 6.58, 6.72 (each 1H, s, HHDP-H). ^{13}C-NMR (acetone-d_6+D_2O) ppm: 61.4 (2C), 69.7, 70.2, 72.5, 73.4, 74.1, 77.9, 79.9 (glc. C-2—6), 93.3 (C-1α), 97.8 (C-1β), 107.4 (2C), 114.5, 114.7, 126.4, 128.0, 136.1, 136.2, 144.3, 145.1 (HHDP-C), 169.5, 170.2, 170.4 (–COO–).

Cercidinin B (2) An off-white amorphous powder, $[\alpha]_D^{22}$ +42.3° (c= 1.0, acetone). *Anal.* Calcd for $C_{34}H_{26}O_{22}\cdot 3H_2O$: C, 48.58; H, 3.85. Found: C, 49.12; H, 3.91. FAB-MS m/z: 787 $(M+H)^+$. ^{1}H-NMR (acetone-d_6) ppm: 4.5—4.7 (3H in total, m, H-5,6), 5.10 (1H, dd, J=4, 9 Hz, H-2), 5.26 (1H, dd, J=3, 8 Hz, H-4), 5.59 (1H, d, J=4 Hz, H-1), 5.72 (1H, dd, J=8, 9 Hz, H-3), 6.48, 6.68 (each 1H, s, HHDP-H), 7.15 (2H, s, galloyl H). ^{13}C-NMR (acetone-d_6+D_2O) ppm: 62.9 (C-6), 67.3 (C-4), 71.4 (C-2), 73.3 (C-3), 74.9 (C-5), 91.1 (C-1), 107.4 (HHDP C-6, 6'), 110.0 (galloyl C-2,6),

114.7 (HHDP C-2,2′), 120.3, 120.8 (galloyl C-1), 126.0, 126.3 (HHDP C-1,1′), 136.4 (HHDP C-4,4′), 139.2, 139.5 (galloyl C-4), 144.4, 145.3, 146.0 (galloyl C-3,5 and HHDP C-3,3′,5,5′), 166.7, 167.1, 169.2, 169.8 (–COO–).

Tannase Hydrolysis of 2 A solution of **2** (108 mg) in water (5 ml) was incubated with tannase at room temperature for 35 min. The solvent was removed by evaporation, and the residue was treated with ethanol. The ethanol-soluble portion was applied to a Sephadex LH-20 column and elution with ethanol gave gallic acid (40 mg) and the partial hydrolysate (29 mg), which was shown to be identical with **13** by physical and spectral (^{1}H-NMR) comparison.

Isolation of Cuspinin (3) from *Castanopsis cuspidata* var. *sieboldii* Extraction and fractionation of the fresh leaves (15 kg) of *C. cuspidata* var. *sieboldii* were described in one of the previous papers.[16] Among seven fractions obtained by initial Sephadex LH-20 chromatography, the final fraction VII (24 g) was subjected to MCI-gel CHP 20P chromatography. Elution with water containing increasing proportions of methanol gave two fractions. The first fraction was chromatographed over Bondapak C_{18}/Porasil B with water and methanol to give cuspinin (**3**) (285 mg) and compound **15** (120 mg).

Cuspinin (3) An off-white amorphous powder, $[\alpha]_D^{24}$ −18.2° (c=0.9, acetone). *Anal.* Calcd for $C_{41}H_{28}O_{26}\cdot 5H_2O$: C, 47.96; H, 3.73. Found: C, 48.17; H, 3.51. FD-MS m/z: 936 $(M)^+$. ^{1}H-NMR (acetone-d_6) ppm: 3.80 (1H, d, J=13 Hz, H-6), 4.40 (1H, dd, J=6, 9 Hz, H-5), 4.90 (2H, t, J=9 Hz, H-2,4), 5.23 (1H, dd, J=6, 13 Hz, H-6), 6.10 (1H, d, J=9 Hz, H-1), 6.60, 6.72, 6.80, 7.12 (each 1H, s, HHDP-H), 7.26 (2H, s, galloyl H). ^{13}C-NMR (acetone-d_6+D_2O) ppm: 63.1 (C-6), 69.6 (C-4), 73.2 (C-2), 77.2 (C-3), 78.2 (C-5), 92.4 (C-1), 108.2 (HHDP C-6,6′), 110.5 (galloyl C-2,6), 111.1, 115.8, 117.5, 117.8 (HHDP C-2,2′), 119.8, 120.0, 126.0, 126.2 (HHDP C-1,1′), 121.9 (galloyl C-1), 136.5, 137.3, 140.0 (HHDP C-4,4′), 138.6 (galloyl C-4), 144.3, 144.5, 144.6, 145.0, 145.4, 145.6 (HHDP C-3,3′,5,5′), 146.2 (galloyl C-3,5), 165.0, 167.3, 168.0, 168.1, 168.5 (–COO–).

Methylation of 3 A mixture of **3** (50 mg), dimethyl sulfate (0.2 ml) and anhydrous potassium carbonate (0.3 g) in dry acetone was heated under reflux for 3 h. The inorganic precipitates were removed by filtration, and the filtrate was subjected to silica gel chromatography. Elution with benzene–acetone (4:1) yielded the pentadecamethyl ether (**3a**) as a white amorphous powder, $[\alpha]_D^{24}$ −18.4° (c=0.6, $CHCl_3$). *Anal.* Calcd for $C_{56}H_{58}O_{26}$: C, 58.63; H, 5.10. Found: C, 58.62; H, 5.30. ^{1}H-NMR ($CDCl_3$) ppm: 3.4—3.95 (OMe), 4.4—5.2 (3H in total, m, H-2,3,4), 5.40 (1H, dd, J=6, 13 Hz, H-6), 6.04 (1H, d, J=8 Hz, H-1), 6.75, 6.91, 7.38 (4H in total, each s, HMDP-H), 7.35 (2H, s, TMB-H).

Alkaline Methanolysis of 3a A solution of **3a** (20 mg) in 2% methanolic sodium methoxide was heated at 70 °C for 2 h. The reaction mixture was neutralized with Amberlite IR-120B (H^+ form), and the products were separated by silica gel chromatography with benzene–acetone and chloroform–methanol to yield dimethyl hexamethoxydiphenoate (**12**) (8 mg) as a colorless syrup, $[\alpha]_D^{26}$ 0° (c=0.8, $CHCl_3$), methyl trimethoxybenzoate (**11**) and glucose.

Tannase Hydrolysis of 3 A solution of **3** (20 mg) in water (2 ml) was incubated with tannase at room temperature for 30 min. The reaction mixture was worked up as described before to give gallic acid and the hydrolysate (**14**) as an off-white amorphous powder, $[\alpha]_D^{24}$ −22.9° (c=0.75, acetone). *Anal.* Calcd for $C_{34}H_{24}O_{22}\cdot 3H_2O$: C, 48.70; H, 3.60. Found: C, 48.73; H, 3.51. ^{1}H-NMR (acetone-d_6+D_2O) ppm: 5.50 (1H, d, J=4 Hz, H-1), 6.63, 6.67, 6.75, 6.79 (4H in total, each s, HHDP-H).

Hydrolysis of 3 with Hot Water A solution of **3** (30 mg) in water was heated at 90 °C for 8.5 h. After cooling, the resulting precipitates were collected by filtration, and chromatographed over Sephadex LH-20. Elution with ethanol afforded 1-*O*-galloyl-4,6-(*S*)-hexahydroxydiphenoyl-β-D-glucose (**16**) (12 mg).

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References and Notes

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