Phyllanemblinins A−F, New Ellagitannins from *Phyllanthus emblica*

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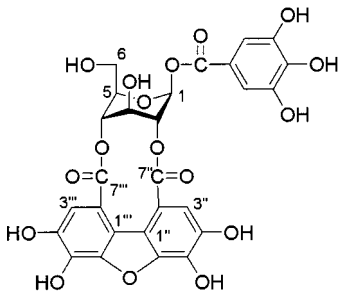
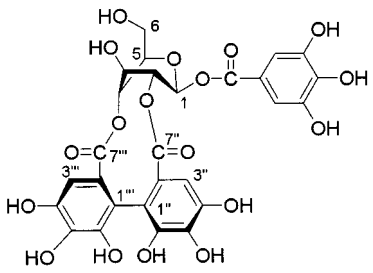
Received July 27, 2001

Six new ellagitannins, phyllanemblinins A−F (**1**−**6**), were isolated from *Phyllanthus emblica*, along with 30 known tannins and related compounds. Their structures were determined by spectral and chemical methods. Phyllanemblinins A (**1**) and B (**2**) were confirmed to be ellagitannins having a tetrahydroxybenzofuran dicarboxyl group and a hexahydroxydiphenoyl group, respectively, by chemical synthesis from furosin (**8**). Phyllanemblinin C (**3**) has a new acyl group at the glucose 2,4-positions and is structurally related to chebulagic acid. Phyllanemblinins D (**4**), E (**5**), and F (**6**) were found to be positional isomers of neochebuloyl 1(*β*)-*O*-galloylglucose.

Phyllanthus emblica L. (Euphorbiaceae) is a shrub or tree distributed in subtropical and tropical areas of the People's Republic of China, India, Indonesia, and the Malay Peninsula. The fruit and its juice have been used widely by the local people for antiinflammatory and antipyretic treatment. The root, leaves, and bark have been used for treating eczema, wart, diarrhea, and headache after a fever in the Southwest of China, and the root is also used as an astringent and hematostatic agent in Nepal.[1,2] In our previous chemical studies on this plant, new galloyl esters of L-malic acid, mucic acid, and mucic acid 1,4-lactone were isolated from the fruit juice,[3] and several novel norbisabolane and bisabolane derivatives were obtained from the root.[4−6] Continuing investigation on the same extract of the fruit juice resulted in the isolation of a new ellagitannin, phyllanemblinin A (**1**), together with 11 known tannins. In addition, the leaves and branches were also chemically studied, and five new ellagitannins, phyllanemblinins B−F (**2**−**6**), were isolated along with 25 known tannins and related compounds. We report herein the isolation and structural elucidation of compounds **1**−**6**.



1



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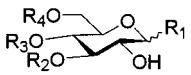

4: R_1=(β)OG, R_2=neoche, R_3=R_4=H
4a: R_1=OH, R_2=neoche, R_3=R_4=H
5: R_1=(β)OG, R_3=neoche, R_2=R_4=H
5a: R_1=OH, R_3=neoche, R_2=R_4=H
6: R_1=(β)OG, R_2=R_3=H, R_4=neoche
6a: R_1=OH, R_2=R_3=H, R_4=neoche

Results and Discussion

As described in the previous paper,[3] a 60% aqueous acetone extract of the fruit juice of *P. emblica* was subjected to MCI-gel CHP 20P column chromatography, affording five fractions. Fractions 2 and 3 were separately chromatographed over Sephadex LH-20, MCI-gel CHP 20P, Chromatorex ODS, and Toyopearl HW-40F to afford compound **1** and 11 known hydrolyzable tannins, identified as 1(*β*)-*O*-,[7] 1(*β*),6-di-*O*-,[8] and 1(*β*),2,3,6-tetra-*O*-galloylglucose,[9] corilagin (**7**),[10] chebulanin,[11] chebulagic acid (**9**),[12,13] elaeocarpusin,[14] punicafolin,[15] tercatain,[16] mallonin,[17] and putranjivain A.[18]

The EtOH extract of the fresh leaves and branches of *P. emblica* was suspended in H_2O and partitioned with Et_2O. The H_2O layer was separated successively by chromatographies as mentioned above to give compounds **2**−**7**. Twenty-five known tannins and related compounds were also isolated and identified as 1(*β*)-*O*-,[7] 1(*β*),4-di-*O*-,[19] and 3,6-di-*O*-galloylglucose,[20] corilagin (**7**),[10] furosin (**8**),[21] chebulanin,[11] chebulagic acid (**9**),[12,13] mallonin,[17] putranjivains A and B,[18] neochebulagic acid,[22] carpinusnin,[23] geraniin (**10**),[24,25] gallic acid 3-*O*-*β*-D-glucoside,[26] gallic acid 3-*O*-(6′-*O*-galloyl)-*β*-D-glucoside,[27] (−)-epiafzelechin,[28] (+)-gallocatechin,[29] (−)-epigallocatechin,[30] (−)-epicatechin,[30] prodelphinidins B-1[31] and B-2,[29] epicatechin-(4*β*→8)-epigallocatechin,[32] prodelphinidin B-2 3′-*O*-gallate,[30] flavogallonic acid bislactone,[33] and chebulic acid,[13,22] by comparison of the physical and spectral data with those of authentic samples.

The molecular formula of compound **1** was assigned as $C_{27}H_{20}O_{17}$ on the basis of the ^{13}C NMR data, negative-ion FABMS (*m*/*z* 615, $[M - H]^-$), and elemental analysis. The presence of a galloyl group was deduced from the observation of a characteristic two-proton singlet (*δ* 7.14), seven

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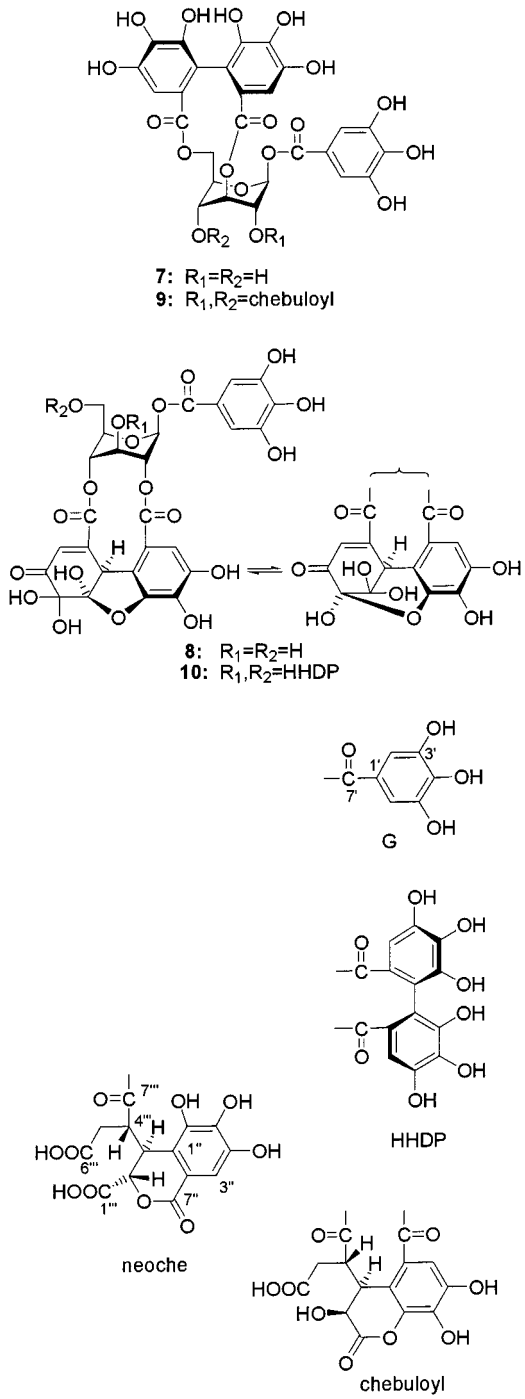
10.1021/np010370g CCC: $20.00
Published on Web 11/27/2001



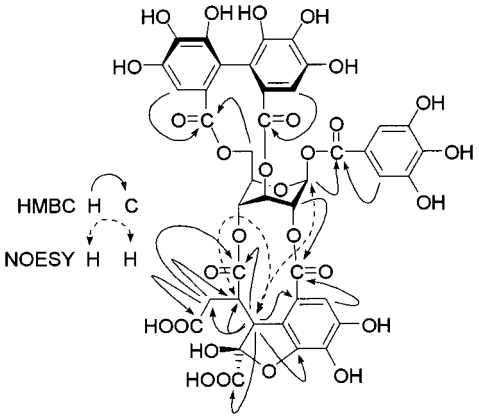


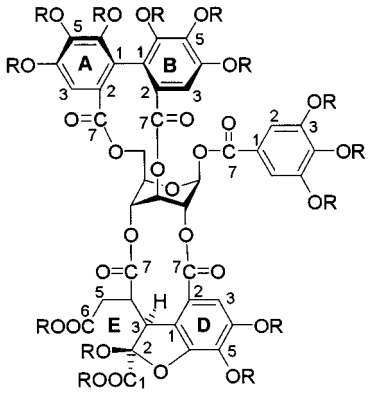
Figure 1. Important HMBC and NOESY correlations of **3**.

sp^2 [δ 146.1 (2C), 139.7, 120.1, 110.1 (2C), and 165.3] carbon signals in the ^{1}H and ^{13}C NMR spectra, respectively. The coupling constants of the sugar proton signals were similar to those of corilagin [1-*O*-galloyl-3,6-(*R*)-hexahydroxydiphenoyl(HHDP)-β-D-glucose] (**7**),[10] characteristic of a $^1C_4$ glucopyranose. The ^{1}H and ^{13}C NMR spectra exhibited two one-proton singlets, 12 aromatic, and two carboxyl carbon signals, indicating the presence of a 1,1′-(3,3′,4,4′-tetrahydroxy)dibenzofurandicarboxyl group, which was originally characterized as the acyl group of mallotusinin.[17] The molecular weight (616) of **1**, which was 18 mass units less than that of corilagin, was also consistent with this result. The location of the acyl groups was determined from the observation of long-rang correlations in the HMBC spectrum of **1** (Figure 1, Supporting Information): the galloyl carboxyl carbon (δ 165.3) was correlated with the anomeric proton (δ 6.30), indicating the galloyl group was attached to C-1. In addition, two one-proton singlet signals (δ 7.30 and 7.16) showed cross-peaks with two carboxyl carbons at δ 167.9 and 169.2, respectively, and HMBC correlations of the carboxyl carbon signal at δ 167.9 with H-2 (δ 5.12) showed that this carboxyl group was linked to C-2 of the glucose moiety. Since the glucose adopted a $^1C_4$ conformation as described above, the dibenzofurandicarboxyl group was suggested to be attached to C-2/C-4 of the pyranose ring. This was confirmed unequivocally by the synthesis of **1**: treatment of furosin (**8**) with pyridine in acetonitrile afforded **1**.[34] Hence, phyllanemblinin A (**1**) was confirmed to be 1-*O*-galloyl-2,4-tetrahydroxydibenzofurandicarboxyl-β-D-glucose. Considering the co-occurrence of **8** in this plant material, the 1,1′-(3,3′,4,4′-tetrahydroxy)dibenzofurandicarboxylic acid may also be biosynthesized from the dehydrohexahydroxydiphenoyl (DHHDP) group by reductive aromatization.

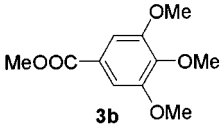
The ^{13}C NMR spectral data of compound **2**, elemental analysis, and the $[M - H]^-$ peak at *m*/*z* 633 in the negative-ion FABMS showed the molecular formula to be $C_{27}H_{22}O_{18}$, which was identical to that of **7**. The ^{1}H and ^{13}C NMR spectra were also related to those of **7** and showed signals due to a galloyl group (δ_H 7.12, 2H, s), an HHDP group (δ_H 7.38 and 6.94, each 1H, s), and a sugar moiety. The configuration of the HHDP group was determined as *R* according to a positive Cotton effect at 267 nm and a negative one at 230 nm in the CD spectrum.[35] The ^{1}H−^{1}H COSY experiment established the assignment of the sugar protons, and the chemical shifts of H-1, H-2, and H-4 indicated esterification of the hydroxyl groups at these positions. In the HMBC spectrum, the galloyl carboxyl carbon (δ 165.4) was correlated with H-1, and one of the HHDP carboxyl carbons (δ 168.6) was correlated with H-2 and an aromatic proton at δ 7.38. Therefore, the galloyl and HHDP groups were concluded to be at C-1 and C-2/C-4, respectively. Furthermore, hydrogenation of furosin (**8**) over Pd−C yielded **2**,[36] confirming the structure of **2** to be 1-*O*-galloyl-2,4-(*R*)-HHDP-β-D-glucose (phyllanemblinin B). Since the coupling constant of H-1 ($J_{1,2}$ = 6.0 Hz) in **2** was much larger than that of the typical $^1C_4$ type tannins, the conformation of the glucopyranose ring of **2** apparently is a skew-boat.[37,38] Glucose with a similar boat conformation was also observed for corilagin (**7**) in dimethyl sulfoxide solution.[38]

To the best of our knowledge, the HHDP group in ellagitannins isolated from plant sources to date are at the C-1/C-6,[39,40] C-3/C-6, C-4/C-6, C-2/C-3, or C-3/C-4[41] positions of the glucopyranose core. Although there were some 2,4-HHDP-glucoses reductively derived from the ellagitannins with an DHHDP group, no 2,4-HHDP glucose has been

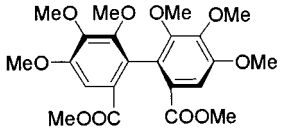
known in nature so far. Hence, phyllanemblinin B (**2**) represents the first ellagitannin having an HHDP group at the glucose C-2/C-4 positions.



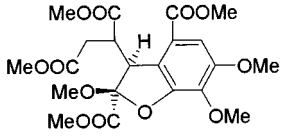
3: R=H
3a: R=Me



3b



3c



3d

The ^{1}H NMR spectrum of **3** showed a two-proton singlet (δ 7.16) due to a galloyl group and two one-proton singlets (δ 7.03 and 6.68) attributable to an HHDP group. The chemical shifts and coupling constants of the sugar proton signals closely resembled those of chebulagic acid (**9**),[12,13] indicating the presence of a fully acylated ^{1}C$_4$ glucopyranose moiety. Besides these signals, ABXY-type signals [δ 1.96 (dd, J = 12.0, 17.5 Hz), 2.65 (dd, J = 2.5, 17.5 Hz), 3.73 (td, J = 2.5, 12.0 Hz), and 4.83 (d, J = 2.5 Hz)] and a one-proton singlet at δ 7.13 arising from another aryl group were observed. In the ^{13}C NMR spectrum, the group showed signals due to a methylene, two methine, an acetal, six aromatic, and four carboxyl carbons. The HMBC spectrum of **3** (Figure 1) showed correlations of the proton signal at δ 7.13 with four aromatic (D_1, D_2, D_4, and D_5) and a carboxyl (D_7) carbon. The carboxyl carbon (D_7) was also coupled with H-2 of the glucose moiety, indicating that this aromatic carboxyl moiety was linked to the C-2 through an ester linkage. On the other hand, two of the aromatic carbons (D_2 and D_6) were correlated with the methine proton at δ 4.83, which was also correlated with two carboxyls (E_1 and E_7), another aliphatic methine (E_4), and methylene (E_5) carbons. Furthermore, the methylene proton (E_5) showed correlation with two carboxyl (E_6 and E_7) and the methine (E_4) carbon. These observations suggested the connectivities of the E_3−E_7, which were similar to those of **9**. After methylation of **3** with dimethyl sulfate and potassium carbonate, the tetradecamethyl derivative **3a** showed HMBC correlations (Figure 2, Supporting Information) between the acetal carbon (E_2) and two methine protons (E_3 and E_4), indicating the location of the acetal carbon between the carboxyl group (E_1) and the methine carbon (E_3). Alkaline hydrolysis and subsequent methylation of **3a** afforded methyl 3,4,5-trimethoxybenzoate (**3b**), dimethyl (*R*)-hexamethoxydiphenate (**3c**), and product **3d**. The presence of seven methoxyl groups in **3d**, as shown by ^{1}H and ^{13}C NMR analyses, suggested the presence of an acetal ring between D_6 and E_2. This was also supported by the chemical shift of E_2 (δ 107.5) in **3**, which is similar to that of the five-membered ring acetal carbon of the DHHDP group of furosin (**8**) (δ 108.8; δ 96.3, six-membered hemiacetal ring).

Location of the three acyl groups on the glucose moiety was determined by the HMBC spectrum of **3a** (Figure 2, Supporting Information), which showed correlations of the anomeric proton (δ 6.51) with the trimethoxybenzoyl carboxyl carbon (δ 164.2), and those of H-3 and H-6 with hexamethoxydiphenoyl carboxyl carbons. As described for the HMBC spectrum of **3**, H-2 was also correlated with the D_7 carboxyl carbon in **3a**. Although H-4 did not show correlation with any carboxyl carbons, the E_7 carboxyl group was deduced to be attached to this position, because both remaining carboxyl groups of E_1 and E_6 were correlated with methoxyl groups. As for the configuration of 2,4-acyl groups, *cis*-geometry between the E_1 carboxyl carbon and E_3 benzyl proton was deduced from NOE correlation between the E_3 proton and the carboxyl methyl group at E_1 (δ 3.80) in the NOESY spectrum of **3d** (Figure 3, Supporting Information). Furthermore, in the NOESY spectrum of **3**, NOE correlation between the E_3 proton and the glucose H-1 suggested the *S* configuration at E_3. The NOE correlation between the methine protons at E_3 and E_4 in the NOESY spectrum of **3a** might suggest the *cis* orientation of these protons; however, it could not be confirmed. On the basis of the above evidence, the structure of **3** was concluded to be as shown. Phyllanemblinin C (**3**) is structurally related to **9** and probably is derived by cleavage of the DHHDP group of geraniin (**10**) or oxidation of **9**.

Compounds **4**, **5**, and **6** exhibited the same $[M - H]^-$ ion peak at *m*/*z* 669 in the negative-ion FABMS spectra. In the ^{1}H NMR spectra, the appearance of two-proton aromatic singlets [**4**, δ 7.21; **5**, δ 7.20; **6**, δ 7.18] indicated the occurrence of galloyl ester groups in each molecule. The sugar moiety of **4** and **5** was deduced to be β-glucopyranose from the large coupling constants (8−10 Hz) of the H-1−H-4 signals. Although the sugar proton signals of **6** were overlapped with solvent signals, comparison of the ^{13}C NMR spectral data with those of **4** and **5** suggested that the sugar moiety of **6** was also β-glucopyranose. In addition to the galloyl and glucose, the ^{1}H NMR spectrum exhibited a one-proton singlet [**4**, δ 7.15; **5**, δ 7.13; and **6**, δ 7.14] and signals due to three methine and one methylene proton. Chemical shifts and coupling constants of these signals were almost the same as those of the neochebuloyl group of neochebulagic acid[22] and carpinusnin,[23] which were isolated from the same plant source. The low-field chemical shifts of the glucose H-1 and H-3 signals in **4** (δ 5.82 and 5.28), H-1 and H-4 signals in **5** (δ 5.78 and 5.05), and H-1 and H-6 signals in **6** (δ 5.70, 4.64, and 4.34) indicated that these positions were esterified. Selective hydrolysis of the galloyl group in **4**−**6** by tannase yielded gallic acid and hydrolysates **4a**, **5a**, and **6a**, respectively. The ^{1}H NMR spectra of **4a**, **5a**, and **6a** showed large upfield shifts of the

glucose H-1 and complex signals due to the α and β anomers. This result indicated that the galloyl group was attached at C-1 in each compound. Thus, **4**−**6** were characterized as 3-*O*- (**4**), 4-*O*- (**5**), and 6-*O*- (**6**) neochebuloyl-1-*O*-galloyl-β-D-glucose and named phyllanemblinins D, E, and F, respectively.

Although galloyl mucic acid was isolated as the major polyphenol of the fruit juice of *P. emblica* in our previous work,[3] the present work revealed the occurrence of 12 hydrolyzable tannins. This result suggested the strong antioxidant activities of the fruit juice, and actually chebulagic acid, the major ellagitannin of the fruit juice, as well as phyllanemblinin C, showed strong scavenging acitivity against DPPH radical. Further study on antioxidant activity of the constituents of *P. emblica* is now in progress. As for the leaves and branches, the major polyphenols were chebulagic acid, corilagin, and geraniin, which were also found in other *Phyllanthus* species.[42−44]

Experimental Section

General Experimental Procedures. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. ^{1}H and ^{13}C NMR spectra were recorded in $(CD_3)_2CO$ and $CDCl_3$ with Varian Unity plus 500 and Varian Gemini 300 spectrometers operating at 500 and 300 MHz for ^{1}H and 125 and 75 for ^{13}C, respectively. Coupling constants are expressed in Hz, and chemical shifts are given on a δ (ppm) scale with tetramethylsilane as the internal standard. MS were recorded on a JEOL JMS DX-303 spectrometer, and glycerol was used as a matrix for FABMS measurement. UV, CD, and IR spectra were measured with JASCO V-560, J-725N, and FT/IR-410K spectrometers, respectively. Column chromatography was performed with MCI-gel CHP 20P (75−150 μm, Mitsubishi Chemical Co.), Sephadex LH-20 (25−100 μm, Pharmacia Fine Chemical Co. Ltd.), Toyopearl HW-40F (37−70 μm, Tosoh Co.), Chromatorex ODS (100−200 mesh, Fuji Silysia Chemical Ltd.), Cosmosil 75C_{18}-OPN (Nacalai Tesque), and Avicel Cellulose (Funakoshi). TLC was performed on precoated Kieselgel 60 F_{254} plates (0.2 mm thick, Merck) with benzene−ethyl formate−formic acid (1:7:1) and precoated Cellulose F_{254} plates (0.1 mm, Merck) with 2% acetic acid, and spots were detected by ultraviolet (UV) illumination and by spraying with ferric chloride and 10% sulfuric acid reagents.

Plant Material. The powdered fruit juice of *Phyllanthus emblica* L. was purchased from the local market of Kunming, and the leaves and branches were collected at Xishuangbanna, Yunnan, People's Republic of China. A voucher specimen is deposited in the Herbarium of Kunming Institute of Botany, Chinese Academy of Sciences.

Extraction and Isolation. Details of fractionation of the 60% aqueous acetone extract of the fruit juice powder (5.0 kg) were described in a previous paper,[3] and the following fraction numbers correspond to those given in that paper.

Fraction 2 (29.96 g) was chromatographed on Sephadex LH-20, Chromatorex ODS (40−100% MeOH), MCI-gel CHP 20P (0−30% MeOH), and Cosmosil 75C_{18}-OPN to give 1(β),6-di-*O*-galloylglucose (119 mg), chebulagic acid (2.01 g), elaeocarpusin (120 mg), punicafolin (49 mg), corilagin (1.65 g), and tercatain (120 mg). Fraction 3 (11.19 g) were repeatedly chromatographed on Sephadex LH-20, MCI-gel CHP 20P (10−80% MeOH), Chromatorex ODS (5−50% MeOH), and Toyopearl HW-40F to afford **1** (60 mg), 1(β),2,3,6-tetra-*O*-galloylglucose (70 mg), chebulanin (99 mg), mallonin (93 mg), and putranjivain A (20 mg).

The fresh leaves and branches (15 kg) were extracted with EtOH at room temperature, four times, to give an extract (980 g), which was suspended in H_2O and partitioned with Et_2O. The H_2O layer was concentrated in vacuo and chromatographed over Sephadex LH-20 (H_2O−MeOH, 1:0−0:1, and then 50% acetone) to give five fractions (fractions 1−5). Fraction 2 was subjected to MCI-gel CHP 20P (0−100% MeOH) and Toyopearl HW-40F (0−40% MeOH) to give 1(β)-*O*-galloylglucose (219 mg) and gallic acid 3-*O*-β-D-glucoside (107 mg). Fraction 3 was separated successively by passage over Chromatorex ODS (0−60% MeOH), Sephadex LH-20 (0−100% MeOH), and MCI-gel CHP 20P (0−60% MeOH) to afford **4** (128 mg), **5** (266 mg), and **6** (60 mg). Fractions 4 and 5 were repeatedly chromatographed over Sephadex LH-20 (0−100% MeOH or EtOH), MCI-gel CHP 20P (0−60% MeOH), Chromatorex ODS (0−60% MeOH), cellulose (2% AcOH), and Toyopearl HW-40F (0−60% MeOH) to yield **2** (10 mg), epiafzelechin (17 mg), epicatechin (24 mg), gallocatechin (30 mg), epigallocatechin (38 mg), epicatechin-(4β→8)-epigallocatechin (8 mg), prodelphinidin B-1 (59 mg), prodelphinidin B-2 (132 mg), prodelphinidin B-2 3′-O-gallate (36 mg), chebulanin (260 mg), neochebulagic acid (167 mg), mallonin (13 mg), carpinusnin (158 mg), corilagin (4.49 g), putranjivain B (35 mg), furosin (110 mg), 3,6-di-*O*-galloylglucose (15 mg), 1(β),4-di-*O*-galloylglucose (9.5 mg), and gallic acid 3-*O*-(6′-*O*-galloyl)-β-D-glucoside (168 mg) from fraction 4, and **3** (200 mg), chebulagic acid (9.91 g), geraniin (3.45 g), putranjivain A (385 mg), flavogallonic acid bislactone (94 mg), and chebulic acid (187 mg) from fraction 5. The known compounds were identified by comparison with reference compounds or literature data.

Phyllanemblinin A (**1**): off-white amorphous powder; $[\alpha]^{22}_D$ −103.0° (*c* 0.21, MeOH); UV (MeOH) λ_{max} (log ε) 277 (4.61), 330 (4.19) (sh) nm; IR [diffussive reflection (DR)] ν_{max} 3243, 1710, 1616, 1536, 1332, 1209, 1057 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) δ 7.30 (1H, s, H-3″), 7.16 (1H, s, H-3‴), 7.14 (2H, s, galloyl H-2′, 6′), 6.30 (1H, d, *J* = 3.5 Hz, H-1), 5.66 (1H, dd, *J* = 2.5, 3.0 Hz, H-3), 5.12 (1H, dd, *J* = 2.5, 3.5 Hz, H-2), 5.09 (1H, dd, *J* = 1.5, 3.0 Hz, H-4), 4.34 (1H, ddd, *J* = 1.5, 5.5, 6.0 Hz, H-5), 3.98 (1H, dd, *J* = 6.0, 11.5 Hz, H-6a), 3.89 (1H, dd, *J* = 5.5, 11.5 Hz, H-6b); ^{13}C NMR (acetone-d_6, 125 MHz) δ 169.2 (C-7‴), 167.9 (C-7″), 165.3 (galloyl C-7′), 147.2, (C-6‴), 147.1 (C-6″), 146.1 (C-3′, 5′), 144.9 (C-6‴), 144.7 (C-4″), 139.7 (C-4′), 135.0 (C-5″), 133.7 (C-5‴), 120.1 (C-1′), 119.6 (C-2‴), 117.2 (C-2″), 116.1 (C-1″), 115.4 (C-1‴), 114.6 (C-3″), 112.3 (C-3‴), 110.1 (C-2′, 6′), 93.3 (C-1), 79.3 (C-5), 76.5 (C-2), 73.4 (C-4), 63.0 (C-6), 62.3 (C-3); FABMS *m/z* 615 [M − H]$^-$ (30); *anal.* C 47.96%, H 3.82%, calcd for $C_{27}H_{20}O_{17}$·7/2H_2O, C 47.73%, H 4.00%.

Preparation of 1. A mixture of furosin (**8**) (100 mg) in pyridine (0.1 mL) and acetonitrile (2.4 mL) was heated at 80 °C for 2 h. After added 5% HCl (1 mL), the mixture was applied to a Sephadex LH-20 column (H_2O, 60−100% MeOH) to yield a product (40.3 mg), which was identical with **1** by $[\alpha]_D$ and ^{1}H and ^{13}C NMR comparisons.

Phyllanemblinin B (2): white amorphous powder; $[\alpha]^{22}_D$ −39.5° (*c* 0.18, MeOH); UV (MeOH) λ_{max} (log ε) 278 (4.24) nm; CD (EtOH) λ_{max} (Δε) 230 (−22.8), 267 (+19.1), 295 (−16.5) nm; IR (DR) ν_{max} 3364, 1713, 1613, 1447, 1317, 1192, 1036 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) δ 7.38 (2H, s, HHDP H-3″), 7.12 (2H, s, galloyl H-2′, 6′), 6.94 (1H, s, HHDP H-3‴), 6.11 (1H, d, *J* = 6.0 Hz, H-1), 5.33 (1H, dd, *J* = 6.0, 1.0 Hz, H-2), 4.88 (1H, dd, *J* = 4.0, 1.0 Hz, H-4), 4.38 (1H, br d, *J* = 4.0 Hz, H-3), 4.37 (1H, br t, *J* = 5.5 Hz, H-5), 3.90 (1H, dd, *J* = 5.5, 11.5 Hz, H-6a), 3.85 (1H, dd, *J* = 5.0, 11.5 Hz, H-6b); ^{13}C NMR (acetone-d_6, 125 MHz) δ 168.6 (HHDP C-7″), 168.2 (HHDP C-7‴), 165.4 (galloyl C-7′), 146.0 (C-3′, 5′), 145.5, 144.7 (C-4‴,6‴), 144.6, 144.5 (C-4″,6″), 139.6 (C-4′), 138.7 (C-5″), 136.0 (C-5‴), 126.5 (C-2‴), 120.9 (C-2″), 119.9 (C-1′), 117.6 (C-1″), 115.7 (C-1‴), 112.7 (C-3″), 109.9 (C-2′, 6′), 107.6 (C-3‴), 92.7 (C-1), 80.8 (C-5), 78.6 (C-2), 72.4 (C-4), 66.6 (C-3), 62.4 (C-6); FABMS *m/z* 633 [M − H]$^-$ (50); *anal.* C 45.75%, H 4.29%, calcd for $C_{27}H_{22}O_{18}$·4H_2O, C 45.90%, H 4.28%.

Preparation of 2. A solution of furosin (**8**) (100 mg) in EtOH (5 mL) was hydrogenated over 5% palladium−carbon (50 mg) at room temperature for 1.5 h. After removal of the catalyst by filtration, the filtrate was concentrated to dryness and then applied to a Sephadex LH-20 column eluting with EtOH to afford a product (13.6 mg), which was shown to be identical with **2** by $[\alpha]_D$ and ^{1}H and ^{13}C NMR comparisons.

Phyllanemblinin C (3): off-white amorphous powder; $[\alpha]^{24}_D$ −26.0° (*c* 0.13, MeOH); UV (MeOH) λ_{max} (log ε) 280 (4.78) nm; IR (DR) ν_{max} 3215, 1738, 1623, 1529, 1445, 1163, 1040

cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) δ 7.16 (2H, s, galloyl H-G$_{2,6}$), 7.13 (1H, s, H-D$_3$), 7.03 (1H, s, HHDP H-A$_3$), 6.68 (1H, s, HHDP H-B$_3$), 6.44 (1H, br s, H-1), 6.03 (1H, br s, H-2), 5.40 (1H, br s, H-4), 5.21 (1H, d, J = 3.5 Hz, H-3), 4.83 (1H, d, J = 2.5 Hz, H-E$_3$), 4.82 (1H, m, H-5), 4.81 (1H, dd, J = 2.5, 12.0 Hz, H-6a), 4.40(1H, dd, J = 7.0, 12.0 Hz, H-6b), 3.73 (1H, td, J = 2.5, 12.0 Hz, H-E$_4$), 2.65 (1H, dd, J = 2.5, 17.5 Hz, H-E$_{5a}$), 1.96 (1H, dd, J = 12.0, 17.5 Hz, H-E$_{5b}$); ^{13}C NMR (acetone-d_6, 75 MHz) δ 173.7 (C-E$_6$), 173.4 (C-E$_7$), 171.0 (C-E$_1$), 168.6 (HHDP C-A$_7$), 165.0 (C-D$_7$), 166.4 (HHDP C-B$_7$), 165.2 (galloyl C-G$_7$), 147.2 (C-D$_4$), 146.6 (C-D$_6$), 145.9 (C-G$_3$, G$_5$), 145.1, 145.3 (C-A$_4$, A$_6$), 144.8 144.5 (C-B$_4$, B$_6$), 139.8 (C-G$_4$), 137.6 (C-B$_5$), 136.3 (C-A$_5$), 135.7 (C-D$_5$), 125.3 (C-A$_2$), 124.4 (C-B$_2$), 120.6 (C-D$_2$), 119.9 (C-G$_1$), 117.2 (C-D$_1$), 117.0 (C-B$_1$), 115.3 (C-A$_1$), 112.1 (C-D$_3$), 110.5 (C-G$_2$, G$_6$), 110.2 (C-B$_3$), 107.8 (C-E2), 107.5 (C-A$_3$), 92.0 (C-1), 73.4 (C-5), 69.7 (C-2), 66.3 (C-4), 63.9 (C-6), 61.3 (C-3), 49.2 (C-E$_3$), 41.5 (C-E$_4$), 30.9 (C-E$_5$); FABMS m/z 969 [M − H]$^-$; *anal.* C 46.80%, H 4.06%, calcd for $C_{41}H_{30}O_{28}$·9/2H$_2$O, C 46.82%, H 3.74%.

Methylation of 3. A mixture of compound **3** (50 mg), dimethyl sulfate (1 mL), and anhydrous potassium carbonate (1 g) in dry acetone (10 mL) was refluxed for 1 h with stirring. After removal of the inorganic compounds by filtration, the filtrate was concentrated to dryness. The residue was applied to a column of silica gel eluting with toluene−acetone (5:1) to give the methyl derivative (**3a**) (39 mg): white amorphous powder, $[\alpha]^{24}_D$ −57.2° (*c* 0.31, CHCl$_3$); IR (DR) ν_{max} 2944, 2844, 1754, 1590, 1464, 1343, 1223, 1180, 1027 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.21 (2H, s, H-G$_{2,6}$), 7.19 (1H, s, H-D$_3$), 6.74 (1H, s, H-A$_3$), 6.67 (1H, s, H-B$_3$), 6.51 (1H, br s, H-1), 5.95 (1H, br s, H-3), 5.41 (1H, br s, H-2), 5.38 (1H, br t, J = 2.0 Hz, H-4), 5.04 (1H, t, J = 11.0 Hz, H-6a), 4.85 (1H, ddd, J = 2.0, 8.0, 11.0 Hz, H-5), 4.78 (1H, d, J = 2.5 Hz, H-E$_3$), 4.45 (1H, dd, J = 8.0, 11.0 Hz, H-6b), 4.12 (3H, s, OMe-D$_5$), 3.97, 3.96, 3.96, 3.95 (each 3H, s, OMe-A$_4$, A$_5$, B$_4$, G$_4$), 3.90 (3H, s, OMe-D$_4$), 3.87 (3H, s, OMe-E$_1$), 3.86 (1H, td, J = 2.5, 11.5 Hz, H-E$_4$), 3.71, 3.69 (each 3H, s, OMe-A$_6$, B$_6$), 3.68 (6H, s, OMe-G$_{3,5}$), 3.63 (3H, s, OMe-E$_2$), 3.61 (3H, s, OMe-E$_6$), 3.23 (3H, s, OMe-B$_4$), 2.46 (1H, dd, J = 2.5, 17.0 Hz, H-E$_{5a}$), 2.07 (1H, dd, J = 11.5, 17.0 Hz, H-E$_{5b}$); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 172.5 (C-E$_6$), 171.8 (C-E$_7$), 168.7 (C-E$_1$), 167.6 (C-A$_7$), 164.6 (C-B$_7$), 164.2 (C-G$_7$), 163.6 (C-D$_7$), 153.3 (C-G$_{3,5}$), 153.2 (C-A$_4$), 152.7, 152.6, 152.5, 152.3 (C-D$_4$, A$_6$, B$_4$, B$_6$), 148.3 (C-D$_6$), 145.3 (C-B$_5$), 145.0 (C-A$_5$), 143.2 (C-G$_4$), 138.1 (C-D$_5$), 128.3 (C-A$_2$), 126.0 (C-B$_2$), 124.2 (C-B$_1$), 123.1 (C-G$_1$), 121.3 (C-A$_1$), 120.1 (C-D$_1$), 119.5 (C-D$_2$), 110.6 (C-E$_2$), 108.8 (C-D$_3$), 107.6 (C-B$_3$), 106.9 (C-G$_{2,6}$), 104.8 (C-A$_3$), 92.6 (C-1), 72.4 (C-5), 67.7 (C-2), 65.0 (C-4), 63.4 (C-6), 61.1, 60.9, 60.8, 60.7, 60.6 (C-3, OMe-D$_5$, A$_6$, B$_6$, A$_5$, B$_5$, G$_4$), 56.5 (OMe-G$_{3,5}$, D$_4$), 56.0 (OMe-A$_4$), 55.3 (OMe-B$_4$), 54.9 (OMe-E$_2$), 53.4 (OMe-E$_1$), 51.7 (OMe-E$_6$), 49.4 (C-E$_3$), 40.0 (C-E$_4$), 29.9 (C-E$_5$); FABMS m/z 1165 [M − H]$^-$ (10); *anal.* C 56.94%, H 5.23%, calcd for $C_{55}H_{58}O_{28}$, C 56.61%, H 5.01%.

Alkaline Treatment of 3a, Followed by Methylation. A solution of **3a** (39 mg) in 5% NaOH [(H$_2$O−MeOH (1:1)) (2 mL) was heated at 70 °C for 30 min. The reaction mixture was acidified with 1 M HCl (10 mL) and extracted with ether three times. The organic layer was dried over Na$_2$SO$_4$, concentrated to dryness, and treated with ethereal diazomethane. After evaporation of the solvent, the syrupy residue was chromatographed over silica gel with toluene−acetone (5:1), furnishing methyl trimethoxybenzoate (**3b**) (7.4 mg), (*R*)-dimethyl hexamethoxydiphenoate (**3c**) (9.1 mg), $[\alpha]^{22}_D$ +15.2° (*c* 0.46, CHCl$_3$), and **3d** (5.1 mg), $[\alpha]^{28}_D$ −65.9° (*c* 0.12, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.11 (1H, s, H-D$_3$), 4.41 (1H, d, J = 2.5 Hz, H-E$_3$), 4.08 (3H, s, OMe-D$_5$), 3.89 (3H, s, OMe-D$_4$), 3.83 (3H, s, OMe-D$_7$), 3.80 (3H, s, OMe-E$_1$), 3.75 (1H, ddd, J = 2.5, 3.5, 11.0 Hz, H-E$_4$), 3.64 (3H, s, OMe-E$_6$), 3.62 (3H, s, OMe-E$_7$), 3.55 (3H, s, OMe-E$_2$), 2.57 (1H, dd, J = 11.0, 17.0 Hz, H-E$_{5a}$), 2.41 (1H, dd, J = 3.5, 17.0 Hz, H-E$_{5b}$); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 173.4 (C-E$_7$), 172.7 (C-E$_6$), 170.0 (C-E$_1$), 166.0 (C-D$_7$), 152.1 (C-D$_4$), 148.9 (C-D$_6$), 137.0 (C-D$_5$), 122.8 (C-D$_1$), 120.7 (C-D$_2$), 110.5 (C-E$_2$), 107.2 (C-D$_3$), 60.6 (OMe-D$_5$), 56.4 (OMe-D$_4$), 54.3 (OMe-E$_2$), 53.1 (OMe-E$_1$), 52.1 (OMe-D$_7$), 51.9 (OMe-E$_7$), 51.7 (OMe-E$_6$), 50.3 (C-E$_3$), 39.8 (C-E$_4$), 33.3 (C-E$_5$); EIMS m/z 470 [M]$^+$.

Phyllanemblinin D (4): white amorphous powder; $[\alpha]^{22}_D$ −7.9° (*c* 0.33, MeOH); UV (MeOH) λ_{max} (log ϵ) 282 (4.16) nm; IR (DR) ν_{max} 3382, 1717, 1614, 1528, 1452, 1376, 1313, 1194, 1067 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) δ 7.21 (2H, s, galloyl H-2′, 6′), 7.15 (1H, s, neochebuloyl H-3″), 5.82 (1H, d, J = 8.0 Hz, H-1), 5.42 (1H, d, J = 1.0 Hz, neochebuloyl H-2‴), 5.28 (1H, t, J = 9.5 Hz, H-3), 3.98 (1H, dd, J = 1.0, 10.5 Hz, H-3‴), 3.91 (1H, dd, J = 2.0, 12.0 Hz, H-6a), 3.83 (1H, dd, J = 8.0, 9.5 Hz, H-2), 3.79 (1H, dd, J = 4.5, 12.0 Hz, H-6b), 3.77 (1H, dd, J = 6.0, 9.5 Hz, H-4), 3.69 (1H, ddd, J = 2.0, 4.5, 6.0 Hz, H-5), 3.22 (1H, ddd, J = 4.5, 10.5, 11.0 Hz, H-4‴), 3.01 (1H, dd, J = 11.0, 17.5 Hz, H-5‴a), 2.49 (1H, dd, J = 4.5, 17.5 Hz, H-5‴b); ^{13}C NMR (acetone-d_6, 75 MHz): δ 174.7, 174.3, 171.2, 165.6, 164.4 (neochebuloyl C-1‴, 6‴, 7‴, 7″, galloyl C-7′), 146.1 (C-3′, 5′, 6″), 143.5 (C-4″), 139.5 (C-5″), 139.2 (C-4′), 120.6 (C-1′), 117.3 (C-2″), 116.7 (C-1″), 110.3 (C-2′, 6′), 109.4 (C-3″), 95.1 (C-1), 79.4 (C-2‴), 78.2 (C-5), 77.7 (C-3), 72.1 (C-2), 68.8 (C-4), 61.9 (C-6), 46.0 (C-3‴), 36.8 (C-4‴), 35.1 (C-5‴); FABMS m/z 669 [M − H]$^-$ (33), 153 (100); *anal.* C 44.95%, H 4.45%, calcd for $C_{27}H_{26}O_{20}$·3H$_2$O, C 44.76%, H 4.45%.

Hydrolysis of 4 with Tannase. A solution of **4** (10 mg) in H$_2$O (1 mL) was incubated with tannase (1 mg) at 37 °C for 2 h. The reaction mixture was separated by chromatography over Sephadex LH-20 with H$_2$O−MeOH to give the hydrolysate (**4a**) (5.4 mg) and gallic acid (2.0 mg). **4a**: pale amorphous powder, $[\alpha]^{24}_D$ +29.9° (*c* 0.57, MeOH); ^{1}H NMR (acetone-d_6, 300 MHz) δ 7.14 (1H, br s, α and β form, neochebuloyl H-3″), 5.40 (1H, br s, α and β form, neochebuloyl H-2‴), 5.38 (1/2H, dd, J = 7.8, 9.9 Hz, α form-glu H-3), 5.25 (1/2H, d, J = 3.9 Hz, α form-glu H-1), 5.12 (1/2H, dd, J = 9.3, 9.6 Hz, β form-glu H-3), 4.70 (1/2H, d, J = 7.8 Hz, β form-glu H-1), 3.22 (1H, m, α and β form H-4‴), 2.97 (1H, dd, J = 10.5, 16.5 Hz, α and β form H-5‴a), 2.44 (1H, br d, J = 16.5 Hz, α and β form H-5‴b).

Phyllanemblinin E (5): white amorphous powder; $[\alpha]^{22}_D$ −8.3° (*c* 0.36, MeOH); UV (MeOH) λ_{max} (log ϵ) 282 (4.22) nm; IR (DR) ν_{max} 3346, 1733, 1618, 1452, 1388, 1348, 1228, 1120, 1081 cm^{-1}; ^{1}H NMR (acetone-d_6, 500 MHz) δ 7.20 (2H, s, galloyl H-2′, 6′), 7.13 (1H, s, neochebuloyl H-3″), 5.78 (1H, d, J = 8.5 Hz, H-1), 5.66 (1H, d, J = 1.0 Hz, neochebuloyl H-2‴), 5.05 (1H, dd, J = 9.5, 10.0 Hz, H-4), 3.90 (1H, dd, J = 9.0, 9.5 Hz, H-3), 3.88 (1H, dd, J = 1.0, 10.5 Hz, H-3‴), 3.79 (1H, J = 2.0, 6.0, 9.5 Hz, H-5), 3.77 (1H, dd, J = 2.0, 12.5 Hz, H-6a), 3.67 (1H, dd, J = 8.5, 9.0 Hz, H-2), 3.63 (1H, dd, J = 6.0, 12.5 Hz, H-6b), 3.14 (1H, ddd, J = 3.0, 10.5, 12.0 Hz, H-4‴), 3.07 (1H, dd, J = 12.0, 17.0 Hz, H-5‴a), 2.37 (1H, dd, J = 3.0, 17.0 Hz, H-5‴b); ^{13}C NMR (acetone-d_6, 75 MHz) δ 174.4, 174.2, 171.3, 165.9, 164.6 (neochebuloyl C-1‴, 6‴, 7‴, 7″, galloyl C-7′), 146.1 (C-6″), 146.0 (C-3′, 5′), 143.4 (C-4″), 139.5 (C-5″), 139.2 (C-4′), 120.5 (C-1′), 117.3 (C-2″), 116.4 (C-1″), 110.2 (C-2′, 6′), 109.3 (C-3″), 95.3 (C-1), 77.4 (C-2‴), 76.4 (C-5), 75.1 (C-3), 74.1 (C-2), 72.0 (C-4), 61.6 (C-6), 45.8 (C-3‴), 37.0 (C-4‴), 34.9 (C-5‴); FABMS m/z 669 [M − H]$^-$ (20), 517 (7), 153 (100); *anal.* C 44.56%, H 4.43%, calcd for $C_{27}H_{26}O_{20}$·3H$_2$O, C 44.76%, H 4.45%.

Hydrolysis of 5 with Tannase. A solution of **5** (10 mg) in H$_2$O (1 mL) was incubated with tannase (1 mg) at 37 °C for 2 h. The reaction mixture was separated by chromatography over Sephadex LH-20 with H$_2$O−MeOH to afford the hydrolysate (**5a**) (5.0 mg) and gallic acid (3.0 mg). **5a**: pale amorphous powder, $[\alpha]^{24}_D$ +7.7° (*c* 0.28, MeOH); ^{1}H NMR (acetone-d_6, 300 MHz) δ 7.13, 7.12 (each 1/2H, s, α and β form neochebuloyl H-3″), 5.59 (1H, br s, α and β form, neochebuloyl H-2‴), 5.21 (1/2H, br s, α form glu H-1), 4.88 (1H, br dd, J = 7.5, 11.1 Hz, α and β form H-3), 4.63 (1/2H, d, J = 8.4 Hz, β form H-1), 4.13 (1H, m, α and β form H-3‴), 3.06 (1H, m, α and β form H-4‴), 2.99 (1H, m, α and β form H-5‴a), 2.32 (1H, br d, J = 15.6 Hz, α and β form H-5‴b). The $[\alpha]_D$ and ^{1}H NMR data of **5a** were identical to those of 4-*O*-neochebuloyl-D-glucose, which was prepared from chebulinic acid by refluxing in H$_2$O for 2 h followed with tannase hydrolysis.

Phyllanemblinin F (6): white amorphous powder; $[\alpha]^{22}_D$ −18.3° (*c* 0.17, MeOH); UV (MeOH) λ_{max} (log ϵ) 281 (4.14) nm; IR (DR) ν_{max} 3343, 1715, 1617, 1528, 1452, 1342, 1204, 1063 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz) δ 7.18(2H, s, galloyl H-2′, 6′), 7.14(1H, s, neochebuloyl H-3″), 5.70 (1H, d, J = 7.8 Hz,

glu H-1), 5.31 (1H, d, J = 0.9 Hz, neochebuloyl H-2‴), 4.64 (1H, dd, J = 1.8, 12.0 Hz, H-6a), 4.34 (1H, dd, J = 4.2, 12.0 Hz, H-6b), 3.93 (1H, dd, J = 0.9, 8.4 Hz, H-3‴), 3.20 (1H, ddd, J = 4.2, 8.4, 11.1 Hz, H-4‴), 2.91 (1H, dd, J = 11.1, 17.1 Hz, H-5‴a), 2.44 (1H, dd, J = 4.2, 17.1 Hz, H-5‴b); ^{13}C NMR (acetone-d_6, 75 MHz) δ 174.3, 174.0, 171.7, 166.0, 164.9 (neochebuloyl C-1‴, 6‴, 7‴, 7″, galloyl C-7′), 146.3 (C-6″), 146.1 (C-3′, 5′), 143.5 (C-4″), 139.6 (C-5″), 139.5 (C-4′), 120.8 (C-1′), 117.6 (C-2″), 116.8 (C-1″), 110.5 (C-2′, 6′), 109.3 (C-3″), 95.7 (C-1), 78.2 (C-2‴), 77.6 (C-5), 75.9 (C-3), 73.6 (C-2), 70.4 (C-4), 64.3 (C-6), 45.8 (C-3‴), 37.0 (C-4‴), 34.9 (C-5‴); FABMS m/z 669 [M − H]$^-$ (32), 153 (100); *anal.* C 46.85%, H 4.38%, calcd for $C_{27}H_{26}O_{20}\cdot 3/2H_2O$, C 46.49%, H 4.19%.

Hydrolysis of 6 with Tannase. A solution of **6** (10 mg) in H_2O (1 mL) was incubated with tannase (1 mg) at 37 °C for 2 h. The reaction mixture was separated by chromatography over Sephadex LH-20 with H_2O−MeOH to afford the hydrolysate (**6a**) (5.5 mg) and gallic acid (2.2 mg). **6a**: pale amorphous powder, $[\alpha]^{24}_D$ +45.0° (*c* 0.20, MeOH); ^{1}H NMR (acetone-d_6, 300 MHz) δ 7.15 (1H, br s, α and β form neochebuloyl H-3″), 5.24(1/2H, br s, α form H-1), 5.18 (1H, br s, α and β form, neochebuloyl H-2‴), 5.16 (1H, dd, J = 4.2, 11.1 Hz, α and β form glu H-6a), 4.62 (2H, br d, J = 11.1 Hz, α and β form H-6b), 4.58 (1/2H, d, J = 7.8 Hz, β form H-1), 3.12 (1H, m, α and β form H-4‴), 2.98 (1H, m, α and β form H-5‴a), 2.38 (1H, br d, J = 17.1 Hz, α and β form H-5‴b).

Acknowledgment. The authors are grateful to Mr. K. Inada and Mr. N. Yamaguchi (Nagasaki University) for NMR and MS measurements. One of the authors (Y.J.Z.) is grateful to the Japanese Government for awarding of the scholarship.

Supporting Information Available: Important HMBC and NOESY correlations of compounds **1**, **3a**, and **3d** (Figures 1−3). This material is available free of charge via the Internet at http://pubs.acs.org.

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NP010370G