Tannins and Related Compounds. CIII.¹⁾ Isolation and Characterization of New Monomeric, Dimeric and Trimeric Ellagitannins, Calamansanin and Calamanins A, B and C, from *Terminalia calamansanai* (BLANCO) ROLFE

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Continuing chemical examination on tannins of Combretaceous Plants has led to the isolation of four new ellagitannins, calamansanin and calamanins A, B, and C, together with ten structurally known tannins and related compounds, from the leaves of *Terminalia calamansanai* (BLANCO) ROLFE. On the basis of chemical and spectroscopic evidence, the structures of calamansanin and calamanin A were established as 1,6-di-*O*-galloyl-2,3-*O*-(*S*)-hexahydroxydiphenoyl-4-*O*-(*S*)-flavogallonyl- α -D-glucose (11) and 1-*O*-galloyl-2,3-*O*-(*S*)-hexahydroxydiphenoyl-4,6-*O*-(*S*)-valoneoyl- α -D-glucose (14), respectively, while calamanin B and calamanin C were characterized as dimeric and trimeric ellagitannins 15 and 16, respectively, in which the glucose units are linked through valoneoyl group(s).

Keywords *Terminalia calamansanai*; Combretaceae; ellagitannin; calamansanin; calamanin; flavogallonic acid; valoneic acid; gallic acid; tannin; oxidative phenol coupling

In previous papers, we demonstrated that tannins in *Terminalia catappa* L.²⁾ and *T. chebula* L.¹⁾ (Combretaceae) consist of esters of various phenolcarboxylic acids which are biosynthetically derived by oxidative carbon-carbon and/or carbon-oxygen couplin(s) of galloyl groups attached to the glucose core. These acids include so-called gallic acid dimers [4,4',5,5',6,6'-hexahydroxydiphenic acid, dehydrohexahydroxydiphenic acid, chebolic acid], trimers (flavogallonic acid, tergallic acid), and tetramers (gallagic acid, terchebolic acid). These structural variations in the tannins of the genus *Terminalia* thus prompted us to examine other *Terminalia* species. The present paper describes the results

of the examination of *T. calamansanai* (BLANCO) ROLFE, which grows in the Philippine Islands and is used medicinally as a lithontripic.

The aqueous acetone extract of the fresh leaves was repeatedly chromatographed over Sephadex LH-20 (H₂O-MeOH and EtOH-H₂O-acetone), MCI-gel CHP 20P (H₂O-MeOH), Fuji-gel ODS G3 (H₂O-MeOH) and cellulose (2% AcOH) to yield four new ellagitannins named calamansanin (11) and calamanins A (14), B (15) and C (16), together with ten known tannins [2,3-*O*-(*S*)-4,4',5,5',6,6'-hexahydroxydiphenoyl (HHDP)-D-glucose (1),³⁾ sanguins H-4 (2)⁴⁾ and H-1 (3),⁵⁾ 1-desgalloyleugenin

(4),⁶ eugenin (5),⁷ rugosin A (6),⁸ 1(α)-*O*-galloylpedunculagin (7),⁹ praecoxin A (8),⁸ punicalin (9)¹⁰ and 1(α)-*O*-galloylpunicalagin (10)¹¹].

Calamansanin (11) showed four one-proton singlet signals (δ 7.49, 7.25, 6.48 and 6.44) and two two-proton singlets (δ 7.25 and 6.73) in the proton nuclear magnetic resonance (¹H-NMR) spectrum. The latter signals suggested the presence of two galloyl groups. The observation of seven aliphatic proton signals [δ 6.55 (d, J =4 Hz), 5.69 (t, J =10 Hz), 5.59 (t, J =10 Hz), 5.27 (dd, J =4, 10 Hz), 4.75 (dd, J =2, 13 Hz), 4.48 (br d, J =10 Hz) and 4.08 (dd, J =3, 13 Hz)] indicated the presence of a hexopyranose core and their chemical shifts showed all the hydroxyl groups to be acylated. Furthermore, the coupling constants implied that the hexose moiety is an α -glucopyranose with a ⁴C₁ conformation. The carbon-13 nuclear magnetic resonance (¹³C-NMR) spectrum more clearly showed the presence of the galloyl groups, the α -glucopyranose moiety and one HHDP group (δ 108.0, 108.8, 114.5 and 126.3). The aromatic carbon signals appearing at δ 110.8, 111.3, 118.2 and 123.7 and two signals at δ 158.5 and 159.8 due to δ -lactones were characteristic of a flavogallonyl group. These findings suggested that 11 possesses phenol carboxylic acid moieties analogous to those of terflavin A (12),² except for the presence of one extra galloyl group.

When calamansanin (11) was subjected to partial hydrolysis with tannase, a hydrolysate (13) was obtained, along with gallic acid, and this product was found to be identical with 2,3-*O*-(*S*)-HHDP-4-*O*-(*S*)-flavogallonyl-D-glucose (terflavin C).² On the basis of these spectral and chemical data, calamansanin was characterized as 1,6-di-*O*-galloyl-2,3-*O*-(*S*)-HHDP-4-*O*-(*S*)-flavogallonyl- α -D-glucopyranose (11).

Calamanin A (14) was shown by ¹H-NMR spectral analysis to possess a galloyl (δ 7.22, 2H, s), an HHDP (δ 6.61 and 6.41, each 1H, s) and a valoneoyl group (δ 7.16,

6.48 and 6.28, each 1H, s) in the molecule. The chemical shifts and coupling patterns of the aliphatic signals, which were analogous to those observed in the spectrum of 11, suggested the occurrence of an α -glucopyranose core with ⁴C₁ conformation. However, the chemical shift of one of the glucose C-6 proton signals, appearing at relatively lower field (δ 5.24), was different from that of 11, and this observation was consistent with the presence of the HHDP or valoneoyl group at the glucose 4,6-positions.⁹

On enzymatic hydrolysis with tannase, 14 furnished gallic acid and a hydrolysate, whose ¹H-NMR spectrum and physical data were found to be identical with those of praecoxin A (8).⁸ Since the anomeric signal was observed at lower field (δ 6.55, d, J =4 Hz), the galloyl group was determined to be located at the C-1 position. Thus, the structure of calamanin A was established to be 1-*O*-galloyl-2,3-*O*-(*S*)-HHDP-4,6-*O*-(*S*)-valoneoyl- α -D-glucopyranose (14).

Calamanin B (15) showed, in the negative fast atom bombardment mass spectrum (FAB-MS), the [M-H]⁻ ion peak at m/z 1871, suggesting that 15 is a dimeric hydrolyzable tannin. The ¹H-NMR spectrum exhibited signals arising from α - and β -glucopyranose moieties, and their chemical shifts and coupling constants were closely related to those of 1(α)-*O*-galloylpedunculagin (7) plus eugenin (5). The presence of three galloyl groups in the molecule was apparent from three two-proton singlet signals at δ 7.34, 7.16 and 6.98. The seven aromatic one-proton resonances suggested the presence of two HHDP groups and one valoneoyl ester. The ¹³C-NMR spectrum showed signals due to α - and β -glucopyranose rings, whose chemical shifts agreed fairly well with those of 7 plus 5. These spectral findings implied that 15 has a dimeric structure consisting of 1(α)-*O*-galloylpedunculagin and eugenin moieties linked through a valoneoyl group.

The structure of 15 was conclusively established on the basis of the result of partial hydrolysis of 15 with hot H₂O (80 °C), which yielded almost equimolar amounts of 1-desgalloyleugenin (4) and calamanin A (14). Accordingly, the structure of calamanin B was determined to be as shown by the formula 15.

Calamanin C (16) was strongly adsorbed on Sephadex LH-20 dextran gels, and was only elutable with 50% aqueous acetone. The ¹H-NMR spectrum was somewhat analogous to that of calamanin B (15), but showed more complex signal patterns. In the aromatic region, five two-proton singlets observed between δ 6.99–7.25 indicated the presence of five galloyl groups, while ten one-proton singlets, of which two (δ 7.17 and 7.13) were assignable to the valoneoyl aromatic protons, implied the presence of two valoneoyl and two HHDP groups. Furthermore, the appearance of three anomeric doublets [δ 6.58 (J =4 Hz), 6.10 (J =8 Hz) and 6.06 (J =8 Hz)], together with sugar signals all possessing large coupling constants (J =8–10 Hz), suggested that 16 has one α - and two β -glucopyranose moieties.

Methylation of 16 with dimethyl sulfate and potassium carbonate in dry acetone yielded the tritetracosamethyl ether. Successive methanolysis with sodium methoxide in MeOH gave methyl 3,4,5-trimethoxybenzoate, dimethyl hexamethoxydiphenolate (17) and trimethyl octa-*O*-methylvalonate (18). The negative sign of the specific optical

rotations of the latter two compounds established the atropisomerism to be in the *S*-series.

In contrast to the case of **15**, partial hydrolysis of **16** with hot H_2O gave a complex mixture of products, which was analyzed by reversed-phase high-performance liquid chromatography (HPLC), and peaks corresponding to those of 1-desgalloyleugeniin (**4**), 2,3-di-*O*-galloyl-4,6-*O*-(*S*)-valoneoyl- D -glucose [rugosin B (**19**)]⁸⁾ and calamanin A (**14**) were observed. These results, in combination with the above-mentioned spectral data, established the structure of calamanin C to be as represented by the formula **16**.

Calamanins B (**15**) and C (**16**) are the first examples of dimeric and trimeric ellagitannins to be isolated from Combretaceae plants. Apart from the tannins in other Combretaceae species, the major tannin (0.4% of fresh weight) of *T. calamansanai* was found to be 1(α)-*O*-galloylpunicalagin (**10**), which possesses a gallagyl ester group at the 4,6-positions of the glucopyranose moiety. The isolation of calamansanin (**11**) in this study thus indicates that the gallagyl group is formed biosynthetically by an oxidative carbon-carbon coupling between the flavogallonyl and the galloyl groups. Further examination of other Combretaceae plants is in progress.

Experimental

Details of the instruments and chromatographic conditions used throughout this work are the same as described in the previous paper,¹⁾ except for the following. HPLC was conducted on a Toyo Soda apparatus equipped with an SP-8700 solvent delivery system and a UV-8 model II spectrophotometer.

Isolation of Tannins The fresh leaves (5.0 kg) of *T. calamansanai* collected in Taiwan (May, 1987) were extracted three times with 80% aqueous acetone at room temperature. The acetone was removed by evaporation under reduced pressure (*ca.* 40°C), and the resulting precipitates, consisting mainly of chlorophylls, were removed by filtration. The filtrate was further concentrated and applied to a column of Sephadex LH-20. Elution with H_2O containing increasing amounts of MeOH and

finally with 50% aqueous acetone gave five fractions; I (30.6 g), II (11.0 g), III (100.7 g), IV (18.0 g) and V (25.0 g). Fraction I was further chromatographed over Sephadex LH-20 with H_2O to afford 2,3-*O*-(*S*)-HHDP- D -glucose (**1**) (320 mg). Fraction II was rechromatographed over MCI-gel CHP 20P (H_2O -MeOH) and Sephadex LH-20 (EtOH) to give punicalin (**9**) (43 mg). Fraction III consisted mainly of 1(α)-*O*-galloylpunicalagin (**10**), and was chromatographed on MCI-gel CHP 20P (H_2O -MeOH) and Avicel cellulose (2% AcOH) to give **10** (20.1 g), sanguin H-4 (**2**) (44 mg) and praecoxin A (**8**) (124 mg). Repeated chromatographies of fraction IV on MCI-gel CHP 20P (H_2O -MeOH), Sephadex LH-20 (60–80% aqueous MeOH), Bondapak C_{18} /Porasil B (H_2O -MeOH) and Avicel cellulose (2% AcOH) yielded sanguin H-1 (**3**) (213 mg), 1-desgalloyleugeniin (**4**) (2.5 g), rugosin A (**6**) (54 mg) and calamansanin (**11**) (186 mg). On similar chromatographies, fraction V gave eugeniin (**5**) (159 mg), 1(α)-*O*-galloylpedunculagin (**7**) (370 mg) and calamanins A (**14**) (523 mg), B (**15**) (385 mg) and C (**16**) (150 mg).

Calamansanin (11) A yellow powder (H_2O), mp 240°C (dec.), $[\alpha]_{\text{D}}^{23} + 243.0^\circ$ ($c = 1.1$, MeOH). *Anal.* Calcd for $\text{C}_{55}\text{H}_{34}\text{O}_{34}$: C, 53.32; H, 2.77. Found: C, 53.61; H, 2.57. Negative FAB-MS m/z : 1237 ($\text{M} - \text{H}$)⁻. ¹H-NMR (acetone- d_6 + D_2O , 270 MHz) δ : 7.49 [1H, s, flavogallonyl (FL)-H], 7.25 (3H, s, galloyl-H and FL-H), 6.73 (2H, s, galloyl-H), 6.55 (1H, d, $J = 4$ Hz, H-1), 6.48, 6.44 (each 1H, s, HHDP-H), 5.67 (1H, t, $J = 10$ Hz, H-3), 5.59 (1H, t, $J = 10$ Hz, H-4), 5.27 (1H, dd, $J = 4$, 10 Hz, H-2), 4.75 (1H, dd, $J = 2$, 13 Hz, H-6), 4.48 (1H, br d, $J = 10$ Hz, H-5), 4.08 (1H, dd, $J = 3$, 13 Hz, H-6). ¹³C-NMR (acetone- d_6 + D_2O , 25.05 MHz) δ : 61.9 (C-6), 67.1, 71.5, 73.7, 75.4 (C-2, 3, 4, 5), 90.6 (C-1), 108.0, 108.8 (HHDP C-3, 3'), 109.8, 110.5 (galloyl C-2, 6), 110.8, 111.3 (FL C-3, 3'), 114.5 (HHDP C-1, 1'), 118.2, 120.4, 120.9, 121.3 (galloyl C-1, FL-C), 123.7, 126.3 (HHDP C-2, 2', FL-C), 136.4, 136.6, 138.7, 139.9 (galloyl C-4, HHDP C-5, 5', FL-C), 144.3, 144.4, 145.0, 145.2, 145.4, 146.3, 146.7, 148.2 (galloyl C-3, 5, HHDP C-4, 4', 6, 6', FL-C), 158.5, 159.8 (δ -lactone), 164.9, 165.2, 166.2, 168.4, 169.1 (COO).

Partial Hydrolysis of 11 with Tannase A solution of **11** (100 mg) in H_2O (5 ml) was incubated with tannase at 35°C for 24 h. The reaction mixture was concentrated and the residue was treated with EtOH. The EtOH soluble portion was subjected to Sephadex LH-20 chromatography with EtOH to yield 2,3-*O*-(*S*)-HHDP-4-*O*-(*S*)-flavogallonyl- D -glucose (terflavin C) (**13**) (20 mg), as a yellow amorphous powder, $[\alpha]_{\text{D}}^{23} + 32.6^\circ$ ($c = 1.2$, MeOH). ¹H-NMR (acetone- d_6 + D_2O , 100 MHz) δ : 7.59, 7.32, 7.31 (FL-H), 6.54, 6.40, 6.39 (HHDP-H).

Calamanin A (14) A tan amorphous powder, $[\alpha]_{\text{D}}^{25} + 123.0^\circ$ ($c = 0.5$, MeOH). *Anal.* Calcd for $\text{C}_{48}\text{H}_{32}\text{O}_{31} \cdot \text{H}_2\text{O}$: C, 47.53; H, 3.57. Found: C,

47.49; H, 3.44. Negative FAB-MS m/z : 1103 (M-H)⁻. ¹H-NMR (acetone-*d*₆ + D₂O, 100 MHz) δ : 7.22 (2H, s, galloyl-H), 7.16, 6.61, 6.48, 6.41, 6.28 (each 1H, s, HHDP-H, valoneoyl-H), 6.55 (1H, d, $J=4$ Hz, H-1), 5.60 (1H, t, $J=10$ Hz, H-3), 5.37 (1H, dd, $J=4, 10$ Hz, H-2), 5.24 (1H, dd, $J=7, 13$ Hz, H-6), 5.14 (1H, t, $J=10$ Hz, H-4), 4.61 (1H, dd, $J=7, 10$ Hz, H-5), 3.74 (1H, d, $J=13$ Hz, H-6). ¹³C-NMR (acetone-*d*₆ + D₂O, 67.80 MHz) δ : 63.3, 69.2, 70.9, 74.1, 75.9, 90.6 (glucose), 165.1, 167.2, 168.1, 168.2, 168.7, 169.6 (COO).

Partial Hydrolysis of 14 with Tannase 14 (30 mg) was hydrolyzed with tannase in a manner similar to that described for 11 to yield praecoxin A (8) (13 mg), as a tan amorphous powder, $[\alpha]_D^{25} + 83.9^\circ$ ($c=1.1$, acetone). ¹H-NMR (acetone-*d*₆ + D₂O) δ : 7.17, 6.60, 6.56, 6.51, 6.37, 6.32, 6.30 (5H, in total, each s, HHDP-H, valoneoyl-H).

Calamanin B (15) A tan amorphous powder, $[\alpha]_D^{25} + 132.0^\circ$ ($c=1.0$, MeOH). Anal. Calcd for C₈₂H₅₆O₅₂ · 1/2H₂O: C, 52.32; H, 3.05. Found: C, 52.20; H, 2.88. Negative FAB-MS m/z : 1871 (M-H)⁻. ¹H-NMR (acetone-*d*₆ + D₂O, 270 MHz) δ : 7.24, 7.16 (each 2H, s, galloyl-H), 7.04 (1H, s, valoneoyl-H), 6.98 (2H, s, galloyl-H), 6.64, 6.61, 6.51, 6.49, 6.43, 6.22 (each 1H, s, HHDP-H, valoneoyl-H), 6.57 (1H, d, $J=4$ Hz, H-1), 6.11 (1H, d, $J=8$ Hz, H-1'), 5.81 (1H, t, $J=10$ Hz, H-3'), 5.59 (1H, dd, $J=9, 10$ Hz, H-3), 5.58 (1H, dd, $J=8, 10$ Hz, H-2'), 5.39 (1H, dd, $J=4, 9$ Hz, H-2), 5.30 (1H, dd, $J=7, 13$ Hz, H-6'), 5.22 (1H, dd, $J=7, 12$ Hz, H-6), 5.18, 5.16 (each 1H, t, $J=10$ Hz, H-4, 4'), 4.64 (1H, dd, $J=7, 10$ Hz, H-5), 4.86 (1H, dd, $J=7, 10$ Hz, H-5'), 3.84 (1H, d, $J=13$ Hz, H-6'), 3.74 (1H, d, $J=12$ Hz, H-6). ¹³C-NMR (acetone-*d*₆ + D₂O, 67.80 MHz) δ : 63.1, 63.3, 69.1, 70.6, 70.8, 71.7, 72.8, 73.4, 74.0, 75.8, 90.6, 93.1 (glucose), 162.5, 165.3, 166.4, 166.8, 167.9, 168.2 (2C), 168.5, 168.7, 169.7 (COO).

Partial Hydrolysis of 15 with Hot H₂O A solution of 15 (200 mg) in H₂O (20 ml) was heated at 80°C for 4 h. After cooling, the resulting precipitates were collected by filtration, and identified as ellagic acid by infrared (IR) spectral comparison. The filtrate was concentrated and subjected to column chromatography on Sephadex LH-20 with 80% aqueous MeOH to yield 1-desgalloyl-leugeniin (4) (25.8 mg) and calamanin A (14) (25.3 mg).

Calamanin C (16) A tan amorphous powder, $[\alpha]_D^{25} + 131.0^\circ$ ($c=1.1$, MeOH). Anal. Calcd for C₁₂₃H₈₄O₇₇: C, 52.88; H, 3.03. Found: C, 52.88; H, 2.73. ¹H-NMR (acetone-*d*₆ + D₂O, 270 MHz) δ : 7.25 (2H, s, galloyl-H), 7.17, 7.13 (each 1H, s, valoneoyl-H), 7.05, 7.04, 7.02, 6.99 (each 2H, s, galloyl-H), 6.67, 6.64, 6.52, 6.51, 6.50, 6.45, 6.22, 6.17 (each 1H, s, HHDP-H, valoneoyl-H), 6.58 (1H, d, $J=4$ Hz, H-1), 6.10, 6.06 (each 1H, d, $J=8$ Hz, H-1', 1''), 5.82, 5.79 (each 1H, t, $J=10$ Hz, H-3', 3''), 5.65–5.54 (3H in total, m, H-3, 2', 2''), 5.04 (1H, dd, $J=4, 10$ Hz, H-2), 5.30–5.16 (3H in total, m, H-6, 6', 6''), 5.16 (3H, br t, $J=10$ Hz, H-4, 4', 4''), 4.66 (1H, dd, $J=6, 10$ Hz, H-5), 4.51–4.44 (2H, m, H-5', 5''), 3.82, 3.79, 3.76 (each 1H, d, $J=13$ Hz, H-6, 6', 6''). ¹³C-NMR (acetone-*d*₆ + D₂O, 67.80 MHz) δ : 63.1, 63.2, 63.3, 69.2, 70.6, 70.7, 70.8, 71.7 (2C), 72.8, 72.9, 73.4 (2C), 74.1, 75.9, 90.7, 93.1 (2C) (glucose), 162.4, 162.5, 165.4, 166.3, 166.4, 166.8, 166.9, 167.9, 168.0, 168.1, 168.2 (2C), 168.5, 168.8, 169.7 (COO).

Methylation of 16, Followed by Alkaline Methanolysis A mixture of 16 (72 mg), dimethyl sulfate (1 ml) and anhydrous potassium carbonate (1.2 g) in dry acetone (20 ml) was heated under reflux with stirring for 4 h. After

removal of inorganic salts by filtration, the filtrate was concentrated to a syrup, which was chromatographed over silica gel. Elution with benzene-acetone (9:1) gave the tritetracontamethyl ether (46 mg), as a white amorphous powder. IR (KBr): 2930, 1750 (CO), 1588, 1460, 1392, 1332 cm⁻¹. A solution of the tritetracontamethyl ether (39 mg) in 2% methanolic sodium methoxide (4 ml) was left standing at room temperature for 20 h, then neutralized with Amberlite IR-120B (H⁺ form) resin and concentrated *in vacuo*. The residue was separated by silica gel chromatography with benzene-acetone (97:3–95:5) to give methyl 3,4,5-trimethoxybenzoate (2 mg), colorless needles, mp 80–81°C, dimethyl (*S*)-4,4',5,5',6, 6'-hexamethoxydiphenolate (17) (1.7 mg), a colorless syrup, $[\alpha]_D^{25} - 24.0^\circ$ ($c=0.1$, CHCl₃), and trimethyl octa-*O*-methylvaloneate (18) (10 mg), a colorless syrup, $[\alpha]_D^{25} - 19.2^\circ$ ($c=1.0$, CHCl₃). IR (CHCl₃): 2950, 1725 (CO), 1595 cm⁻¹.

Partial Hydrolysis of 16 with Hot H₂O A solution of 16 (10 mg) in H₂O (2 ml) was heated at 80°C for 8 h. The reaction mixture was analyzed by HPLC to detect 1-desgalloyl-leugeniin (4), rugosin B (19) and calamanin A (14). HPLC: column, Zorbax SIL (4.6 mm i.d. × 250 mm); solvent, hexane-MeOH-tetrahydrofuran-formic acid (45:27:9:1) containing oxalic acid (250 mg/l); flow rate, 1.0 ml/min; t_R 11.7 and 12.5 min for 4, t_R 13.9 and 14.5 min for 19 and t_R 15.6 min for 14.

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