Structures and Biogenesis of Rhoipteleanins, Ellagitannins Formed by Stereospecific Intermolecular C–C Oxidative Coupling, Isolated from *Rhoiptelea chiliantha*

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Seven novel ellagitannins named rhoipteleanin A—G were isolated from the fruits of *Rhoiptelea chiliantha* and their structures were unequivocally established on the basis of spectroscopic and chemical evidence. In the molecules of rhoipteleanin A—F, (*S*,*S*)-flavogallonyl esters spanned two glucopyranose moieties; hence, these tannins represent the first dimeric ellagitannins generated by stereospecific intermolecular C–C oxidative coupling between the galloyl and hexahydroxydiphenoyl groups. The change in the ^{1}H-NMR chemical shifts of specific proton signals of 1(*β*)-*O*-galloylpedunculagin, the biogenetic precursor of rhoipteleanin A, in deuterium oxide at various concentrations suggested that the stereochemically regulated hydrophobic interaction between two molecules of the precursor restricts the intermolecular C–C coupling to *S*-biphenyl bond formation.

Key words tannin; *Rhoiptelea chiliantha*; Rhoipteleaceae; polyphenol; hydrophobic association

Rhoiptelea chiliantha DIELS *et* HAND.-MAZZ, the sole species of Rhoipteleaceae, is distributed in southern China and northern Vietnam. Recently, we have reported on the structures of some characteristic constituents of this plant, such as triterpene lignan esters having a dimeric structure,[1] triperpenoids[2] and diarylheptanoids.[3] Although the systematic position of the Rhoipteleaceae has not yet been established, our results chemotaxonomically support the viewpoint of the Takhtajan system of plant classification in which Rhoipteleaceae independently constitutes the order Rhoipteleales.[4] The presence of ellagitannins described in this paper is strong chemotaxonomical evidence for the independence of this family from related Juglandaceae, Myricaceae, Betulaceae and Fagaceae. Here we present a full account of the isolation and structure elucidation of the novel ellagitannins named rhoipteleanins,[5] which are the major phenolic constituents of the fruits of *R. chiliantha*. These tannins are important from the viewpoint of chemotaxonomy, and are unique in terms of the metabolism of hydrolyzable tannins in higher plants. Biogenesis of these tannins and related dimeric ellagitannins is also discussed on the basis of the hydrophobic interaction between two molecules of 1(*β*)-*O*-galloylpedunculagin (**8**),[6] the precursor of rhoipteleanin A.

Results and Discussion

The combined MeOH extract and 70% acetone extract of the dried fruits was partitioned with ethyl ether and ethyl acetate successively, and the aqueous layer was fractionated by MCI gel CHP 20P column chromatography. Each fraction was repeatedly chromatographed on Sephadex LH-20, Bondapak ODS and MCI gel CHP 20P with water containing increasing proportions of MeOH and Avicel cellulose with 2% acetic acid to afford seven new ellagitannins designated rhoipteleanins A (**1**), B (**2**), C (**3**), D (**4**), E (**5**), F (**6**) and G (**7**), along with thirteen known compounds, *i.e.*, flavogallonic acid bislactone (**1c**),[7] 2,3-(*S*)-hexahydroxydiphenoyl(HHDP)-D-glucose,[8] 5-desgalloylpunicacortein A,[9,10] strictinin,[11] pedunculagin,[8] casuariin,[10,11] casuarinin,[10,11] pterocarinin A,[12] 1(*β*)-*O*-galloylpedunculagin (**8**),[6] myricetin 3-*O*-*β*-D-galactopyranoside,[13] myricetin 3-*O*-*α*-L-arabinopyranoside,[14] myricetin 3-*O*-*α*-L-rhamnopyranoside[13] and myricetin 3-*O*-*β*-D-(6′-*O*-galloyl)galactopyranoside[15] which were identified by comparison of spectral data with those of authentic samples or with those reported in the literature. Rhoipteleanin A was the major phenolic constituent of the fruits, and the isolation yield was 0.16%. Rhoipteleanins A (**1**), C (**3**), D (**4**), E (**5**) and G (**7**) were also isolated from the dried leaves.

Structure Elucidation of Rhoipteleanins Rhoipteleanin A (**1**) was obtained as a pale yellow amorphous powder and gave dark blue coloration with $FeCl_3$ reagent. The ^{1}H-NMR spectrum (Table 1) showed nine aromatic singlets including a two-proton signal due to a galloyl group and fourteen aliphatic proton signals, the chemical shifts and large *J* values of which indicated that these signals were attributable to two fully acylated *β*-glucopyranose residues possessing $^4C_1$-conformation. The presence of two glucopyranose moieties was also supported by the analysis of the ^{13}C-NMR spectrum in which the chemical shifts of the glucose moieties were similar to those of **8**. Besides sugar signals, the ^{13}C-NMR spectrum exhibited ten ester carbon signals along with signals due to ten pyrogallol-type aromatic rings, including that of a galloyl group. The acyl groups were determined chemically in the following way: methylation of **1** with $(CH_3)_2SO_4$ and K_2CO_3 in dry acetone gave a permethyl ether, which was hydrolyzed under alkaline conditions and subsequently methylated with CH_2N_2 to afford methyl 3,4,5-trimethoxybenzoate, dimethyl (*S*)-hexamethoxydiphenate (**1a**) ($[\alpha]_D^{15}$ −28.7°)[16] and trimethyl (*S*,*S*)-nonamethylflavogallonate (**1b**) ($[\alpha]_D^{15}$ −29.0°).[16] Taking into account the $[M-H]^-$ peak at *m/z* 1869 in the negative ion FAB-MS of **1**, these spectroscopic and chemical results indicated that one galloyl, three HHDP, and one flavogallonyl groups were attached to two glucopyranose residues through ester linkages in the molecule of **1**.

To determine the location of the ester groups, **1** was partially hydrolyzed in hot water (80 °C, 24 h). The HPLC

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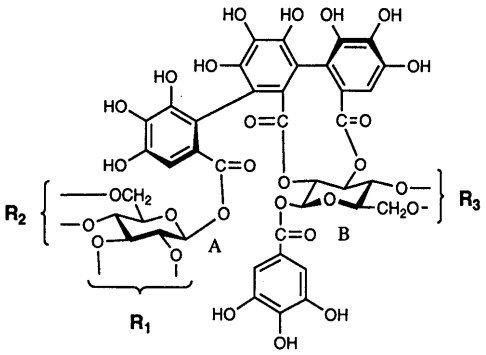
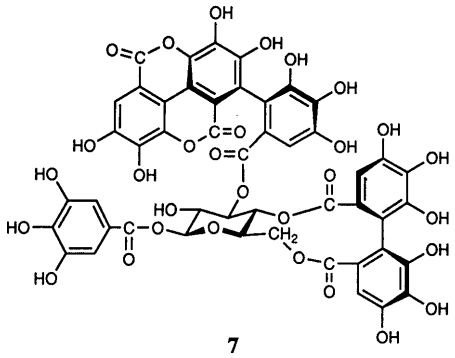


	R_1	R_2	R_3
1	HHDP	HHDP	HHDP
2	H, H	HHDP	HHDP
3	HHDP	H, H	HHDP
4	HHDP	HHDP	H, H
5	HHDP	H, H	H, H
6	H, H	H, H	H, H



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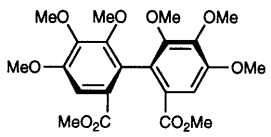
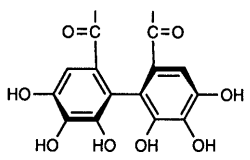
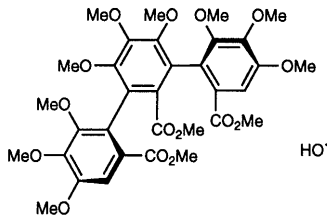


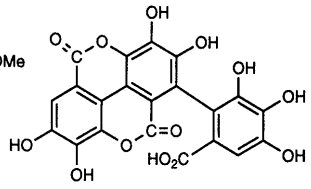
1a

HHDP :





1b



1c

Chart 1

Table 1. ^{1}H-NMR Spectral Data for Rhoipteleanins A—G (**1**—**7**) in Acetone-d_6 + D_2O[a]

	1[b]	**2**[b]	**3**[b]	**4**[b]	**5**[b]	**6**[c]	**7**[c]
Glucose A							
1	5.87 (d, 9)	5.40 (d, 8)	5.84 (d, 8)	5.90 (d, 9)	5.85 (d, 9)	5.37 (d, 8)	5.76 (d, 8)
2	5.06 (t, 9)	3.40 (t, 9)	4.94 (t, 8)	5.08 (t, 9)	4.97 (dd, 9, 10)	3.35—3.45	3.90 (t, 9)
3	5.31 (dd, 9, 10)	3.69 (t, 10)	5.10 (t, 9)	5.31 (t, 10)	5.10 (t, 10)	3.35—3.45	5.19 (t, 9)
4	5.13 (t, 10)	4.77 (t, 10)	3.89 (t, 10)	5.13 (t, 10)	3.89 (t, 10)	3.35—3.45	5.00 (t, 9)
5	4.34 (m)	3.92 (m)	3.65 (m)	4.33 (m)	3.67 (ddd, 3, 6, 10)	3.35—3.45	4.20 (m)
6	5.28 (dd, 5, 13)	5.15 (dd, 6, 13)	3.96 (dd, 2, 12)	5.28 (dd, 6, 13)	3.98 (dd, 3, 12)	3.82 (d, 12)	5.22 (dd, 6, 13)
	3.97 (d, 13)	3.67 (d, 13)	3.83 (dd, 5, 12)	3.98 (d, 13)	3.83 (dd, 6, 12)	3.66 (dd, 5, 12)	3.78 (d, 13)
Glucose B							
1	5.66 (d, 9)	5.62 (d, 8)	5.59 (d, 9)	5.62 (d, 8)	5.55 (d, 9)	5.57 (d, 8)	—
2	4.93 (t, 9)	4.94 (t, 9)	4.91 (t, 9)	4.77 (t, 9)	4.76 (dd, 9, 10)	4.77 (dd, 8, 9)	—
3	5.40 (dd, 9, 10)	5.40 (dd, 9, 10)	5.40 (t, 10)	5.16 (t, 9)	5.16 (t, 10)	5.18 (t, 9)	—
4	5.10 (t, 10)	5.09 (t, 10)	5.10 (t, 10)	3.85 (t, 10)	3.81 (t, 10)	3.82 (t, 9)	—
5	4.34 (m)	4.34 (m)	4.35 (m)	3.63 (m)	3.67 (ddd, 3, 6, 10)	3.68 (m)	—
6	5.28 (dd, 5, 13)	5.27 (dd, 6, 13)	5.27 (dd, 6, 13)	3.87 (dd, 2, 12)	3.89 (dd, 3, 12)	3.90 (d, 12)	—
	3.82 (d, 13)	3.81 (d, 13)	3.82 (d, 13)	3.74 (dd, 5, 12)	3.74 (dd, 6, 12)	3.78 (dd, 6, 12)	—
Aromatic protons							
	6.96 (2H, s)	6.96 (2H, s)	6.94 (2H, s)	6.91 (2H, s)	6.90 (2H, s)	6.93 (2H, s)	7.19 (2H, s)
	6.75 (s), 6.67 (s)	6.73 (s), 6.64 (s)	6.72 (s), 6.64 (s)	6.77 (s), 6.74 (s)	6.79 (s)	6.80 (s)	7.60 (s)
	6.64 (s), 6.61 (s)	6.63 (s), 6.613 (s)	6.62 (s), 6.52 (s)	6.66 (s), 6.54 (s)	6.73 (s)	6.54 (s)	7.20 (s)
	6.53 (s), 6.50 (s)	6.609 (s), 6.50 (s)	6.47 (s), 6.46 (s)	6.47 (s), 6.36 (s)	6.47 (s)		6.63 (s)
	6.46 (s), 6.35 (s)				6.45 (s)		6.39 (s)

a) Assignments were achieved on the basis of ^{1}H–^{1}H COSY, HSQC and HMBC spectra. *b*) Measured at 500 MHz *c*) Measured at 300 MHz.

analysis of the reaction mixture indicated the presence of nine products, among which six were isolated and identified as ellagic acid, 2,3-(*S*)-HHDP-D-glucose and rhoipteleanins C (**3**), D (**4**), E (**5**) and G (**7**) by comparison of their spectral data. The retention times of the remaining three products coincided with those of rhoipteleanins B (**2**) and F (**6**) and flavogallonic acid bislactone (**1c**). The negative ion FAB-MS [*m/z* 1567 $(M-H)^-$] of **2**, **3** and **4** indicated that these compounds were generated by hydrolysis of an HHDP group from **1**. Comparison of the ^{1}H-NMR spectra (Table 1) with that of **1** clearly showed the positions from which the HHDP esters had been removed. The large upfield shift of the H-2 and H-3 signals of glucose A in the spectrum of **2** indicated that an HHDP

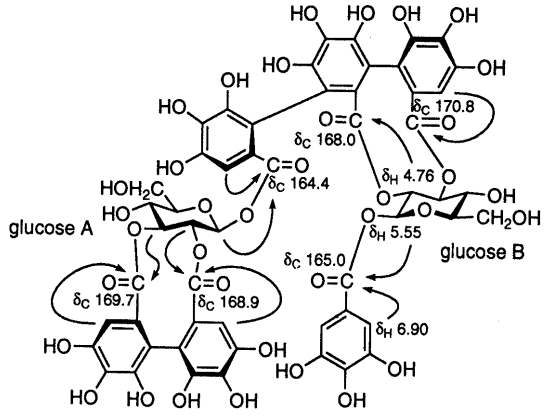


Fig. 1. Important HMBC Correlations (H→C) for **5**

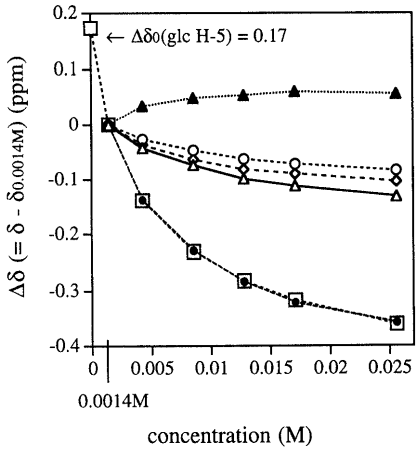


Fig. 2. ^{1}H-NMR Chemical Shift Change of **8** in D_2O at Various Concentrations

○, glc H-1; ●, glc H-5; ◇, glc H-6; △, galloyl-H; ▲, the aromatic proton of the pyrogalloyl ring connected to glucose C-2; □, simulated data for glc H-5 from a hypothetical dimerization with $K = 127\,M^{-1}$. Other proton signals were shifted to upper field with smaller $\Delta\delta$ values ($-0.056\,ppm \leq \Delta\delta \leq -0.022\,ppm$).

group was attached to these positions in the molecule of **1**. Similarly, **3** and **4** were assigned as the products generated by hydrolysis of the HHDP groups at the 4, 6-positions of glucose A and at the 4, 6-positions of glucose B of **1**, respectively. Furthermore, the analogous comparison of the negative ion FAB-MS [**5**: *m/z* 1265 $(M-H)^-$, **6**: *m/z* 963 $(M-H)^-$] and ^{1}H-NMR spectra indicated that hydrolysis of two HHDP groups at the 4, 6-positions of both of the glucose moieties gave **5** and hydrolysis of all of the HHDP groups yielded **6**. The location of the galloyl group was unequivocally confirmed by analysis of the heteronuclear multiple-bond correlation (HMBC) spectrum of **5** (Fig. 1), which showed three-bond long-range couplings between the aromatic proton (δ 6.90) and an ester carbonyl carbon (δ 165.0) and between the ester carbon and the anomeric proton of glucose B (δ 5.55). Since the chemical shifts of aromatic carbons of the HHDP and the flavogallonyl groups are very similar, complete assignments of the carbon signals could not be achieved; however, the correlation between H-2 (δ 4.76) of glucose B and the carboxyl carbon (δ 168.0) which does not correlate with any aromatic proton, indicated that the central ester carbonyl of the flavogallonyl group is attached to the C-2 hydroxy group of glucose B (Fig. 1). On the basis of this spectroscopic and chemical evidence, the structures of rhoipteleanins A—F were concluded to be represented by the formulae **1**—**6**, respectively.

Rhoipteleanin G (**7**) showed an $[M-H]^-$ peak at *m/z* 1085 in the negative ion FAB-MS. The ^{1}H-NMR spectra (Table 1) indicated that this compound has a monomeric structure with an acylated β-glucopyranose in which four hydroxy groups at the C-1, C-3, C-4 and C-6 were acylated. In addition, the appearance of one of the aromatic singlets at lower field (δ 7.60) in the ^{1}H-NMR spectrum and a pair of carboxyl carbon signals at δ 160.4 and 158.6 in the ^{13}C-NMR spectrum was similar to that of flavogallonic acid bislactone (**1c**).[7] Since **7** was also obtained by partial hydrolysis of **1**, the atropisomerism of both of the biphenyl bonds of the HHDP and flavogallonyl groups was deduced to be in the *S* series. Accordingly, rhoipteleanin G was characterized as 1-*O*-galloyl-3-*O*-(*S*)-flavogallonyl-4,6-*O*-(*S*)-HHDP-β-D-glucose (**7**). From the isolation yields (see Experimental) and the results of the partial hydrolysis of **1** in hot water, rhoipteleanins B(**2**)—G(**7**) were deduced to be derived from **1**. It is difficult to rule out the possibility that **2**—**7** were artifacts generated during the drying, storage or extraction and isolation procedures.

Biogenesis of Rhoipteleanin A Although numerous oligomeric ellagitannins have so far been isolated from various families of higher plants, all of them were biogenetically derived by intermolecular oxidative C–O coupling[17] or dehydrative C–C bond formation between the pyrogallol ring and benzylic carbon of *C*-glycosidic ellagitannins.[18] Rhoipteleanin A (**1**) represents the first example of a dimeric ellagitannin generated by stereospecific intermolecular oxidative C–C coupling between the galloyl group of one molecule of 1(β)-*O*-galloylpedunculagin (**8**) and the HHDP group at C-2, 3 of the other molecule of **8**, leading to formation of an (*S*)-biphenyl bond of the flavogallonyl group. The intermolecular C–O and C–C bond formation generating dimeric ellagitannins, including **1**, is probably regulated by enzymes, because the types of dimeric ellagitannins are usually specific to each plant, even if they are derived from the same biogenetic precursors.[17] The stereospecificity of the intermolecular radical coupling in the biogenesis of **1** indicated that the relative orientation of the two molecules of the precursor **8** is stereochemically regulated prior to the coupling. We postulated that the regulation might occur spontaneously by hydophobic self-association[19]; therefore, the behavior of **8** in aqueous solution was examined by ^{1}H-NMR spectroscopy. The ^{1}H-NMR spectrum of **8** in deuterium oxide at various concentrations (at 20 °C) showed a large upfield shift of the glucose H-5 signal and a lowfield shift of the signal due to the aromatic proton of the pyrogallol ring attached to the glucose C-2 with higher concentration (Fig. 2). The remaining proton signals were all shifted up field and the changes in chemical shift were much smaller than that of glucose H-5. On the assumption that these shifts are caused by the association of two molecules of **8** in D_2O, the chemical shift change of glucose H-5 was simulated by a curve-fitting method.[20] The curve obtained by computer-aided calculation was in good agreement with the observed data, as shown in Fig. 2. From this curve, the association constant and the intrinsic chemical shift

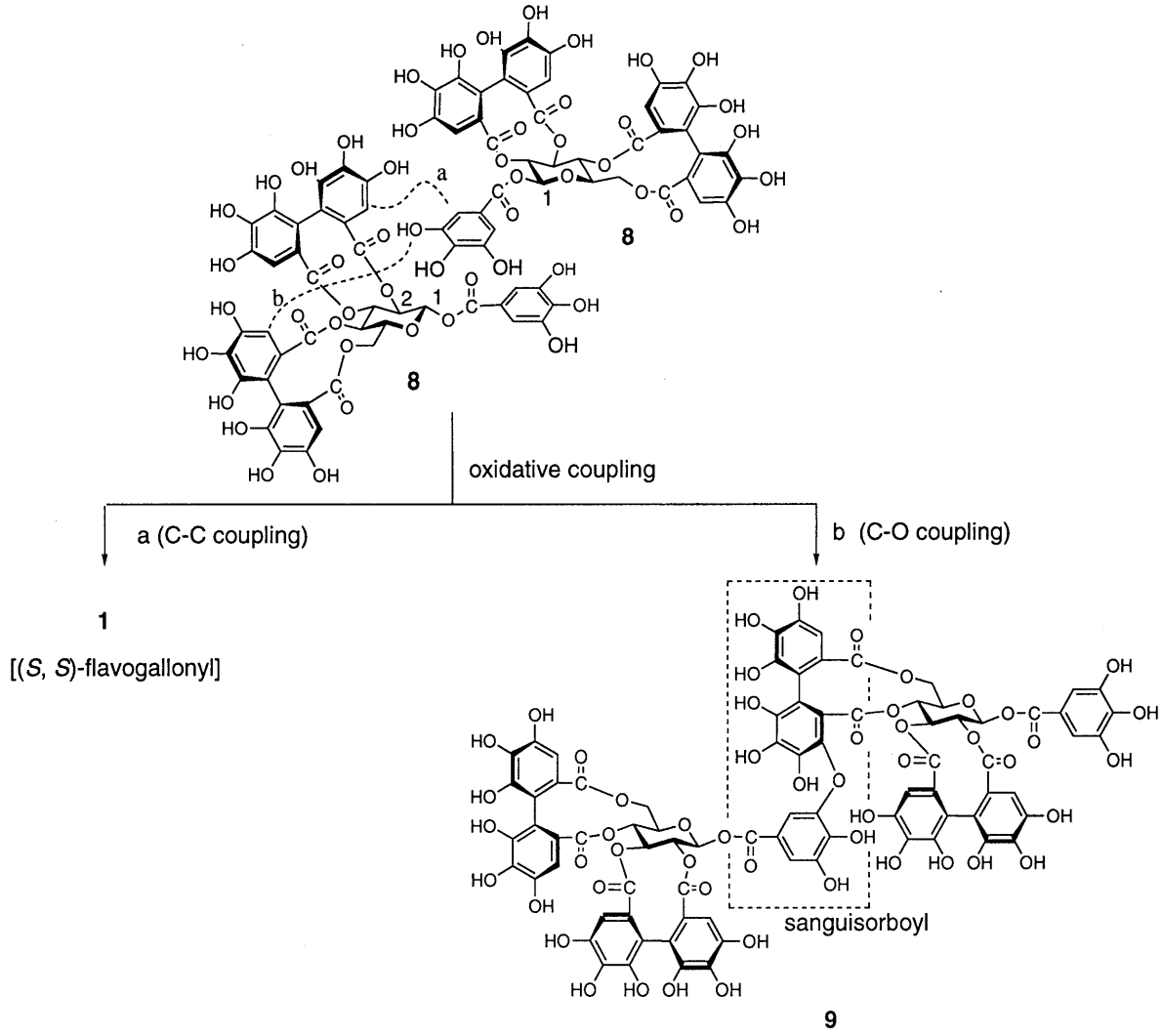


Chart 2. A Model of the Intermolecular Hydrophobic Association of **8** in Water and the Site of Intermolecular Oxidative Couplings Leading to Dimeric Ellagitannin

(δ_0) of the uncomplexed species were estimated to be $127\,M^{-1}$ and 4.56 ppm, respectively. The δ_0 value was comparable to the chemical shift (glc H-5: 4.51 ppm) measured in acetone-d_6. Since it is known that the hydrophobic association of hydrolyzable tannins occurs preferentially at the galloyl group attached to the anomeric position of the glucose core,[21] the shifts of the specific proton signals of **8** (upfield shift of glucose H-5 and lowfield shift of one of the HHDP protons) were considered to be caused by the anisotropic effect of the galloyl group of the other molecule of **8** in the complex. Therefore, the two molecules of **8** seem to be arranged so as to mutually cover the most hydrophobic site of the molecule, *i.e.*, around H-5 of the glucopyranose ring, with the galloyl group in the most effective manner. In this stereochemically regulated association, the galloyl group of **8** is probably situated above glucose H-5 and at the side of the aromatic proton of the pyrogallol ring linked to the glucose C-2 of the other molecule of **8** (Chart 1). If the enzymatic intermolecular C–C coupling between the galloyl group and the pyrogallol ring attached to H-2 occurs in this complex (route a in Chart 2), the resulting biphenyl bond is restricted to *S* configuration, which is in agreement with that of **1**. On the other hand, oxidative C–O coupling between the galloyl group and the pyrogallol ring attached to H-4 (route b) forms a dimer having a sanguisorboyl group, namely lambertianin A (**9**), which has already been isolated from *Rubus lambertianus*[22] (Chart 2).

The absence of the dimeric ellagitannins having HHDP esters spanning two glucopyranose cores is explained by the instability of the HHDP esters, because the possible free rotation around the C–C linkage lead to lactonization with the proximate phenolic hydroxy group liberating ellagic acid.[23] In contrast, the stability of **1** is considered to be attributable to the restriction of free rotation around the newly formed C–C bond caused by fixation of the aromatic ring of the HHDP group attached to the C-2 position of the bulky 1-*O*-galloyl-*β*-D-glucopyranose moiety, as well as the steric interaction between the two closely arranged ellagitannin units. This steric hindrance is also suggested by the observation of the strong shielding of the anomeric protons by the flavogallonyl moiety: the anomeric proton signals appear at significantly higher field (δ 5.87 and 5.66) compared with those of the biogenetic precursor, **8** (δ 6.22).

Experimental

Optical rotations were measured with a JASCO DIP-370 digital polarimeter. Analytical HPLC was performed on a Tosoh apparatus equipped with a CCPM solvent delivery system, UV-8000 spectrometer (280 nm) and a Cosmosil $5C_{18}$-AR (Nacalai Tesque Inc.) column (4.6 mm i.d. × 250 mm) (mobile phase, acetonitrile–50 mM phosphoric acid, gradient elution from 5→25% acetonitrile (40 min); flow rate, 0.8 ml/min). Column chromatographies were performed with Sephadex LH-20 (25—100 μm, Pharmacia Fine Chemical Co. Ltd.), MCI-gel CHP 20P (75—150 μm, Mitsubishi Chemical Industries, Ltd.), Chromatorex-ODS (100 μm, Fuji Sylysia), Bondapak ODS (37—55 μm, Waters), TSK-gel Toyopearl HW-40F (30—60 μm, Tosoh Co.), Avicel Cellulose (Funakoshi) and Silica gel 60 (Merck). Thin layer chromatographies were performed on precoated Silica gel 60 F_{254} plates (0.2 mm thick, Merck) with benzene–ethyl formate–formic acid (1 : 7 : 1 or 1 : 5 : 2, v/v) and precoated cellulose (0.1 μm thick, Merck) with 2% AcOH, and spots were detected by ultraviolet (UV) illumination and by spraying 2% ethanolic $FeCl_3$ reagent or 5% H_2SO_4, followed by heating. Negative and positive FAB-MS were recorded on a JEOL JMX DX-303 spectrometer with glycerol or *m*-nitrobenzyl alcohol as a matrix. ^{1}H- and ^{13}C-NMR spectra were obtained with Varian Unity Plus 500 and Varian Gemini 300 spectrometers operating at 500 and 300 MHz for ^{1}H, and 125 and 75 MHz for ^{13}C, respectively; coupling constants are given in hertz, and chemical shifts are reported in parts per million on the δ scale from internal tetramethylsilane unless otherwise stated.

Isolation. a) From the Fruits The air-dried fruits (495 g) were extracted with MeOH and then 70% acetone. The extracts were combined and the organic solvent was evaporated under reduced pressure. The resulting aqueous solution was partitioned with Et_2O and EtOAc successively to afford the Et_2O extract (24.0 g), the EtOAc extract (9.0 g) and the aqueous extract (26.4 g). The H_2O layer was chromatographed on MCI gel CHP 20P [0—100% MeOH—acetone–H_2O (1 : 1)] to give five fractions: Fr. 1 (1.6 g), Fr. 2 (3.8 g), Fr. 3 (2.0 g), Fr. 4 (4.1 g) and Fr. 5 (4.9 g). Fr. 1 was applied to a column of Sephadex LH-20 with 0—10% MeOH to afford 2, 3-(*S*)-HHDP-glucose (92 mg) and 5-desgalloyl punicacortein A (22 mg). Fr. 2 was separated by Bondapak ODS chromatography (0—50% MeOH) to furnish rhoipteleanin D (**4**) (185 mg), rhoipteleanin E (**5**) (124 mg) and rhoipteleanin F (**6**) (13 mg). Chromatography of Fr. 3 on Sephadex LH-20 with 50—100% MeOH to afford casuariin (12 mg) and pterocarinin A (13 mg). Separation of Fr. 4 by repeated chromatography on Sephadex LH-20 (60—100% MeOH), Avicel cellulose (2% acetic acid) and Bondapak ODS (0—40% MeOH) gave strictinin (114 mg), pedunculagin (112 mg), flavogallonic acid bislactone (**1c**) (103 mg), casuarinin (343 mg), rhoipteleanin A (**1**) (768 mg), rhoipteleanin B (**2**) (29 mg) and rhoipteleanin C (**3**) (60 mg). Fr. 5 was subjected to Sephadex LH-20 chromatography [60—100% MeOH—acetone–H_2O (1 : 1)] to afford myricetin 3-*O*-β-D-galactopyranoside (280 mg), myricetin 3-*O*-α-L-arabinopyranoside (12 mg), 1(β)-*O*-galloyl-pedunculagin (**8**) (32 mg) and rhoipteleanin G (**7**) (300 mg).

b) From the Leaves The air-dried leaves (510 g) were extracted and partitioned in a manner similar to that described for the fruits to give an Et_2O layer (30.0 g), EtOAc layer (31.0 g) and H_2O layer (51.3 g). The EtOAc layer was subjected to MCI gel CHP 20P chromatography (0—100% MeOH). The fractions eluted with 20—60% MeOH were applied to a column of Sephadex LH-20 (40—100% MeOH) to afford myricetin 3-*O*-β-D-galactopyranoside (39 mg) and myricetin 3-*O*-α-L-rhamnopyranoside (535 mg). The H_2O layer was chromatographed over Sephadex LH-20 (0—100% MeOH) to give four fractions: Fr. 1 (16.0 g), Fr. 2 (25.5 g), Fr. 3 (4.2 g) and Fr. 4 (5.7 g). Chromatography of Fr. 3 over MCI gel CHP 20P (0—50% MeOH) yielded rhoipteleanin C (**3**) (152 mg), rhoipteleanin D (**4**) (93 mg), pedunculagin (400 mg) and myricetin 3-*O*-β-D-(6′-*O*-galloyl)-galactopyranoside (96 mg). Fr. 4 was separated by the chromatographies over Chromatorex ODS (0—40% MeOH) and Bondapak ODS (0—60% MeOH) to furnish casuarinin (39 mg), rhoipteleanins A (**1**) (105 mg), E (**5**) (82 mg) and G (**7**) (165 mg).

Rhoipteleanin A (1) A pale yellow amorphous powder, $[\alpha]_D^{15}$ +59.6° (c=0.3, MeOH). *Anal.* Calcd for $C_{82}H_{54}O_{52}\cdot 7H_2O$: C, 49.31; H, 3.43. Found: C, 49.42; H, 3.66. Negative FAB-MS *m/z*: 1869 $(M-H)^-$. ^{1}H-NMR [500 MHz, acetone-d_6+D_2O] δ: 6.96 (2H, s, galloyl), 6.75 (1H, s, glc A-4, 6-HHDP-H-3′), 6.67 (1H, s, flavogallonyl-H-3), 6.64 (1H, s, glc B-4, 6-HHDP-H-3′), 6.61 (1H, s, glc B-4, 6-HHDP-H-3), 6.53 (1H, s, glc A-4, 6-HHDP-H-3), 6.50 (1H, s, flavogallonyl-H-3″), 6.46 (1H, s, glc A-2, 3-HHDP-H-3), 6.35 (1H, s, glc A-2, 3-HHDP-H-3′), glucose protons: see Table 1. ^{13}C-NMR [125 MHz, acetone-d_6+D_2O] δ: 170.4 (flavogallonyl-7″), 169.4 (glc A-2, 3-HHDP-7′), 168.6 (glc A-2, 3-HHDP-7), 168.24 (glc B-4, 6-HHDP-7′), 168.19 (glc A-4, 6-HHDP-7′), 168.0 (glc A-4, 6-HHDP-7), 167.9 (glc B-4, 6-HHDP-7), 167.4 (flavogallonyl-7′), 164.6 (galloyl-7), 164.0 (flavogallonyl-7), 145.6 (2C, galloyl-3, 5), 145.4, 145.3 (2C), 145.22 (2C), 145.19, 145.12, 145.06, 144.8, 144.50, 144.48, 144.42, 144.38 (3C), 144.27, 144.19, 144.0 (flavogallonyl-4, 4′, 4″, 6, 6′, 6″, HHDP-4, 4′, 6, 6′), 139.5 (galloyl-4), 138.6 (flavogallonyl-5), 137.1 (flavogallonyl-5″), 136.67, 136.58, 136.5, 136.4, 136.3, 136.2, 135.9 (HHDP-5, 5′, flavogallonyl-5′), 127.7, 126.28, 126.24 (2C), 125.9, 125.7, 125.6, 125.5 (flavogallonyl-2, 2″, HHDP-2, 2′), 119.6 (galloyl-1), 119.3 (flavogallonyl-2′), 118.1 (flavogallonyl-1), 116.2, 116.1, 115.8, 115.7, 115.3, 115.0, 114.6, 114.3, 114.2 (flavogallonyl-1″, 1′, 3″, HHDP-1, 1′), 111.2 (flavogallonyl-3), 110.5 (galloyl-2, 6), 108.4 (glc A-4, 6-HHDP-3′), 108.0 (glc B-4, 6-HHDP-3′), 107.9 (flavogallonyl-3″), 107.7 (glc A-2, 3-HHDP-3), 107.6 (glc B-4, 6-HHDP-3), 107.5 (glc A-4, 6-HHDP-3), 107.2 (glc A-2, 3-HHDP-3′), 92.0 (glc B-1), 91.8 (glc A-1), 77.4 (2C, glc A-3, glc B-3), 75.7 (glc B-2), 75.6 (glc A-2), 73.4 (glc A-5), 73.1 (glc B-5), 69.1 (2C, glc-A-4, glc B-4), 63.1 (glc B-6), 63.0 (glc A-6). Assignments were achieved on the basis of ^{1}H–^{1}H correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC) and HMBC spectra.

Methylation Followed by Methanolysis A mixture of **1** (100 mg), dimethyl sulfate (2 ml), and potassium carbonate (2 g) in dry acetone (25 ml) was heated under reflux for 3 h with stirring. After removal of the inorganic salts by filtration, the filtrate was concentrated under reduced pressure, and subjected to silica gel chromatography. Stepwise elution with benzene containing increasing proportions of acetone furnished a methyl ether as a white amorphous powder (52 mg), $[\alpha]_D^{15}$ −14.2° (c=0.7, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.17 (2H, s), 6.81, 6.75, 6.72, 6.70, 6.69, 6.65, 6.63, 6.47 (each 1H, s), 5.62 (1H, d, J=9 Hz), 5.54 (1H, d, J=9 Hz), 4.02, 4.003, 3.996, 3.952, 3.947, 3.937, 3.909, 3.906, 3.896, 3.885, 3.87, 3.85, 3.82, 3.809, 3.804, 3.78, 3.76, 3.75, 3.74, 3.71, 3.69, 3.67, 3.64, 3.61, 3.55, 3.088 (totally 30 methyls). The methyl ether (18 mg) was subsequently hydrolyzed with 5% NaOH in MeOH–H_2O (3 : 1, v/v, 4 ml) at 80 °C for 2 h. The mixture was acidified with 1 M HCl and extracted with ether. The ether layer was treated with ethereal diazomethane and separated by silica gel column chromatography. Elution with benzene–acetone (97 : 3—91 : 9) afforded methyl trimethoxybenzoate (3 mg), dimethyl hexamethoxydiphenate (**1b**) (4 mg), colorless syrup, $[\alpha]_D^{15}$ −28.7° (c=0.3, $CHCl_3$) and trimethyl nonamethylflavogallonate (**1c**) (4 mg), colorless syrup, $[\alpha]_D^{15}$ −29.0° (c=0.2, acetone), ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.27 (2H, s), 3.94, 3.91, 3.79, 3.69, 3.60 (each 6H, s), 3.99, 3.12 (each 3H, s).

Rhoipteleanin B (2) A pale yellow amorphous powder, $[\alpha]_D^{15}$ +33.3° (c=0.7, MeOH). *Anal.* Calcd for $C_{68}H_{48}O_{44}\cdot 7.5H_2O$: C, 47.96; H, 3.79. Found: C, 47.92; H, 3.73. Negative FAB-MS *m/z*: 1568 $(M-H)^-$. ^{1}H-NMR [500 MHz, acetone-d_6+D_2O] δ: 6.96 (2H, s, galloyl), 6.73, 6.64, 6.63, 6.613, 6.609, 6.50 (each 1H, s), glc see Table 1. ^{13}C-NMR [75 MHz, acetone-d_6+D_2O]: δ 170.4, 170.0, 168.4, 168.3, 168.2, 167.9, 166.0, 164.5 (flavogallonyl-7, 7′, 7″, galloyl-7, HHDP-7, 7′), 145.5 (2C, galloyl-3, 5), 145.3 (2C), 145.2 (3C), 145.0 (2C), 144.7, 144.4 (2C), 144.2, (2C), 144.14, 144.07 (flavogallonyl-4, 4′, 4″, 6, 6′, 6″, HHDP-4, 4′, 6, 6′), 139.6 (galloyl-4), 138.3, 137.2, 136.6, 136.4, 136.2, 136.1 (2C) (flavogallonyl-5, 5′, 5″, HHDP-5, 5′), 126.9, 126.5, 126.1 (2C), 125.4, 125.3 (flavogallonyl-2, 2″, HHDP-2, 2′), 119.8 (galloyl-1), 119.4, 117.0, 116.1, 116.0, 115.74, 115.66, 115.3, 114.9, 114.7 (flavogallonyl-1, 1′, 1″, 2′, 3′, HHDP-1, 1′), 112.4 (flavogallonyl-3), 110.6 (galloyl-2, 6), 108.1, 107.81 (2C), 107.75, 107.54 (flavogallonyl-3″, HHDP-3, 3′), 95.9 (glc A-1), 91.7 (glc B-1), 77.2 (glc B-3), 76.1 (glc-B-2), 74.8 (glc A-3), 73.0 (2C, glc A-5, glc-B-5), 72.7 (glc A-2), 72.1 (glc A-4), 69.0 (glc B-4), 63.3 (glc-A-6), 63.0 (glc B-6).

Rhoipteleanin C (3) A pale yellow amorphous powder, $[\alpha]_D^{15}$ +65.0° (c=0.4, MeOH). *Anal.* Calcd for $C_{68}H_{48}O_{44}\cdot 7H_2O$: C, 48.18; H, 3.69. Found: C, 48.35; H, 3.91. Negative FAB-MS *m/z*: 1568 $(M-H)^-$. ^{1}H-NMR [500 MHz, acetone-d_6+D_2O] δ: 6.94 (2H, s, galloyl), 6.72, 6.64, 6.62, 6.52, 6.47, 6.46 (each 1H, s), glc see Table 1. ^{13}C-NMR [75 MHz, acetone-d_6+D_2O] δ: 170.3, 169.6, 168.8, 168.2, 167.9, 167.7, 164.5, 164.1 (flavogallonyl-7, 7′, 7″, galloyl-7, HHDP-7, 7′), 145.5 (2C, galloyl-3, 5), 145.15 (3C), 145.09 (2C) 144.8, 144.7 (2C), 144.4 (2C), 144.2, 144.1 (2C), 144.0 (flavogallonyl-4, 4′, 4″, 6, 6′, 6″, HHDP-4, 4′, 6, 6′), 139.7 (galloyl-4), 138.4, 137.2, 136.6, 136.2 (2C), 136.1, 135.7 (flavogallonyl-5, 5′, 5″, HHDP-5, 5′), 127.5, 126.7, 126.1, 126.0, 125.4, 125.3 (flavogallonyl-2, 2″, HHDP-2, 2′), 119.1 (galloyl-1), 117.9, 116.1 (2C), 115.6, 115.3, 114.7, 114.38, 114.34, 114.13 (flavogallonyl-1, 1′, 1″,

2′, 3′, HHDP-1, 1′), 111.3 (flavogallonyl-3), 110.7 (galloyl-2, 6), 108.0, 107.8, 107.5 (2C), 107.4 (flavogallonyl-3″, HHDP-3, 3′), 91.9 (glc B-1), 91.6 (glc A-1), 80.1 (glc A-3), 78.6 (glc A-5), 77.2 (glc B-3), 75.7 (glc B-2), 75.1 (glc A-2), 73.0 (glc B-5), 69.0 (glc B-4), 67.2 (glc A-4), 63.0 (glc B-6), 61.1 (glc A-6).

Rhoipteleanin D (4) A pale yellow amorphous powder, $[\alpha]_D^{15}$ +68.5° (c=0.5, MeOH). *Anal.* Calcd for $C_{68}H_{48}O_{44}\cdot 6H_2O$: C, 48.70; H, 3.61. Found: C, 49.05; H, 3.98. Negative FAB-MS m/z: 1568 $(M-H)^-$. ^{1}H-NMR [500 MHz, acetone-d_6+D_2O] δ: 6.91 (2H, s, galloyl), 6.77, 6.74, 6.66, 6.54, 6.47, 6.36 (each 1H, s), glc see Table 1. ^{13}C-NMR [75 MHz, acetone-d_6+D_2O] δ: 170.9, 169.5, 168.6, 168.3, 168.0, 167.7, 165.2, 164.1 (flavogallonyl-7, 7′, 7″, galloyl-7, HHDP-7, 7′), 145.3 (2C, galloyl-3, 5), 145.1, 145.0 (3C) 144.9 (2C), 144.7 (2C), 144.2 (3C), 144.1 (3C) (flavogallonyl-4, 4′, 4″, 6, 6′, 6″, HHDP-4, 4′, 6, 6′), 139.4 (galloyl-4), 138.4, 136.8, 136.4, 136.3, 136.2, 136.1, 135.4 (flavogallonyl-5, 5′, 5″, HHDP-5, 5′), 127.9, 125.8, 125.7, 125.6, 125.5, 125.3 (flavogallonyl-2, 2″, HHDP-2, 2′), 119.3 (galloyl-1), 118.8, 117.5, 115.8, 115.6, 114.9, 114.8, 114.2, 114.0, 113.8 (flavogallonyl-1, 1′, 1″, 2′, 3′, HHDP-1, 1′), 111.1 (flavogallonyl-3), 110.4 (galloyl-2, 6), 108.1, 107.6, 107.3 (2C), 107.0 (flavogallonyl-3″, HHDP-3, 3′), 91.6 (2C, glc A-1, glc B-1), 80.0 (glc B-3), 77.8 (glc B-5), 77.2 (glc A-3), 75.3 (glc A-2), 74.9 (glc B-2), 73.1 (glc A-5), 68.9 (glc A-4), 67.2 (glc B-4), 62.9 (glc A-6), 61.2 (glc B-6).

Rhoipteleanin E (5) A pale yellow amorphous powder, $[\alpha]_D^{15}$ +71.9° (c=0.5, MeOH). *Anal.* Calcd for $C_{54}H_{42}O_{36}\cdot 6H_2O$: C, 46.86; H, 4.01. Found: C, 47.13; H,4.27. Negative FAB-MS m/z: 1265 $(M-H)^-$. ^{1}H-NMR [500 MHz, acetone-d_6+D_2O] δ: 6.90 (2H, s, galloyl), 6.79 (1H, s, flavogallonyl-H-3″), 6.73 (1H, s, glc A-2, 3-HHDP-H-3′), 6.47 (1H, s, flavogallonyl-H-3), 6.45 (1H, s, glc A-2, 3-HHDP-H-3), glc see Table 1. ^{13}C-NMR [125 MHz, acetone-d_6+D_2O] δ: 170.8 (flavogallonyl-7″), 169.7 (HHDP-7′), 168.9 (HHDP-7), 168.0 (flavogallonyl-7′), 165.0 (galloyl-7), 164.4 (flavogallonyl-7), 145.3 (2C, galloyl-3, 5), 145.2, 145.1, 144.97, 144.8, 144.7, 144.3, 144.18, 144.14, 144.12, 144.08 (flavogallonyl-4, 4′, 4″, 6, 6′, 6″, HHDP-4, 4′, 6, 6′), 139.6 (galloyl-4), 136.2, 136.1 (HHDP-5, 5′), 138.5, 137.1, 135.6 (flavogallonyl-5, 5′, 5″), 125.9, 125.7 (HHDP-2, 2′), 126.7, 127.5 (flavogallonyl-2, 2″), 119.2 (galloyl-1), 117.7 (flavogallonyl-1), 113.9, 114.1 (flavogallonyl-1′, 3′), 118.9 (flavogallonyl-2′), 115.6 (flavogallonyl-1″), 114.3, 114.8 (HHDP-1, 1′), 110.6 (galloyl-2, 6), 107.4 (HHDP-3), 107.3 (HHDP-3′), 111.4 (flavogallonyl-3), 107.9 (flavogallonyl-3″), 91.6 (2C, glc A-1, glc B-1), 80.1 (glc A-3), 80.0 (glc B-3), 78.6 (glc B-5), 78.1 (glc A-5), 75.3 (glc B-2), 75.1 (glc A-2), 67.3 (glc B-4), 67.2 (glc A-4), 61.3 (glc B-6), 61.1 (glc A-6).

Rhoipteleanin F (6) A pale yellow amorphous powder, $[\alpha]_D^{15}$ +1.9° (c=0.4, MeOH). *Anal.* Calcd for $C_{40}H_{36}O_{28}\cdot 4.5H_2O$: C, 45.94; H, 4.34. Found: C, 46.06; H, 4.11. Negative FAB-MS m/z: 963 $(M-H)^-$. ^{1}H-NMR [300 MHz, acetone-d_6+D_2O] δ: 6.93 (2H, s, galloyl), 6.80, 6.54 (each 1H, s), glc see Table 1. ^{13}C-NMR [75 MHz, acetone-d_6+D_2O] δ: 170.7, 169.5, 166.3, 165.1 (flavogallonyl-7, 7′, 7″, galloyl-7), 145.2 (2C, galloyl-3, 5), 145.3, 144.9, 144.6, 144.4, 144.24, 144.21 (flavogallonyl-4, 4′, 4″, 6, 6′, 6″), 139.5 (galloyl-4), 138.1, 136.9, 135.7 (flavogallonyl-5, 5′, 5″), 127.3, 125.6 (flavogallonyl-2, 2″), 120.1, 119.6, 119.2, 116.9, 115.0, 114.7 (galloyl-1, flavogallonyl-1, 1′, 1″, 2′, 3′), 111.9 (flavogallonyl-3), 110.5 (galloyl-2, 6), 107.7 (flavogallonyl-3″), 95.1 (glc A-1), 91.4 (glc B-1), 80.0 (glc B-3), 77.8 (glc B-5), 77.6 (glc A-5), 76.7 (glc A-3), 75.4 (glc B-2), 72.4 (glc A-2), 69.9 (glc A-4), 67.2 (glc B-4), 61.4 (glc A-6), 61.2 (glc B-6).

Rhoipteleanin G (7) A tan amorphous powder, $[\alpha]_D^{15}$ +8.0° (c=0.4, MeOH). *Anal.* Calcd for $C_{48}H_{30}O_{30}\cdot 4H_2O$: C, 49.75; H, 3.31. Found: C, 49.94; H, 3.65. Negative FAB-MS m/z: 1086 $(M-H)^-$. ^{1}H-NMR [300 MHz, acetone-d_6+D_2O] δ: 7.19 (2H, s, galloyl), 7.60, 7.20, 6.63, 6.39 (each 1H, s), glc see Table 1. ^{13}C-NMR [75 MHz, acetone-d_6+D_2O] δ: 168.25, 168.20, 166.1 (flavogallonyl lactone-7, HHDP-7, 7′), 165.4 (galloyl-7), 160.4, 158.6 (flavogallonyl lactone-7′, 7″), 146.0 (galloyl-3, 5), 139.6 (galloyl-4), 148.4, 146.6, 145.2, 144.9, 144.6, 144.2, 144.1 (2C), 139.6, 139.0, 138.0, 137.3, 136.5, 136.4, 136.3 (flavogallonyl lactone-4, 4′, 4″, 5, 5′, 5″, 6, 6′, 6″, HHDP-4, 4′, 5, 5′, 6, 6′), 126.3, 125.6, 125.1 (flavogallonyl lactone-2, HHDP-2, 2′), 120.7 (galloyl-1), 120.1 (2C), 118.0, 115.7, 115.5, 113.9, 113.6, 109.3 (flavogallonyl lactone-1, 1′, 1″, 2′, 2″, 3′, HHDP-1, 1′), 111.11, 111.05 (flavogallonyl lactone-3, 3″), 110.1 (galloyl-2, 6), 108.4, 107.9 (HHDP-3, 3′), 95.6 (glc-1), 75.1 (glc-3), 72.6 (glc-5), 72.2 (glc-2), 70.6 (glc-4), 63.2 (glc-6).

Partial Hydrolysis of 1 A solution of **1** (320 mg) in H_2O (100 ml) was heated at 80 °C for 24 h. The resulting precipitates were collected by filtration (19 mg). This product was identical with ellagic acid on IR and TLC comparisons. The filtrate was concentrated and subjected to a Sephadex LH-20 column chromatography (H_2O–MeOH) to afford 2, 3-(*S*)-HHDP-D-glucose (13.4 mg), **3** (42 mg), **4** (60 mg), **5** (34 mg), and **7** (22.2 mg), along with recovery of **1** (37 mg). The presence of **2**, **6** and flavogallonic acid bislactone (**1c**) was confirmed by HPLC analysis prior to separation (t_R: **2**, 26.8 min; **6**, 14.8 min; **1c**, 18.3 min).

Measurement of ^{1}H-NMR Chemical Shift Change of 8 in D_2O The ^{1}H-NMR spectra (300 MHz) of **8** in D_2O (0.75 ml) at various concentrations (0.0014 M, 0.0043 M, 0.0086 M, 0.0128 M, 0.0171 M and 0.0256 M) were measured at 20 °C, and the $\Delta\delta$ value (δ value − δ value at 0.0014 M) was calculated. Chemical shifts are reported in parts per million on the δ scale from external sodium 2, 2-dimethyl-2-silapentane-5-sulfonate and corrected by referring to the MeOH signal (0.0005 M). δ (0.0014 M): 7.200 (galloyl-H), 6.809 [HHDP(glc-6)-H], 6.740 [HHDP-(glc-4)-H], 6.662 [HHDP(glc-2)-H], 6.523 [HHDP(glc-3)-H], 6.204 (glc H-1), 5.568 (glc H-3), 5.330 (glc H-4), 5.125 (glc H-2), 4.391 (glc H-5), 4.014 (glc H-6). The other glc H-6 signal overlapped with the glc H-4 signal and its precise δ value could not be measured in this experiment. Assignments of the aromatic proton signals were achieved by analysis of the HMBC spectrum. Simulation of the $\Delta\delta$ value of glucose H-5 and estimation of the association constant for dimerization was achieved by a curve-fitting method (SigmaPlot, Jandel Scientific Corporation) using the equation[20]:

$$\Delta\delta_i=\Delta\delta_0-(\Delta\delta_0-\Delta\delta_{max})\left\{\left(1+\frac{1}{4K[T_0]}\right)-\sqrt{\left(1+\frac{1}{4K[T_0]}\right)^2-1}\right\}$$

where $\Delta\delta_i$=change in chemical shift (ppm) from the δ value at 0.0014 M, $\Delta\delta_{max}$=maximum change in chemical shift (ppm) from the δ value at 0.0014 M, $\Delta\delta_0$=the difference (ppm) between the intrinsic chemical shift of the uncomplexed species (δ_0) and the δ value at 0.0014 M, $[T_0]$=total concentration of tannin (M) and K=dimerization constant=$[T_2]/([T_0]-2[T_2])^2$, where $[T_2]$=concentration of the dimer (M). Values of K, $\Delta\delta_0$ and $\Delta\delta_{max}$ were calculated to be 127 M^{-1}, 0.173 ppm, and −0.616 ppm, respectively.

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