Dimeric and Trimeric Hydrolyzable Tannins from *Quercus coccifera* and *Quercus suber*

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Received September 26, 2001

Three new hydrolyzable tannins, cocciferins D_1 (**1**), D_2 (**2**), and T_1 (**4**), were isolated from the leaves of *Quercus coccifera*. Cocciferin D_2 (**2**) and two additional new tannins, cocciferins D_3 (**3**) and T_2 (**5**), were also obtained from the leaves of *Quercus suber*. Their oligomeric structures were elucidated on the basis of spectroscopic methods and chemical evidence. Compounds **2**, **3**, and **5** were rare oligomers possessing glucose cores with both open-chain and pyranose forms.

The wood, bark, and leaves of *Quercus* species (Fagaceae) are rich sources of ellagitannins and condensed tannins. The aqueous extract of *Quercus coccifera* L. was reported to show potent antimicrobial activity against *Streptococcus aureus*, though no active principles were assigned.[1] The outer bark of *Quercus suber* L., which is a common tree of the Mediterranean region, is well known as a material of stoppers and corkboards used for insulation. The occurrence of triterpenoids,[2,3] lignins,[4] tannins,[4] and phenylpropanoids,[5] besides the major component, suberin, in the cork was reported. However, the tannins and related polyphenols of the leaves of the above two plants have been little investigated. This paper deals with the isolation and structural elucidation of five new hydrolyzable tannins from the leaves of *Q. coccifera* and *Q. suber*.

Results and Discussion

A concentrated 70% aqueous acetone homogenate of the dried leaves of *Q. coccifera* was extracted successively with Et_2O, EtOAc, and *n*-BuOH to give respective extracts and a water-soluble portion. The EtOAc extract was subjected to a combination of column chromatography over Toyopearl HW-40, MCI GEL CHP-20P, and/or YMC-gel ODS-AQ 120-50S to afford a new ellagitannin dimer named cocciferin D_1 (**1**) and nine known tannins and related polyphenols, (+)-catechin, ellagic acid, valoneic acid dilactone, pedunculagin,[6] casuarictin,[6] tellimagrandin II,[7] kaempferol 3-*O*-(6″-*O*-galloyl)-*β*-D-glucopyranoside,[8] and phillyraeoidins A and E.[9] The *n*-BuOH extract was similarly chromatographed to give a new ellagitannin trimer, cocciferin T_1 (**4**), along with acutissimin B[10,11] and phillyraeoidins B and C.[9] A new dimeric ellagitannin, cocciferin D_2 (**2**), and three known *C*-glucosidic ellagitannins, acutissimin B, castalagin,[12,13] and vescalagin,[13,14] were isolated from the water-soluble portion by a similar separation procedure.

The concentrated aqueous acetone homogenate from the leaves of *Q. suber* was treated in a way similar to *Q. coccifera* to yield two new tannins, cocciferins D_3 (**3**) and T_2 (**5**), along with cocciferin D_2 (**2**) and 13 known tannins and related polyphenols. The known compounds were identified as (+)-gallocatechin, quercetin, quercitrin, pedunculagin, acutissimin B, castalagin, vascalagin, tellimagrandin I,[7] castavaloninic acid,[15] isocastavaloninic acid,[16] mongolicain A,[17] and desgalloylstachyurin.[18]

Cocciferin D_1 (**1**) was found to be a dimeric hydrolyzable tannin with the molecular formula $C_{75}H_{56}O_{48}$, as indicated by ESIMS [*m*/*z* 1742 $(M + NH_4)^+$] and NMR analyses. The ^1H NMR spectrum of **1** was complicated owing to the formation of a mixture of α- and *β*-anomers (4:1), and each signal appeared essentially in duplicate. The presence of six galloyl groups and one valoneoyl group was indicated by paired aromatic signals due to six 2H singlets and three 1H singlets. These acyl components were chemically identified by production of methyl tri-*O*-methylgallate (**9**) and trimethyl octa-*O*-methylvaloneate (**10**) upon methylation of **1** with dimethyl sulfate and potassium carbonate in acetone and subsequent methanolysis. Assignment of the sugar proton signals by $^1H-^1H$ COSY revealed the presence of two sets of *C1* glucopyranose cores (Table 1). The signals of C-6 methylene protons on the fully acylated glucose core (glucose I) showed a large difference (Δ*δ* 1.52 ppm; *δ* 5.27 and 3.75) in their chemical shifts, indicating the presence of a valoneoyl group bridged on O-4/O-6.[7,19] It was thus implied that the monomeric constituent units of cocciferin D_1 are 2,3,4,6-tetra-*O*-galloyl-D-glucose (**12**)[20] and tellimagrandin II (**13**). This was supported by close resemblance of the sugar carbon resonances in the ^{13}C NMR spectrum of **1** (Table 1) to those of the proposed monomeric units.[13] On the basis of these data, cocciferin D_1 was deduced to be an ellagitannin dimer, which might be produced biogenetically by intermolecular C−O oxidative coupling between a hexahydroxydiphenoyl (HHDP) group of **12** and a galloyl group of **13** forming a valoneoyl group. The location of the valoneoyl group in **1** was determined by the HMBC spectrum as follows. The H-6 signal (*δ* 5.27, 3.75) on glucose I was correlated through three-bond coupling with an ester carbonyl carbon resonance (*δ* 167.8), which, in turn, showed a correlation with the aromatic proton at *δ* 6.17. This aromatic proton was assigned to H-3′ of the valoneoyl group on the basis of its correlation through two-bond coupling with the signal attributed to the ethereal carbon resonance C-4′ (*δ* 146.7)[19] of the valoneoyl group. The remaining valoneoyl protons (H-3 and H-6″) as well as the other acyl protons were similarly correlated through respective carbonyl carbons with glucose protons as illustrated in the formula (Figure 1). This structural assignment was chemically supported by partial hydrolysis yielding 2,3,6-tri-*O*-galloyl-D-glucose (**14**) and rugosin A (**15**).[21] The atropisomerism of the chiral valoneoyl group was determined to be *S*-series by a large positive Cotton effect at 226 nm ([*θ*] $+1.2 \times 10^5$) in the circular dichroism (CD) spectrum[22] and

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10.1021/np010465i CCC: $22.00
Published on Web 02/19/2002

Table 1. ^{1}H and ^{13}C NMR Spectral Data for the Sugar Moieties of Compounds **1**−**5** in Acetone-d_6 + D_2O[a]

Position	**1** α-anomer δ_H	**1** α-anomer δ_C	**1** β-anomer δ_H	**1** β-anomer δ_C	**2** δ_H	**2** δ_C	**3** δ_H	**3** δ_C	**4** α-anomer δ_H	**4** α-anomer δ_C	**4** β-anomer δ_H	**4** β-anomer δ_C	**5** α-anomer δ_H	**5** α-anomer δ_C	**5** β-anomer δ_H	**5** β-anomer δ_C
Glucose I																
1	6.12 d (8)	93.7			6.12 d (8)	92.1	5.59 d (8)	95.7	5.37 d (4)	91.5	5.01 d (8)	95.1	5.45 d (4)	90.9	4.48 d (8)	96.1
2	5.82 br t (8)	71.6			5.11 dd (8, 10)	75.8	3.49 dd (8, 9)	74.2	5.02 dd (4, 10)	75.5	4.83 dd (8, 10)	78.1	5.01 dd (4, 10)	72.2	5.15 dd (8, 10)	73.9
3	5.83 t (8)	73.1			5.35 t (10)	77.3	3.71 br t (9)	75.7	5.42 t (10)	75.7	5.15 t (10)	77.5	5.78 t (10)	71.2	5.51 t (10)	74.1
4	5.32 t (8)	70.5			5.10 t (10)	68.9	4.93 br t (10)	72.3	4.97 t (10)	69.9	4.97 t (10)	69.4	5.06 t (10)	71.6	5.08 t (10)	71.0
5	4.47 dd (8, 10)	72.6			4.39 dd (7, 10)	73.3	4.05 dd (6, 10)	73.1	4.52 m	67.1	4.13 m	72.2	4.65 m	66.7	4.38 dd (6.5, 10)	71.3
6	5.27 br d (13)	63.0			5.25 dd (7, 13)	62.9	5.20 d (6, 13)	63.5	5.10 dd (7, 13)	63.5	5.15 dd (6, 13)	63.5	5.25 br d (13)	63.1	5.28 dd (6.5, 13)	63.1
	3.75 m				3.84 d (13)		3.79 d, (13)		3.62 dd (1.5, 13)		3.70 dd (1.5, 13)		3.79 d (13)		3.79 d (13)	
Glucose II																
1'	5.52 d (4)	90.8	5.02 d (8)	96.0	5.39 d (5)	66.9	5.33 d (5)	67.2	6.07 d (8)	93.1			5.93 d (8)	6.05 d (8)	91.9	
2'	5.14 dd (4, 10)	72.6	5.21 dd (8, 10)	73.3	4.77 dd (2, 5)	73.5	4.75 dd (2, 5)	73.5	5.51 dd (8, 10)	71.5			5.10 dd (8, 10)	5.10 dd (8, 10)	76.3	
3'	5.98 t (10)	71.3	5.50 t (10)	71.3	4.90 dd (2, 7)	66.1	4.88 dd (2, 7)	66.2	5.78 t (10)	73.3			5.36 t (10)	5.41 t (10)	77.4	
4'	5.68 t (10)	69.3	5.64 t (10)	68.7	5.10 t (7)	68.9	5.10 t (7)	69.0	5.15 t (10)	70.7			5.04 t (10)	5.04 t (10)	68.9	
5'	4.32 d (10)	67.8	4.56 m	70.5	5.54 dd (2, 7)	71.3	5.56 dd (3, 7)	71.4	4.44 m	72.8			4.36 dd (7, 10)	4.19 dd (7, 10)	73.0	
6'	4.75 m	63.2	4.15 m	63.0	5.12 br d (13)	65.3	5.16 dd (3, 13)	65.5	5.25 dd (6, 13)	62.6			5.29 dd (7, 13)	5.29 dd (7, 13)	63.6	
	3.96 d (13)		3.59 d (13)		3.98 d (13)		3.96 d (13)		3.75 d (13)				3.84 d (13)	3.84 d (13)		
Glucose III																
1"									6.08 d (8)	93.4			5.45 d (5)	67.1		
2"									5.55 dd (8, 10)	71.6			4.77 dd (1.5, 5)	73.5		
3"									5.57 t (10)	73.3			4.91 br d (7.5)	66.1		
4"									5.69 t (10)	68.8			5.12 t (7.5)	69.1		
5"									4.21 dd (10, 12)	73.3			5.54 br d (7.5)	71.4		
6"									4.57 m	63.2			5.11 dd (1.5, 13)	65.4		
									4.22 d (12)				4.01 d (13)			

[a] ^{1}H NMR, 500 MHz, coupling constants (J in Hz) in parentheses; ^{13}C NMR, 126 MHz.

by the production of **15** as a partial hydrolysate of **1**. On the basis of these findings, the structure of cocciferin D_1 was established as **1**, which corresponds to a degalloyl derivative of phillyraeoidin A (**6**).

Phillyraeoidins A (**6**), B (**7**), and C (**8**) were first isolated from *Quercus phillyraeoides*.[9] However, the binding sites of the valoneoyl group in the reported structures remained unassigned. The HMBC experiments of these dimers gave three-bond correlations of the valoneoyl protons−carbonyl carbons−glucose protons similar to those in **1**. The orientations of the valoneoyl group in phillyraeoidins A, B, and C were thus established as shown in the formulas **6**, **7**, and **8**, respectively.

Cocciferins D_2 (**2**) and D_3 (**3**) were isolated as light brown amorphous powders, and their molecular formulas (**2**, $C_{82}H_{52}O_{52}$; **3**, $C_{68}H_{46}O_{44}$) were deduced by ESIMS and NMR analyses. The ^{1}H NMR spectra of **2** and **3** exhibited the sugar proton signals characteristic of an open-chain glucose and a glucopyranose with the C_1 conformation, respectively (Table 1). Upon methylation with dimethyl sulfate and potassium carbonate followed by methanolysis, **2** and **3** gave common products, trimethyl octa-*O*-methylvaloneate (**10**) and dimethyl hexamethoxydiphenate (**11**). The ^{1}H NMR spectrum of **2** showed eight 1H singlets in the aromatic region. The signals due to sugar moieties in the ^{1}H and ^{13}C NMR spectra (Table 1) of **2** suggested that **2** is a dimer composed of monomeric units, casuarictin (**16**) and castalagin (**17**). The location of the valoneoyl group in **2** was determined from the HMBC spectrum measured in methanol-d_4 at 45 °C, which showed three-bond correlations δ_H 6.447 (valoneoyl H_H-3)−δ_C 167.8 (carbonyl)−δ_H 5.09 (glucose H-4′); δ_H 7.28 (valoneoyl H_A-6)−δ_C 165.7 (carbonyl)−δ_H 6.12 (glucose H-1); δ_H 6.60 (valoneoyl H_J-3)−δ_C 170.9 (carbonyl)−δ_H 3.99 (glucose H-6′). The location of the other acyl groups was also indicated by HMBC correlations as shown in the formula **2** (Figure 1). Partial hydrolysis of **2** in hot water gave pedunculagin (**18**) as a hydrolysate.

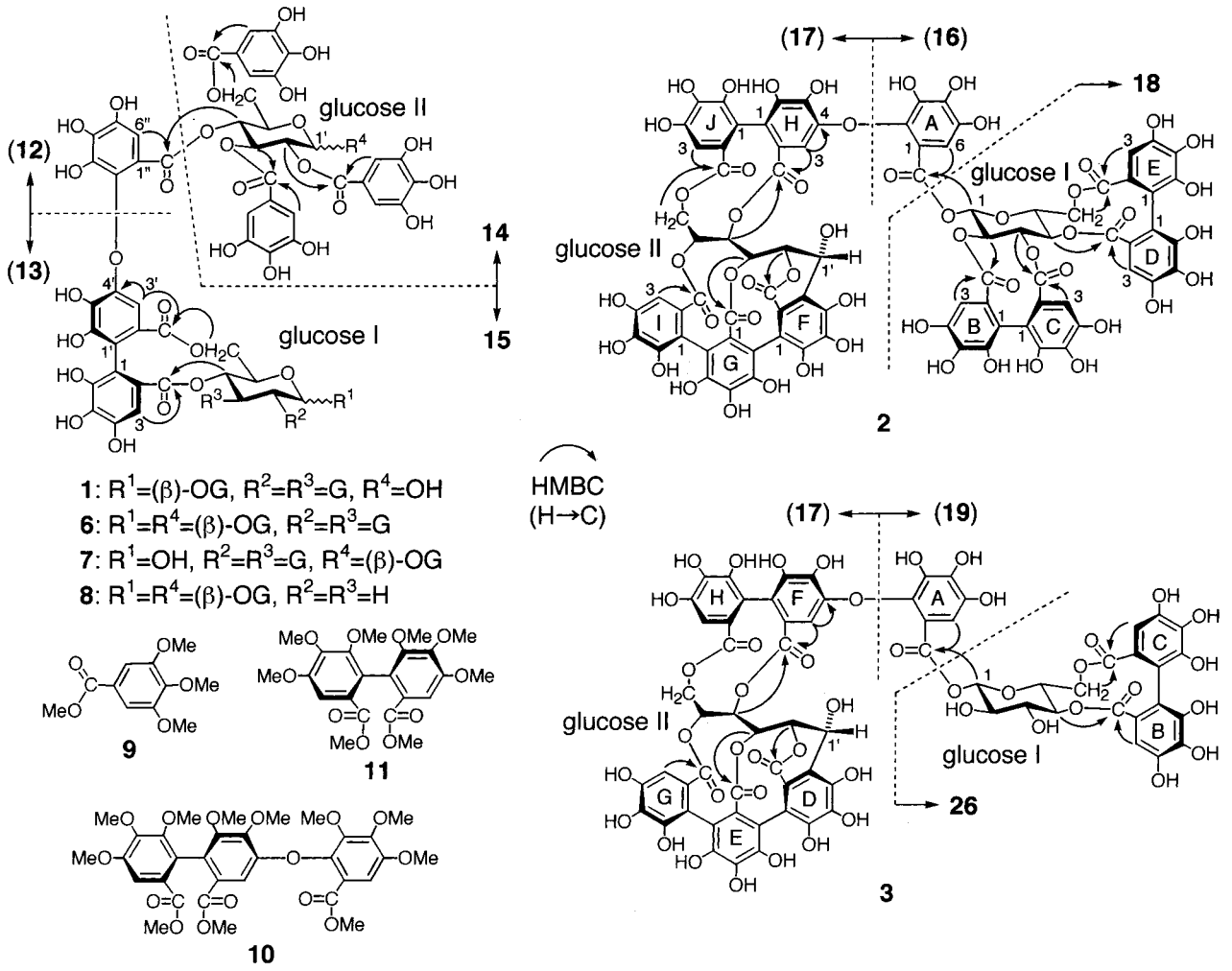

Figure 1. Structures and selected HMBC correlations of **1**−**3** and structures of **6**−**11** (compounds in parentheses mean consistent units). G = galloyl.

The ^{1}H NMR spectrum of **3** was similar to that of **2**, except for the absence of signals due to a second HHDP group. Among the signals of the *C1* glucopyranose core of **3**, the H-2 and H-3 resonances [δ 3.49 (dd, J = 8, 9 Hz) and δ 3.71 (br t, J = 9 Hz)], assigned via ^{1}H−^{1}H COSY, appeared in the high-field region, indicating the absence of acylation at C-2 and C-3 (Table 1). This was substantiated by partial hydrolysis of **3**, which yielded 4, 6-(*S*)-HHDP-D-glucose (**26**). Six aromatic signals (each 1H, s) in the ^{1}H NMR spectrum of **3** were consistent with the presence of a valoneoyl, an HHDP, and a flavogallonyl unit as the acyl groups in the molecule. In addition, the ESIMS spectrum of **3** exhibited an ion peak at *m*/*z* 1584 (M + NH_4)$^+$, which is 302 mass units, corresponding to an HHDP group ($C_{14}H_6O_8$) lower than that of **2** [*m*/*z* 1886 (M + NH_4)$^+$]. The monomeric constituents of **3** were thus assumed to be castalagin (**17**) and strictinin (**19**).[6,13] This was supported by close similarity of the sugar resonances of **3** to those of **17** and **19** in the ^{13}C NMR spectra (Table 1). The binding modes of the acyl groups in **3** were evidenced from the HMBC correlations in a manner similar to **2** (Figure 1). The *S*-configuration of the valoneoyl and HHDP groups in **2** and **3** was confirmed by a large positive Cotton effect around at 235 nm in the CD spectra.[22] On the basis of these data, the structures of cocciferin D_2 and D_3 were established as formulas **2** and **3**.

The trimeric nature of cocciferins T_1 (**4**) and T_2 (**5**) was shown by their ESIMS [**4**, *m*/*z* 2676 (M + NH_4)$^+$; **5**, *m*/*z* 2670 (M + NH_4)$^+$] and retention times which were larger than those of other dimeric hydrolyzable tannins on normal-phase HPLC.[23] Methylation of **4** and **5** and subsequent methanolysis gave commonly **9**, **10**, and **11**, indicating the presence of galloyl, HHDP, and valoneoyl groups in both tannins. In the ^{1}H and ^{13}C NMR spectra of **4**, the resonances in the aliphatic region were similar to those of pedunculagin (**18**) and phillyraeoidin A (**6**), both of which co-occur in *Q. coccifera* (Table 1). The ^{1}H NMR spectrum of **4** displayed six 2H singlets and eight 1H singlets in the aromatic region, the latter of which appeared as duplicate signals (see Experimental Section), suggesting the presence of six galloyl groups, an HHDP group, and two valoneoyl groups in the molecule. On the basis of these data, cocciferin T_1 was presumed to be a trimeric hydrolyzable tannin composed of phillyraeoidin A (**6**) and pedunculagin (**18**). The linkage mode of each acyl unit in **4** was established by partial degradation of **4** in hot water, which afforded phillyraeoidin B (**7**), praecoxins A (**20**) and D (**21**),[24] and 2,3-(*S*)-HHDP-D-glucose (**22**)[25] as the partial hydrolysates (Figure 2). The *S*-configuration at the chiral HHDP and valoneoyl groups in **4** was evident from the production of the above partial hydrolysates and also by the strong positive Cotton effect at 225 and 239 nm in the CD spectrum of **4**. Consequently, the structure of cocciferin T_1 was elucidated as **3**, which is the first trimeric hydrolyzable tannin found in *Quercus* species.

On the basis of the assignments of the ^{1}H NMR signals using the ^{1}H−^{1}H COSY spectrum of **5**, cocciferin T_2 was deduced to be a trimeric hydrolyzable tannin composed of

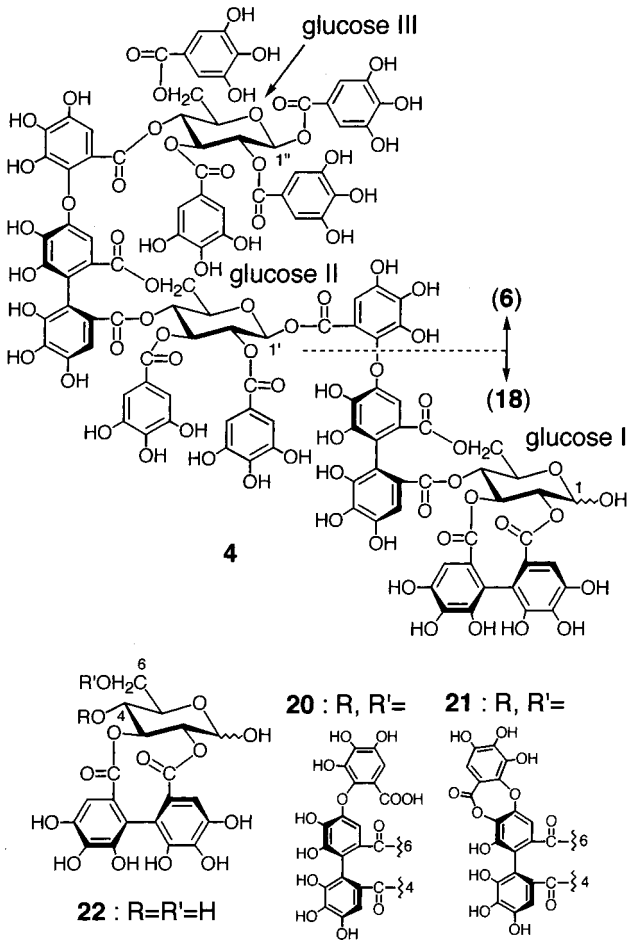

Figure 2. Structures of **4** and its degradation products (compounds in parentheses mean consistent units).

an open-chain glucose and two *C1* glucopyranose cores (Table 1). The ^{1}H NMR spectrum of **5** showed a duplication of some sugar signals owing to an anomer mixture (α:β = 1:4), suggesting that one of two C_1 glucopyranose cores has a free hydroxyl group at the anomeric center. The spectrum also displayed a 2H singlet ascribable to a galloyl group and 11 1H singlets due to one flavogallonyl, two HHDP, and two valoneoyl groups in the aromatic region. The resonances due to the sugar moieties in the ^{1}H and ^{13}C NMR spectra (Table 1) were similar to those of cocciferin D_2 (**2**) and tellimagrandin I (**23**). One of the valoneoyl groups in **5** should thus result from intermolecular C−O coupling between a galloyl group of **23** and an HHDP group of **2**. The location of the valoneoyl group was evidenced from the HMBC spectrum [δ_H 6.16 (valoneoyl H_F-3)−δ_C 169.2 (carbonyl)−δ_H 5.10 (glucose H-2′); δ_H 6.98 (valoneoyl H_A-3)−δ_C 169.4 (carbonyl)−δ_H 5.15 (glucose H-2); δ_H 6.63 (valoneoyl H_G-3)−δ_C 164.9 (carbonyl)−δ_H 5.41 (glucose H-3′)]. The other HMBC correlations led to the structure **5** for this trimer (Figure 3). Chemical evidence for the proposed structure **5** was obtained by partial hydrolysis of **5** in hot water, giving castavaloninic acid (**24**), cornusiin B (**25**),[26] 4,6-(*S*)-HHDP-D-glucose (**26**), gemin D (**27**),[27] and camelliatannin H (**28**),[28] which were identified by HPLC comparison with authentic specimens (Figure 3). The CD spectrum of **5** showed an intensive positive Cotton effect at 232 and 237 nm, establishing the chiralities of biphenyl moieties in **5** to be all *S*-configurations. On the basis of these findings, the structure of cocciferin T_2 was elucidated as **5**. Cocciferin T_2 is the first example of a trimeric hydrolyzable tannin composed of a *C*-glucosidic tannin

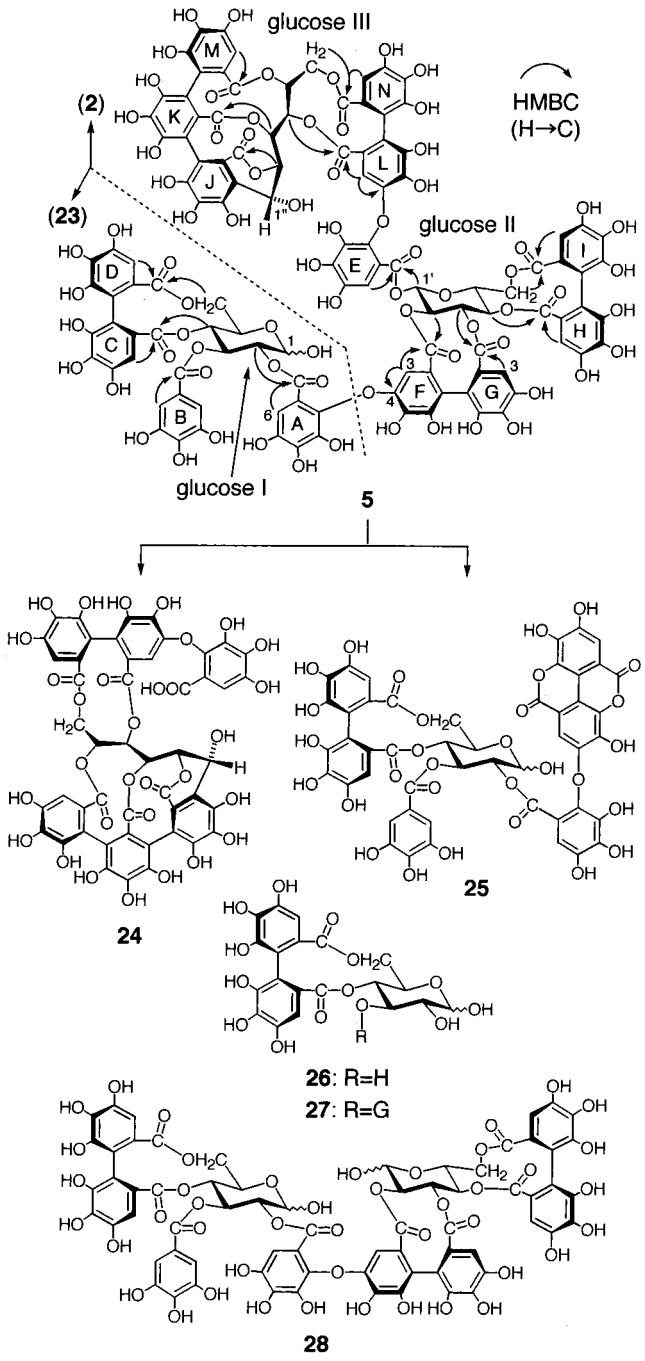

Figure 3. Structures of **5** and its degradation products (compounds in parentheses mean consistent units).

monomer and ellagitannins with a *C1* glucopyranose core.

Cocciferins D_1 (**1**) and T_1 (**4**) as well as phillyraeoidins A, B, and C isolated from *Q. coccifera* have a galloyl moiety of the valoneoyl group at O-4 of one monomer and an HHDP moiety at O-4/O-6 of the other monomer. It is noteworthy that this type of oligomer has been previously found only in *Q. phillyraeoides* (phillyraeoidins A−D)[9] and melastomataceous plants (nobotanins).[13]

Experimental Section

General Experimental Procedures. Optical rotations were measured on a JASCO DIP-1000 polarimeter, UV spectra on a HITACHI U-2001 spectrophotometer, and CD spectra on a JASCO J-720W spectrometer. ESIMS was performed with a Micromass Auto Spec OA-TOF spectrometer using 50%

MeOH containing 0.1% NH_4OAc as a solvent. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-500 (500 MHz for ^1H and 126 MHz for ^{13}C), and chemical shifts are given in δ (ppm) values relative to that of the solvent [acetone-d_6 (δ_H 2.04; δ_C 29.8), methanol-d_4 (δ_H 3.35; δ_C 49.0)] on a tetramethylsilane scale. The standard pulse sequences programmed for the instrument (VXR 500) were used for each 2D measurement. J_{CH} was set at 6 Hz in the HMBC spectra. Normal-phase HPLC was conducted on a YMC-Pack SIL A-003 (YMC Co., Ltd.) column (4.6 i.d. × 250 mm) developed with *n*-hexane−MeOH−tetrahydrofuran−formic acid (60:45:15:1) containing oxalic acid (500 mg/L) (flow rate, 1.5 mL/min; detection, 280 nm) at room temperature. Reversed-phase HPLC was performed on a YMC-Pack ODS-A A-302 (4.6 i.d. × 150 mm) (YMC Co., Ltd.) column developed with 10 mM H_3PO_4−10 mM KH_2PO_4−EtOH−EtOAc (40:40:15:5, solvent A; 42.5:42.5:10:5, solvent B; 47.5:47.5:3:2, solvent C) or 60% aqueous MeOH (solvent D) (flow rate, 1.0 mL/min; detection, 280 nm) at 40 °C. Column chromatography was performed with Diaion HP-20 and MCI GEL CHP-20P (Mitsubishi Kasei Co.), Toyopearl HW-40 (coarse grade) (Tosoh Co.), YMC-GEL ODS AQ 120-50S (YMC Co., Ltd.), Sephadex LH-20 (Pharmacia Fine Chemicals Co., Ltd.), and Mega Bond Elut C_{18} (Varian Inc.).

Plant Materials. *Quercus coccifera* L. and *Q. suber* L. were collected in El Kala National Park, Province of Attaref, Algeria, in April 1996 and November 1995, respectively. These plants were identified by Dr. Kaabache Mohamed, Laboratory of Phytosociology, Faculty of Science, University Ferhat Abbas, Setif, Algeria. Voucher specimens are deposited at the Laboratory of Phytosociology, UFA.

Extraction and Isolation. A homogenate, in 70% aqueous acetone (2L × 3), of the dried leaves (300 g) of *Q. coccifera* was filtered. The filtrate was concentrated and extracted with Et_2O (0.6 L × 4), EtOAc (0.6 L × 5), and *n*-BuOH saturated with water (0.6 L × 5), successively. Fractionations were achieved by monitoring normal- and/or reversed-phase HPLC. A part (4.5 g) of the EtOAc extract (7.5 g) was chromatographed over Toyopearl HW-40 (2.2 i.d. × 59 cm) with aqueous MeOH (20% → 30% → 40% → 50% → 60% → 70% MeOH) → MeOH−H_2O−acetone (3:2:1 → 3:1:2) → 70% aqueous acetone. The 40%, 50%, 60%, and 70% MeOH eluates yielded (+)-catechin (204 mg), pedunculagin (**18**) (66 mg), kaempferol 3-*O*-(6″-*O*-galloyl)-*β*-D-glucopyranose (61 mg), and valoneic acid dilactone (77 mg), respectively. The eluate of MeOH−H_2O−acetone (3:2:1) was further chromatographed over MCI GEL CHP-20P and/or YMC-GEL ODS AQ 120-50S (each 1.1 i.d. × 25 cm) with aqueous MeOH to give cocciferin D_1 (**1**) (87 mg), casuarictin (**16**) (4 mg), tellimagrandin II (**13**) (5 mg), and phillyraeoidins A (**6**) (336 mg) and E (6 mg). The MeOH−H_2O−acetone (3:1:2) eluate was purified by Mega Bond Elut C_{18} with aqueous MeOH to give ellagic acid (15 mg). The rest (3.0 g) of the EtOAc extract was similarly fractionated and purified by a combination of column chromatography over Toyopearl HW-40, MCI GEL CHP-20P, and/or YMC-GEL ODS AQ 120-50S to furnish additional crops of **1** (104 mg), **6** (306 mg), **18** (56 mg), (+)-catechin (123 mg), valoneic acid dilactone (25 mg), and kaempferol 3-*O*-(6″-*O*-galloyl)-*β*-D-glucopyranose (42 mg). A part (8.0 g) of the *n*-BuOH extract (17.1 g) was chromatographed over Diaion HP-20 (6.5 i.d. × 45 cm) with H_2O → aqueous MeOH (10% → 20% → 30% → 40% → 60% MeOH) → MeOH → 70% aqueous acetone. The 20% and 30% MeOH eluates were separately chromatographed over Toyopearl HW-40 (2.2 i.d. × 40 cm) with aqueous MeOH (20% → 30% → 40% → 50% → 60% → 70% MeOH) → MeOH−H_2O−acetone (3:2:1 → 3:1:2 → 1:1:1) → 70% aqueous acetone, to afford acutissimin B (45 mg in total) from 20% and 30% MeOH eluates. The MeOH−H_2O−acetone (3:1:2) eluate from the separation by column chromatography over Toyopearl HW-40 of 40% and 60% MeOH eluates were combined and further purified on MCI GEL CHP-20P and/or YMC-GEL ODS AQ 120-50S with aqueous MeOH to furnish **6** (50 mg), phillyraeoidins B (**7**) (12 mg) and C (**8**) (15 mg), and cocciferin T_1 (**4**) (11 mg). A part (16.0 g) of the aqueous extract (34.7 g) was chromatographed over Diaion HP-20 (6.5 i.d. × 40 cm) with H_2O containing increasing amounts of MeOH in a stepwise gradient mode. The eluates of 10%, 20%, and 30% MeOH were separately subjected to column chromatography over Toyopearl HW-40 (2.2 i.d. × 40 cm), yielding **7** (107 mg), castalagin (**17**) (179 mg in total), and vescalagin (132 mg). The MeOH−H_2O−acetone (1:1:1) fraction from the 30% MeOH eluate was further purified by MCI GEL CHP-20P (1.1 i.d. × 20 cm) column chromatography and/or Mega Bond Elut C_{18} cartridge column chromatography to give cocciferin D_2 (**2**) (26 mg).

The dried leaves (800 g) of *Q. suber* were homogenized in 70% aqueous acetone (2 L × 5), and the concentrated solution (650 mL) was extracted with Et_2O (0.6 L × 5), EtOAc (0.6 L × 8), and *n*-BuOH saturated with water (0.6 L × 8), successively. A part (5.0 g) of the EtOAc extract (9.7 g) was chromatographed over Toyopearl HW-40 (2.2 i.d. × 60 cm) with aqueous MeOH (40% → 50% → 60% → 70% MeOH) → MeOH−H_2O−acetone (3:1:1 → 1:1:1) → 70% aqueous acetone. The 50% and 60% MeOH eluates afforded **18** (210 mg) and tellimagrandin I (**23**) (67 mg), respectively. The eluates of 40% and 70% MeOH were separately subjected to column chromatographies over MCI GEL CHP-20P and/or YMC-GEL ODS AQ 120-50S with aqueous MeOH to give quercetin (10 mg), quercitrin (11 mg), and kaempferol 3-*O*-(6″-*O*-galloyl)-*β*-D-glucopyranose (14 mg) from the former and mongolicain A (35 mg) from the latter. The aqueous extract (50.0 g) was fractionated by column chromatography over Diaion HP-20 (7.0 i.d. × 70 cm) and developed with H_2O and increasing amounts of MeOH [H_2O → 20% MeOH → 40% MeOH → 60% MeOH → MeOH] and 70% aqueous acetone in a stepwise gradient mode. The 20% MeOH eluate was further chromatographed over Toyopearl HW-40 (2.2 i.d. × 60 cm) with aqueous MeOH (20% → 30% → 50% → 60% → 70% MeOH) → MeOH−H_2O−acetone (7:2:1) → 70% aqueous acetone and finally purified on YMC-GEL ODS AQ 120-50S (1.1 i.d. × 45 cm) with aqueous MeOH to yield **17** (13 mg), acutissimin B (5 mg), vescalagin (42 mg), castavaloninic acid (**24**) (11 mg), isocastavaloninic acid (4 mg), desgalloylstachyurin (3 mg), and cocciferin T_2 (**5**) (6 mg). The eluate of 40% MeOH from the Diaion HP-20 column was similarly fractionated and purified on Toyopearl HW-40 (2.2 i.d. × 60 cm) and YMC-GEL ODS AQ 120-50S (1.1 i.d. × 40 cm) with aqueous MeOH to give **2** (57 mg), **3** (10 mg), **5** (67 mg), **17** (5 mg), and **24** (2 mg).

Cocciferin D_1 (1): light brown amorphous powder; $[\alpha]^{23}_D$ +93.8° (*c* 1.0, MeOH); UV (MeOH) λ_{max} (log ϵ) 217 (4.28), 278 (3.89) nm; CD (MeOH) [θ] (nm) $+1.2 \times 10^5$ (226), -2.6×10^4 (256), $+6.3 \times 10^4$ (282); ^1H NMR (acetone-d_6 + D_2O) δ 7.00−7.35 (12H in total, each s, galloyl-H), 6.944, 6.940, 6.53, 6.52, 6.21, 6.17 (3H in total, each s, valoneoyl-H), sugar protons, see Table 1; ^{13}C NMR (acetone-d_6 + D_2O) δ 167.9, 167.8, 167.1, 167.0, 166.6 (2C), 166.1 (2C), 165.2, 165.1, 164.9, 164.8 (ester carbonyl carbons), 146.0, 145.90, 145.87, 145.8, 145.7, 145.6 (each 2C, galloyl C-3, 5), 146.7, 146.6 (1C in total, valoneoyl C-4′), 145.3, 145.2, 145.0 (3C in total, valoneoyl C-5, 5′), 144.6, 144.5 (1C in total, valoneoyl C-5″), 143.5 (valoneoyl C-3″), 140.6, 140.4, 139.8, 139.4, 139.3, 139.2, 139.1, (galloyl C-4), 139.8 (valoneoyl C-4″), 139.4 (valoneoyl C-2″), 136.6, 136.4 (valoneoyl C-5, 5′), 126.1, 125.1 (valoneoyl C-2, 2′), 121.3, 120.2, 120.1, 120.0, 119.7, 119.3, 119.2 (galloyl C-1), 117.1 (valoneoyl C-1′), 115.5 (valoneoyl C-1), 113.5 (valoneoyl C-1″), 110.3 (2C), 110.3 (4C), 110.2 (4C), 110.1 (4C), 110.0 (2C) (galloyl C-2, 6), 110.0 (valoneoyl C-6″), 107.5 (valoneoyl C-3), 104.2 (valoneoyl C-3′), sugar carbons, see Table 1; ESIMS *m*/*z* 1742 $[M + NH_4]^+$; *anal.* C 47.83%, H 3.85%, calcd for $C_{75}H_{56}O_{48}\cdot 9H_2O$, C 47.72%, H 3.92%.

Methylation of 1 Followed by Methanolysis. To a solution of **1** (2 mg) in dry acetone (1 mL) were added Me_2SO_4 (10 μL) and K_2CO_3 (10 mg), and the mixture was stirred overnight at room temperature and then refluxed for 2 h. After centrifugation, the supernatant was evaporated and the reaction mixture was directly methanolyzed in 2% NaOMe in MeOH (1 mL) at room temperature for 8 h. After acidification with acetic acid and removal of the solvent, the residue was further treated with CH_2N_2 in Et_2O (1 mL) for 2 h and the solvent was evaporated. The residue was redissolved in MeOH

and analyzed by reversed-phase HPLC (solvent D), which showed the production of methyl tri-*O*-methylgallate (**9**) and trimethyl octa-*O*-methylvaloneate (**10**).

Partial Hydrolysis of 1. An aqueous solution (1 mL) of **1** (1 mg) was heated in a boiling water bath for 1 h. The reaction mixture was analyzed by normal- and reversed-phase HPLC (solvent B) to show the peaks due to 2,3,6-tri-*O*-galloyl-D-glucose (**14**) and rugosin A (**15**).

Cocciferin D_2 (2): light brown amorphous powder; $[\alpha]^{23}_D$ −64.4° (*c* 1.0, MeOH); UV (MeOH) λ_{max} (log ϵ) 219 (4.38), 283 (3.87) nm; CD (MeOH) [θ] (nm) $+1.7 \times 10^5$ (235), -7.1×10^4 (263), $+1.1 \times 10^4$ (287); ^{1}H NMR (acetone-d_6 + D_2O) δ 7.28 (1H, s, H_A-6), 6.87 (1H, s, H_I-3), 6.67 (1H, s, H_E-3), 6.60 (1H, s, H_J-3), 6.55 (1H, s, H_D-3), 6.45, 6.44 (each 1H, s, H_B-3, H_H-3), 6.42 (1H, s, H_C-3), sugar protons, see Table 1; ^{13}C NMR (acetone-d_6 + D_2O) δ 169.0, 166.1, 163.5 ($C_{A,H,J}$-7), 167.1, 165.7, 164.5 ($C_{F,G,I}$-7), 169.4, 169.1, 168.1, 168.0 (C_{B-E}-7), 146.8 (C_H-4), 145.1 (2C) (C_J-4, 6), 144.9 (C_H-6), 143.4 (C_A-5), 141.4 (C_A-3), 140.4 (C_A-4), 145.3, 144.3 (C_F-3, 5), 146.2, 145.9, 145.0 (2C), 144.9, 144.5 (2C), 144.3 (2C), 144.0, 143.1 (C_{B-E}-4, 6, $C_{G,I}$-3, 5), 137.0, 136.3 (3C) (C_{B-E}-5), 136.4 (C_H-5), 136.0 (C_J-5), 137.8, 137.6, 134.9 ($C_{F,G,I}$-4), 127.7, 126.6, 126.0, 125.9 (2C), 125.6, 125.5, 125.1, 125.0, 122.0 (C_{B-E}-2, $C_{A,H,J}$-2, $C_{F,G,I}$-1), 117.1 (C_H-1), 114.7 (C_J-1), 113.3 (C_A-1), 118.0 (C_F-6), 115.9, 115.7 (2C), 113.0 ($C_{F,G,I}$-2, C_G-6), 115.4, 114.7, 114.5, 114.3 (C_{B-E}-1), 109.7 (C_A-6), 107.6 (C_J-3), 107.5 (C_H-3′), 108.8 (C_I-6), 108.2, 107.4, 107.2, 105.8 (C_{B-E}-3), sugar carbons, see Table 1; ^{1}H NMR (methanol-d_4, 45 °C) δ 7.28 (1H, s, H_A-6), 6.87 (1H, s, H_I-3), 6.67 (1H, s, H_E-3), 6.60 (1H, s, H_J-3), 6.55 (1H, s, H_D-3), 6.450 (1H, s, H_B-3), 6.447 (1H, s, H_H-3), 6.42 (1H, s, H_C-3), 6.12 [1H, d, J = 8.5 Hz, glucose (glc) H-1], 5.58 (1H, m, glc H-5′), 5.42 (1H, t, J = 10 Hz, glc H-3), 5.38 (1H, d, J = 5 Hz, glc H-1′), 5.35 (1H, dd, J = 7, 13 Hz, glc H-6), 5.26 (1H, t, J = 10 Hz, glc H-4), 5.20 (1H, br t, J = 9 Hz, glc H-2), 5.16 (1H, dd, J = 3, 13 Hz, glc H-6′), 5.09 (1H, t, J = 7 Hz, glc H-4′), 4.93 (1H, br d, J = 6 Hz, glc H-3′), 4.80 (1H, dd, J = 1.5, 5 Hz, glc H-2′), 4.33 (1H, m, glc H-5), 3.99 (1H, d, J = 13 Hz, glc H-6′), 3.95 (1H, d, J = 13 Hz, glc H-6); ^{13}C NMR (methanol-d_4, 45 °C) δ 171.5 (C_C-7), 171.0 (C_B-7), 170.9 (C_J-7), 170.2 (C_E-7), 169.7 (C_D-7), 169.0 (C_I-7), 167.8 (C_H-7), 167.3 (C_G-7), 166.9 (C_F-7), 165.7 (C_A-7), 148.3 (C_H-4), 147.9, 147.0, 146.8, 146.74, 146.66 (2C), 146.6, 146.4, 146.2, 145.9 (2C), 145.8, 145.7, 145.62, 145.57, 145.53, 145.47, 145.1, 145.0, 143.1, 141.7, 140.1, 139.0, 138.9, 138.5, 138.4, 138.3, 137.9, 136.9, 129.1, 127.4, 127.2, 127.1, 126.8, 126.7, 126.2, 126.1, 123.0, 119.9, 118.4, 117.4, 117.3, 116.9, 116.3, 116.15, 116.09, 116.0, 114.9, 114.7, 111.2, 110.6, 110.0, 109.23, 109.17, 108.9, 108.7, 107.3, 93.8, 78.7, 77.0, 75.4, 74.9, 73.1, 70.6, 70.3, 68.4, 67.6, 66.7, 64.5; ESIMS *m/z* 1886 $[M + NH_4]^+$; *anal.* C 46.22%, H 3.85%, calcd for $C_{82}H_{52}O_{52}\cdot 15H_2O$, C 46.02%, H, 3.85%.

Methylation of 2 and 3 Followed by Methanolysis. Methylation of **2** and **3** (each 1 mg) was performed in a way similar to that described for **1**. Each reaction mixture was directly methanolyzed in 2% NaOMe in MeOH (1 mL) at room temperature for 8 h. After the usual workup, the reaction mixtures obtained from the individual tannins were analyzed by reversed-phase HPLC (solvent D) to detect common peaks identical with those of authentic compound **10** and dimethyl hexamethoxydiphenate (**11**).

Partial Hydrolysis of 2 and 3. Each aqueous solution (1 mL) of **2** and **3** (each 1 mg) was heated in a boiling water bath for 1 h. The reaction mixtures of **2** and **3** showed peaks identical with those of pedunculagin (**18**) and 4,6-(*S*)-HHDP-D-glucose (**26**), respectively, on reversed-phase HPLC (solvent B).

Cocciferin D_3 (3): light brown amorphous powder; $[\alpha]^{23}_D$ −87.2° (*c* 1.0, MeOH); UV (MeOH) λ_{max} (log ϵ) 216 (4.20), 276 (3.66) nm; CD (MeOH) [θ] (nm) $+1.7 \times 10^5$ (231), -4.2×10^4 (261), $+1.0 \times 10^3$ (286); ^{1}H NMR (acetone-d_6 + D_2O) δ 7.30 (1H, s, H_A-6), 6.79 (1H, s, H_G-3), 6.68 (1H, s, H_B-3), 6.61 (1H, s, H_H-3), 6.49 (1H, s, H_F-3), sugar protons, see Table 1; ^{13}C NMR (acetone-d_6 + D_2O) δ 169.1 (C_H-7), 168.4 (C_C-7), 168.3 (C_B-7), 167.1 (C_G-7), 166.2 (C_F-7), 165.6 (C_E-7), 164.2 (C_A-7), 163.9 (C_D-7), 147.3 (C_F-4), 145.1, 145.0 (C_H-4, 6), 144.9 (C_F-6), 143.5 (C_A-5), 140.8 (C_A-3), 140.6 (C_A-4), 145.3 (2C) (C_D-3, 5), 146.4, 144.7, 144.6, 144.4, 144.3, 144.2, 144.0, 143.1 ($C_{B,C}$-4, 6, $C_{E,G}$-3, 5), 136.4 (C_F-5), 136.1 (C_H-5), 137.7, 137.3, 134.8 ($C_{D,E,G}$-4), 136.8, 136.2 ($C_{B,C}$-5), 129.6, 128.0, 126.7, 126.4, 126.3, 125.5, 125.4, 122.5 ($C_{A,F,H}$-2, $C_{D,E,G}$-1, $C_{B,C}$-2), 118.1 (C_D-6), 117.0 (C_H-1), 114.5 (C_F-1), 112.9 (C_A-1), 116.0, 115.8, 115.5, 115.1 ($C_{D,E,F}$-2, C_E-6), 114.5, 114.4 ($C_{B,C}$-1), 110.0 (C_A-6), 109.1 (C_G-6), 107.8 (C_H-3), 106.3 (C_F-3), 108.2 (2C) ($C_{B,C}$-3), sugar carbons, see Table 1; ESIMS *m/z* 1584 $[M + NH_4]^+$; *anal.* C 47.92%, H 3.97%, calcd for $C_{68}H_{46}O_{44}\cdot 10H_2O$, C 46.74%, H 3.79%.

Cocciferin T_1 (4): light brown amorphous powder; $[\alpha]^{23}_D$ +45.8° (*c* 1.0, MeOH); UV (MeOH) λ_{max} (log ϵ) 220 (4.10), 278 (4.75) nm; CD (MeOH) [θ] (nm) $+1.7 \times 10^5$ (225), $+8.0 \times 10^4$ (239), -3.1×10^4 (260), $+3.1 \times 10^4$ (282); ^{1}H NMR (acetone-d_6 + D_2O) δ 7.19, 7.06, 7.05, 7.01, 7.00, 6.90 (each 2H, s, galloyl H), 7.11, 7.10, 6.961, 6.958, 6.60, 6.59, 6.53, 6.487, 6.485, 6.47, 6.362, 6.357, 6.20, 6.19, 6.16, 6.15 (each 1H, s, HHDP, valoneoyl H), sugar protons, see Table 1; ^{13}C NMR (acetone-d_6 + D_2O) δ 169.4, 169.0, 168.1, 168.0 (2C), 167.9, 167.8, 166.8, 166.5, 166.1, 166.0, 165.2, 164.8, 162.3 (ester carbonyl carbons), 146.8, 146.5 (valoneoyl C-4′), 146.1, 146.0, 145.9, 145.8, 145.7, 145.7, 145.6 (each 2C, HHDP C-3, 5), 145.3 (2C), 145.2, 145.1, 145.0, 144.9, 144.6 (2C), 144.3, 144.2, 143.5, 143.2 (HHDP C-4, 6, 6′, valoneoyl C-4, 4″, 6, 6′, 5″), 141.2, 140.6, 140.5, 140.3, (valoneoyl C-3″, 4″), 140.0, 139.5, 139.4 (2C), 139.2, 139.1 (galloyl C-4), 137.8, 136.5 (2C), 136.3 (2C), 136.2 (valoneoyl C-5, 5′, 2″), 136.9, 136.1 (HHDP C-5, 5′), 126.6, 126.4, 126.2, 125.8, 125.5, 125.3 (HHDP C-2, 2′, valoneoyl C-2, 2′), 121.0, 120.0, 119.9, 119.8, 119.5, 119.4 (galloyl C-1), 117.6, 117.1, 115.8, 115.2, 114.8, 114.2, 113.8, 112.9 (HHDP C-1, 1′, valoneoyl C-1, 1′,1″), 110.4 (2C), 110.2 (4C), 110.1 (2C), 110.0 (4C) (galloyl C-2, 6), 110.2, 110.1 109.9, 107.7, 107.5, 107.3, 105.0 (HHDP C-3, 3′, valoneoyl C-3, 3′, 6″), sugar carbons, see Table 1; ESIMS *m/z* 2676 $[M + NH_4]^+$; *anal.* C 46.60%, H 4.12%, calcd for $C_{116}H_{82}O_{74}\cdot 20H_2O$, C 46.47%, H 4.04%.

Methylation of 4 and 5 Followed by Methanolysis. A mixture of **4** (or **5**) (each 1 mg), Me_2SO_4 (10 μL), and K_2CO_3 (10 mg) in dry acetone (1 mL) was stirred overnight at room temperature and then heated under reflux for 2 h. After removal of inorganic material by centrifugation, the reaction mixture was directly methanolyzed in 2% NaOMe in MeOH (1 mL) at room temperature for 8 h. The reaction mixture was evaporated in vacuo. Reversed-phase HPLC (solvent D) of each residue showed peaks identical with those of the authentic compounds **9**, **10**, and **11**.

Partial Hydrolysis of 4. A solution of **4** (1 mg) in H_2O (1 mL) was heated in a boiling water bath for 1 h. Normal- and reversed-phase HPLC (solvent B) showed peaks due to phillyraeoidin B (**7**), praecoxins A (**20**) and D (**21**), and 2,3-(*S*)-HHDP-D-glucose (**22**).

Cocciferin T_2 (5): light brown amorphous powder; $[\alpha]^{23}_D$ +9.8° (*c* 1.0, MeOH); UV (MeOH) λ_{max} (log ϵ) 220 (4.01), 264 (3.81) nm; CD (MeOH) [θ] (nm) $+1.0 \times 10^5$ (220), $+1.6 \times 10^5$ (232), $+1.7 \times 10^5$ (237), -7.6×10^4 (263), $+2.3 \times 10^4$ (285); ^{1}H NMR (acetone-d_6 + D_2O) δ 7.05 (1H, s, H_N-3), 6.98 (1H, s, H_B-2, 6), 6.98 (1H, s, H_A-6), 6.77 (1H, s, H_M-3), 6.65 (1H, s, H_D-3), 6.63 (1H, s, H_G-3), 6.61 (1H, s, H_E-6), 6.49 (1H, s, H_H-3), 6.45 (1H, s, H_C-3), 6.43 (1H, s, H_L-3), 6.36 (1H, s, H_I-3), 6.16 (1H, s, H_F-3), sugar protons, see Table 1; ^{13}C NMR (acetone-d_6 + D_2O) δ 169.4 (C_A-7), 169.2 (C_F-7), 169.0 (C_N-7), 168.7 (C_I-7), 168.2 (C_D-7), 168.0 (C_C-7), 167.8 (C_H-7), 167.1 (C_B-7), 167.0 (C_M-7), 166.1 (C_L-7), 165.6 (C_K-7), 164.9 (C_G-7), 164.6 (C_J-7), 163.0 (C_E-7), 147.4 (C_F-4), 146.7 (C_L-4), 146.3−143.0 ($C_{J,K,M}$-3, 5, $C_{C,D,H,I}$-4, 5, $C_{A,E}$-4, 6, $C_{F,L}$-6), 144.0, 143.2, ($C_{F,L}$-5), 144.3 (2C) (C_B-3, 5), 141.3, 140.6, 140.4, 140.2 ($C_{F,L}$-3, 4), 139.3 (C_B-4), 137.9, 137.7, 134.9 ($C_{J,K,M}$-4), 137.1−136.2 ($C_{C,D,F,G,H,I,L,M}$-5), 127.8, 126.2 (2C), 126.1, 125.8, 125.7, 125.6 (2C), 125.5, 125.2, 124.9, 122.1 ($C_{C,D,F,G,H,IL,N}$-2, $C_{J,K,M}$-1), 120.2 (C_B-1), 118.0 (C_J-6), 115.9, 115.7 (2C), 113.0 ($C_{J,K,M}$-2, C_K-6), 117.1, 116.5, 115.8, 115.0, 114.1, 113.0 ($C_{A,E,F,G,L,N}$-1), 115.5, 114.6, 114.5, 114.4 ($C_{C,D,H,I}$-1), 110.2 (2C) (C_B-2, 6), 108.2, 107.9, 107.5, 106.9 ($C_{C,D,H,I}$-3), 110.3, 109.9, 108.1, 107.7, 105.9, 103.9 ($C_{H,I}$-6, $C_{F,G,L,N}$-3) (for major peaks), sugar carbons, see Table 1; ESIMS *m/z* 2670 $[M + NH_4]^+$; *anal.* C 47.96%, H 3.69%, calcd for $C_{116}H_{76}O_{74}\cdot 15H_2O$, C 47.64%, H 3.63%.

Partial Hydrolysis of 5. An aqueous solution (1 mL) of **5** (1 mg) was heated in a boiling water bath for 2 h. The reaction mixture was analyzed by reversed-phase HPLC (solvent C) to exhibit the peaks due to castavaloninic acid (**24**), cornusiin B (**25**), 4,6-(*S*)-HHDP-D-glucose (**26**), gemin D (**27**), and camelliatannin H (**28**).

Acknowledgment. The authors are grateful to the SC-NMR Laboratory of Okayama University for the NMR experiments. Thanks are due to Mr. Sari Djamel from El Kala National Park, Algeria, for providing the plants of *Q. coccifera* and *Q. suber*.

Supporting Information Available: Structures of known compounds and ^{13}C NMR spectral data for the sugar moieties of compounds **6**, **12**, **13**, **16**−**19**, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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NP010465I