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HYDROLYSABLE TANNINS ISOLATED FROM *SYZYGIUM AROMATICUM*: STRUCTURE OF A NEW C-GLUCOSIDIC ELLAGITANNIN AND SPECTRAL FEATURES OF TANNINS WITH A TERGALLOYL GROUP

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Abstract – Eighteen hydrolysable tannins, including a new C-glucosidic tannin named aromatinin A (**1**), were isolated from an aqueous acetone extract of dried flower buds of *Syzygium aromaticum* Merr. et Perry. We determined that **1** had a gallic acid C-glucoside structure, based on the spectral data and synthesis from casuarinin (**18**) and gallic acid (**20**). This is a rare example of hydrolysable tannins with gallic acid C-glucoside structure. We also report the ¹H nuclear magnetic resonance (NMR) spectral features of syzyginin A (**2**), bicornin (**3**), and platycaryanin A (**4**), which were also isolated from *S. aromaticum*, based on their structures with a tergalloyl group or its depsidone form. The remaining known compounds were identified as alunusnin A (**5**), rugosin C (**6**), 1,2,3-tri-O-galloyl-β-D-glucose (**7**), 1,2,3,6-tetra-O-galloyl-β-D-glucose (**8**), tellimagrandin II (**9**), casuarictin (**10**), heterophyllin D (**11**), rugosin D (**12**), rugosin F (**13**), euprostin A (**14**), 1,2-di-O-galloyl-3-O-digalloyl-4,6-O-(S)-hexahydroxydiphenoyl-β-D-glucose (**15**), alienanin B (**16**), squarrosanin A (**17**), and **18**. The antifungal effects of hydrolysable tannins, **9**, **12**, and **18** against *Candida* strains are also described.

INTRODUCTION

Cloves are aromatic flower buds of *Syzygium aromaticum*, a woody plant belonging to the family Myrtaceae. Cloves have been used as a spice and as a constituent material for traditional East Asian

medicines. Previously, we reported that eugenol, the major constituent of clove essential oil, and related compounds show antifungal effects against *Candida* species.¹ Isolation of tannins with tergalloyl, syzygyl, and valoneoyl groups from *S. aromaticum* leaves has also been reported.^{2,3} Our further investigation of the hydrophilic constituents of cloves led to the isolation of 18 tannins, including a new *C*-glucosidic ellagitannin. This study considers the isolation and structures of those tannins and the spectral features of tannins with a tergalloyl group. Our preliminary study indicated that several tannins showed antifungal effects against *Candida* species, which are also described.

RESULTS AND DISCUSSION

An aqueous acetone homogenate of dried *S. aromaticum* flower buds was concentrated and extracted with *n*-hexane, Et₂O, EtOAc, and *n*-BuOH, successively. Each extract was separated by chromatography using Diaion HP-20, Toyopearl HW-40, Sephadex LH-20, or MCI-gel CHP-20P, followed by preparative reversed phase high performance liquid chromatography (HPLC) to yield tannins **1–18** (Figures 1-4).

Compound **1** was obtained as an off-white amorphous powder. The high-resolution electrospray-ionization mass spectrum (HRESIMS) with negative-ion mode established the molecular formula as C₄₈H₃₂O₃₀. The ¹H NMR spectrum of **1** showed glucose proton signals (Table 1) with chemical shifts and coupling constants similar to those of *C*-glucosidic tannins, such as casuarinin (**18**) and stachyurin (**19**).⁴ The spectrum also showed a two-proton singlet due to a galloyl group at δ 7.21 and four one-proton singlets at δ 7.18, 6.88, 6.544, and 6.539 in the aromatic proton region. Three one-proton singlets at δ 6.88, 6.544, and 6.539 among them accounted for two hexahydroxydiphenoyl (HHDP) groups, one of which participates in the *C*-glucosidic linkage arising from a phenol-aldehyde coupling.⁵ These ¹H NMR data indicate the existence of two HHDP groups at O-2/O-3 and O-4/O-6 of the glucose core, and suggest that a galloyl group is at O-5 of the glucose core in **1**, as observed for **18** and **19**. The remaining aromatic proton signal at δ 7.18 was attributed to an additional galloyl group (ring A in formula **1**) forming another *C*-glucosidic linkage. The ¹³C NMR spectrum of **1** showed glucose carbon signals at δ 41.3 (C-1), 82.6 (C-2), 75.3 (C-3), 73.0 (C-4), 71.4 (C-5), and 64.2 (C-6), whose chemical shifts were similar to those of the corresponding carbon signals in squarrosanin A (**17**)⁶ [δ 41.4 (C-1), 82.0 (C-2), 75.1 (C-3), 72.8 (C-4), 71.1 (C-5), and 64.5 (C-6)], indicating the presence of two *C*-glucosidic linkages at the anomeric carbon. The heteronuclear multiple bond correlation (HMBC) spectrum of **1** showed correlations between glucose H-1 and A-ring C-3, and between glucose H-2 and A-ring C-2 (arrows in Figure 1), indicating that the galloyl group (i.e., A ring) was linked to glucose C-1. The glucose H-2, H-3, H-4, and H-6 signals showed three-bond correlations with the ester carbonyl

carbon signals in the HHDP groups (Figure 1), further indicating that the HHDP groups are at O-2/O-3 and O-4/O-6 of the glucose residue. The configuration at glucose C-1 was assigned to be *S* based on the characteristic singlet of the H-1 signal, as observed for **19** and other *C*-glucosidic tannins.⁷ The circular dichroism (CD) spectrum of **1** showed a positive Cotton effect in the short-wavelength region ($[\theta]_{235} +1.4 \times 10^5$), indicating the *S* configuration of both HHDP groups.⁸

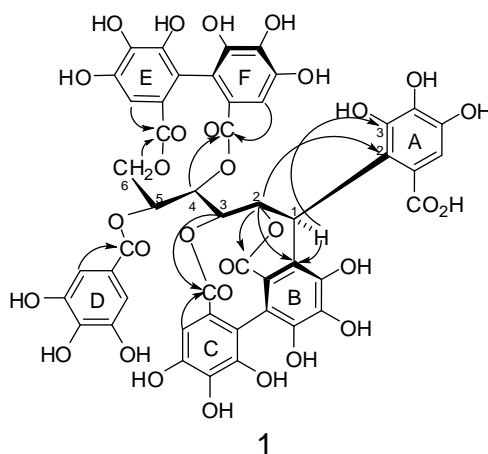


Figure 1. Structure of the new *C*-glucosidic ellagitannin **1**

Table 1. ¹H NMR spectral data for glucose protons of **1-5**, and **9** [acetone-*d*₆+D₂O, *J* (Hz) in parenthesis]

	1	2	3	4	5	9
H-1	5.19, s	6.19, d (8.5)	6.15, d (8.5)	6.18, d (8.0)	6.18, d (8.5)	6.18, d (8.5)
H-2	4.86, s	5.63, dd (8.5, 10.0)	5.60, dd (8.5, 9.5)	5.17, dd (8.0, 9.0)	5.44, dd (8.5, 10.0)	5.61, dd (8.5, 9.0)
H-3	5.17, s	5.84, t (10.0)	5.80, t (9.5)	5.43, t (9.0)	5.20, t (10.0)	5.82, t (9.0)
H-4	5.84, d (9.0)	5.26, t (10.0)	5.24, t (9.5)	5.18, t (9.0)	5.18, t (10.0)	5.20, t (9.0)
H-5	5.31, dd (3.5, 9.0)	4.54, dd (6.5, 10.0)	4.54, dd (6.5, 9.5)	4.49, dd (6.0, 9.0)	4.49, dd (6.5, 10.0)	4.53, dd (6.0, 9.0)
H-6	4.94, dd (3.5, 13.0)	5.32, dd (6.5, 12.0)	5.24, dd (6.5, 13.0)	5.29, dd (6.0, 13.0)	5.24, dd (6.5, 13.0)	5.32, dd (6.0, 13.0)
H-6	4.07, d (13.0)	3.91, d (12.0)	3.94, d (13.0)	3.89, d (13.0)	3.93, d (13.0)	3.86, d (13.0)

The structure **1** assigned to this compound was further confirmed by acid-catalyzed condensation of **18** with gallic acid (**20**) to afford **1**. This compound was new and was named aromatinin A. Although norbergenin (**21**)⁹ (Figure 5) was a known example of a C-glucoside of galloyl ester, compound **1** is a rare example of hydrolysable tannins with gallic acid C-glucoside structure.

Compound **2** was obtained as an off-white amorphous powder. HRESIMS of **2** indicated its molecular formula to be C₄₈H₃₄O₃₁. The ¹H NMR spectrum exhibited three two-proton singlets at δ 7.10, 7.00, and 6.93, due to the galloyl groups, and three one-proton singlets at δ 6.80, 6.49, and 6.46, attributable to a triphenoyl group in the aromatic region. The coupling pattern of the glucose proton signals (Table 1) was almost identical to that of tellimagrandin II (**9**),^{4,10} indicating the presence of a β-glucopyranose core with ⁴C₁ conformation, and that a diphenoyl moiety of the triphenoyl group was at O-4/O-6 of the glucose core. The ¹³C NMR spectrum of **2** indicated that the triphenoyl group was assignable to a tergalloyl group (see Experimental). The ¹H signal pattern for **2** was similar to that for syzyginin A (**22**) (Figure 2), which was previously isolated from the leaves of this plant.² However, the proton signal assignable to H-6'' (δ 6.80) in **2** shifted upfield relative to the corresponding proton of **22** [H-6'' (δ 6.98)]. Furthermore, a carboxyl carbon signal and C-1'' of the tergalloyl group in the ¹³C NMR spectrum of **2** shifted downfield relative to the corresponding signals of **22** [δ 170.6 → 171.5 (C-7''), δ 114.3 → 116.1 (C-1'')]. We assumed that these differences could be due to salt formation of the carboxyl group in the tergalloyl group, and examined the effect of adding deuterium chloride (DCI) to an acetone-*d*₆ solution of **2** on the ¹H chemical shifts. The addition caused a downfield shift of the tergalloyl proton H-6'' of **2** from δ 6.80 to δ 6.91, accompanied by the formation of a free carboxyl group. Based on these data, compound **2** was assigned to the salt form of **22**.

Compound **3** was obtained as an off-white amorphous powder. HRESIMS in the negative-ion mode established the molecular formula as C₄₈H₃₂O₃₀. The ¹H NMR spectrum showed three two-proton singlets due to galloyl groups at δ 7.06, 6.97, and 6.95, and three one-proton singlets attributable to a triphenoyl group at δ 6.93, 6.84, and 6.52. The spectrum also showed sugar proton signals (Table 1) in which the coupling constants were of a β-glucopyranose core with a ⁴C₁ conformation. Their chemical shifts were similar to those of tannins in which three galloyl groups are at O-1–O-3, and the diphenoyl part of the triphenoyl group is at O-4/O-6 of the glucose core.¹⁰ Although the chemical shifts of the galloyl and glucose protons were closely similar to those of the corresponding protons of **2**, those of three one-proton singlets (δ 6.93, 6.84, and 6.52) in the ¹H NMR spectrum of **3** were different from those of the corresponding protons (δ 6.80, 6.49, and 6.46) of **2**. Comparisons of the ¹³C NMR spectrum of **3** to that of

2 showed upfield shifts in the following triphenoyl carbon signals: C-ring C-7'' (δ 171.5 \rightarrow 163.5), B-ring C-4' (δ 149.6 \rightarrow 148.2), and B-ring C-6' (δ 150.0 \rightarrow 145.1), in contrast to the downfield shifts of the carbon signals of B-ring C-1' (δ 115.9 \rightarrow 120.8), B-ring C-3' (δ 107.9 \rightarrow 112.4), and B-ring C-5' (δ 136.7 \rightarrow 142.8). These changes in ^{13}C chemical shifts, coupled with the $[\text{M-H}]^-$ ion peak at m/z 1087 in the ESIMS, which was 18 mass units lower than that of **2**, indicated that the triphenoyl group in **3** formed a depsidone structure at the carbon *ortho* to the phenoxy moiety on the diphenoyl group. The carbon signal of B-ring C-6' (δ 145.1) shifted upfield compared to the carbon signal of B-ring C-4' (δ 148.2), and the neighboring carbons, B-ring C-1' (δ 120.8) and B-ring C-5' (δ 142.8), shifted downfield ($\Delta\delta$ +4.9 and +6.1) compared to the corresponding B-ring C-1' (δ 115.9) and B-ring C-5' (δ 136.7) signals in **2**, respectively. Therefore, the depsidone linkage was assigned at C-6' rather than at C-4'. In the HMBC spectrum (in CD_3OD), the H-3' signal of the depsidone-forming tergalloyl group at δ 6.90 showed connectivity with the glucose H-6 signal at δ 5.32 via a common tergalloyl carbonyl carbon C-7' (δ 168.2). Furthermore, the tergalloyl H-3 signal at δ 6.49 was correlated with the glucose H-4 signal at δ 5.30 via the ester carbonyl signal tergalloyl C-7 (δ 169.1). These data agree with the orientation of the

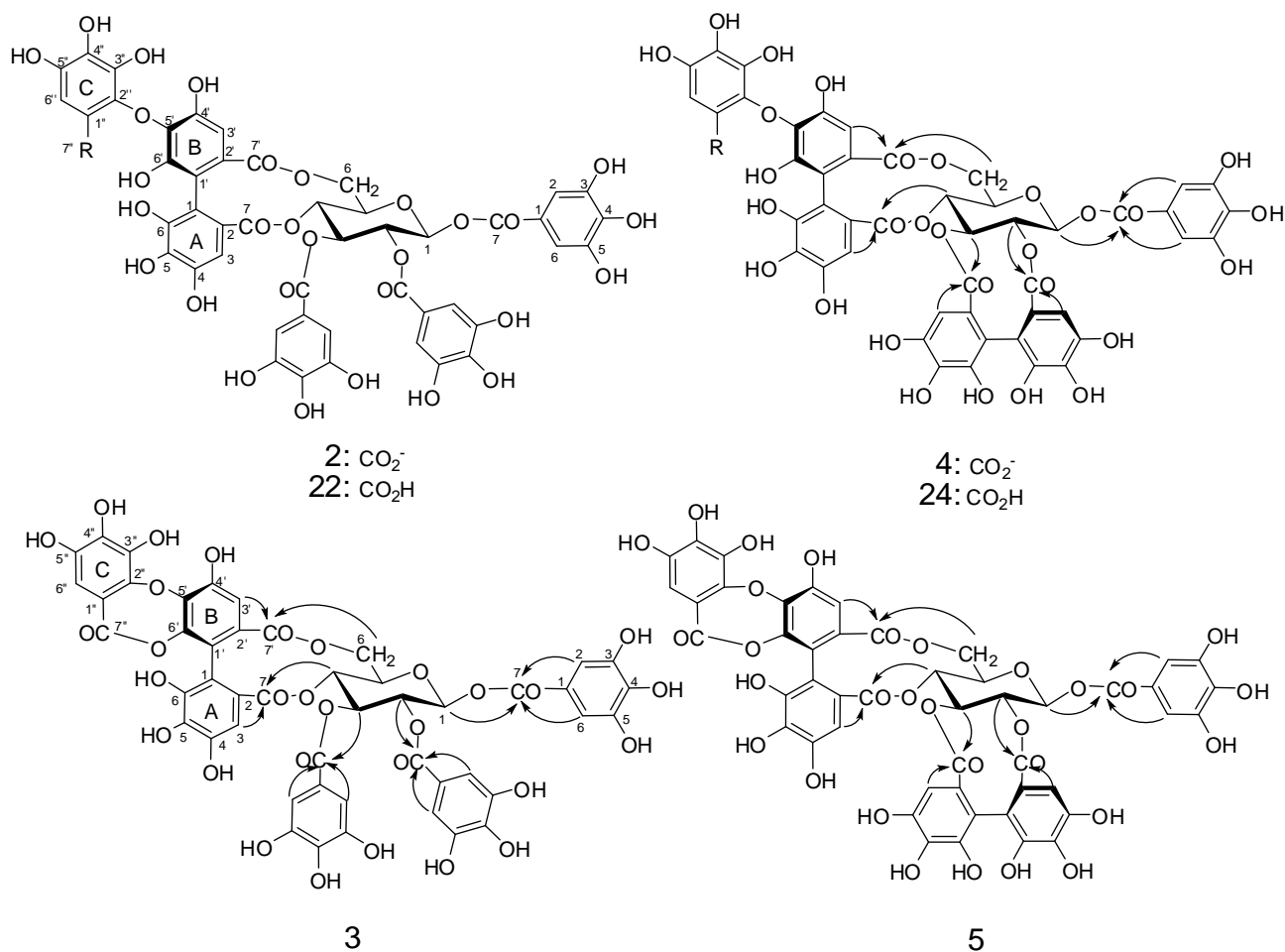


Figure 2. Structures of the monomeric hydrolysable tannins, **2**, **3**, **4**, **5**, **22**, and **24**

depsidone-forming tergalloyl group in **3**, as shown in the formula. The CD spectrum of **3** showed a positive Cotton effect in the short wavelength region ($[\theta]_{224} +4.9 \times 10^4$), indicating the *S* configuration of the tergalloyl group. The structure thus assigned for **3** was further supported by the formation of **2** from **3**, based on cleavage of the depside linkage. Previously, structure **3** was given the revised structure for bicornin based on spectral comparison.¹¹ The depsidone structure of bicornin was thus substantiated by a successful chemical correlation in the present experiment.

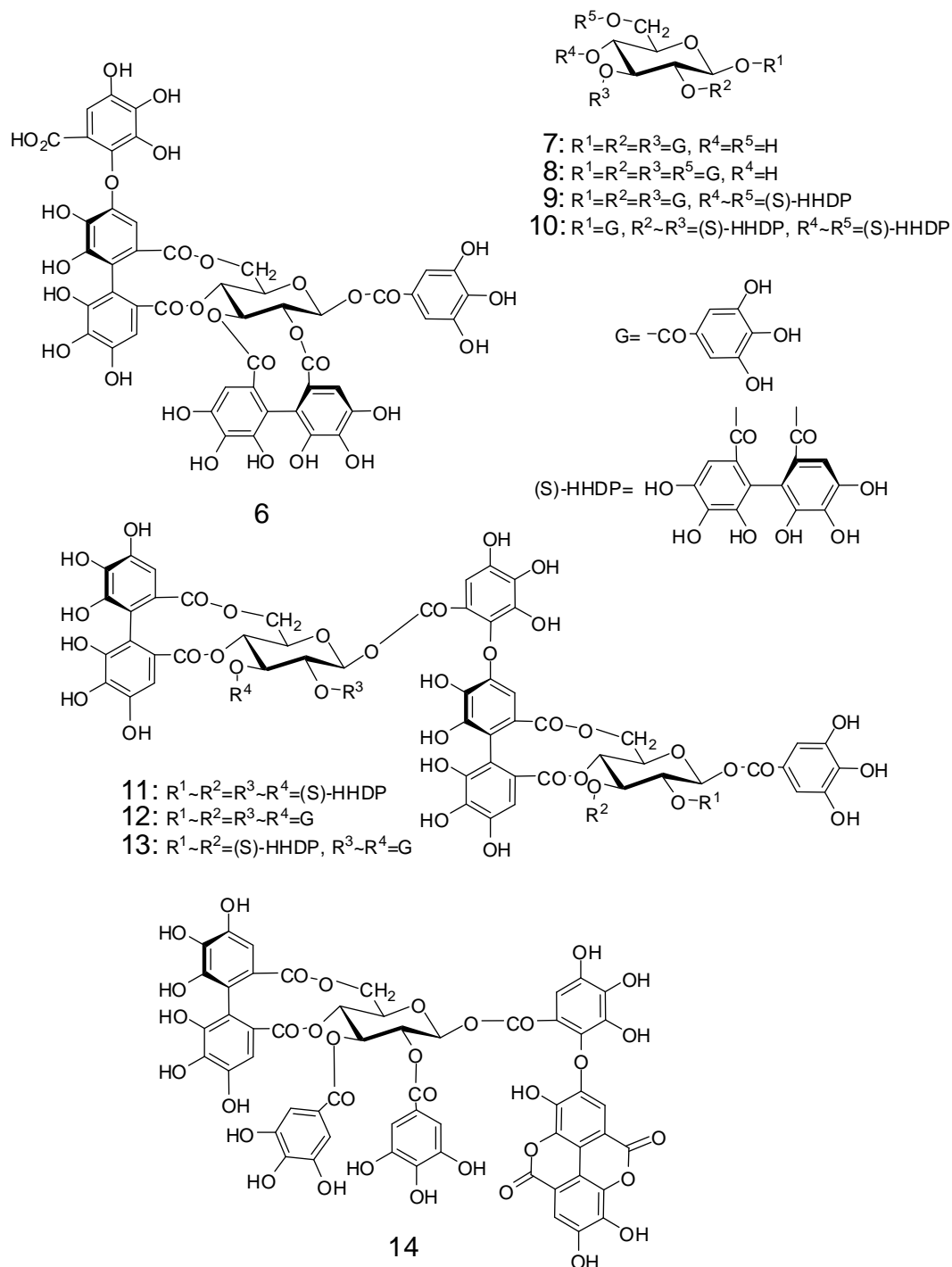


Figure 3. Structures of **6**–**14**

Compound **4** was obtained as an off-white amorphous powder. The negative ESIMS of **4** showed an $[M-H]^-$ ion peak at m/z 1103, which corresponded to the molecular formula $C_{48}H_{32}O_{31}$. The 1H and ^{13}C NMR spectra of **4** were similar to those of glansrin A (**23**)¹² (Figure 5), whereas those of platycaryanin A (**24**)¹³ showed some differences in the tergalloyl group chemical shifts. However, adding DCI to an

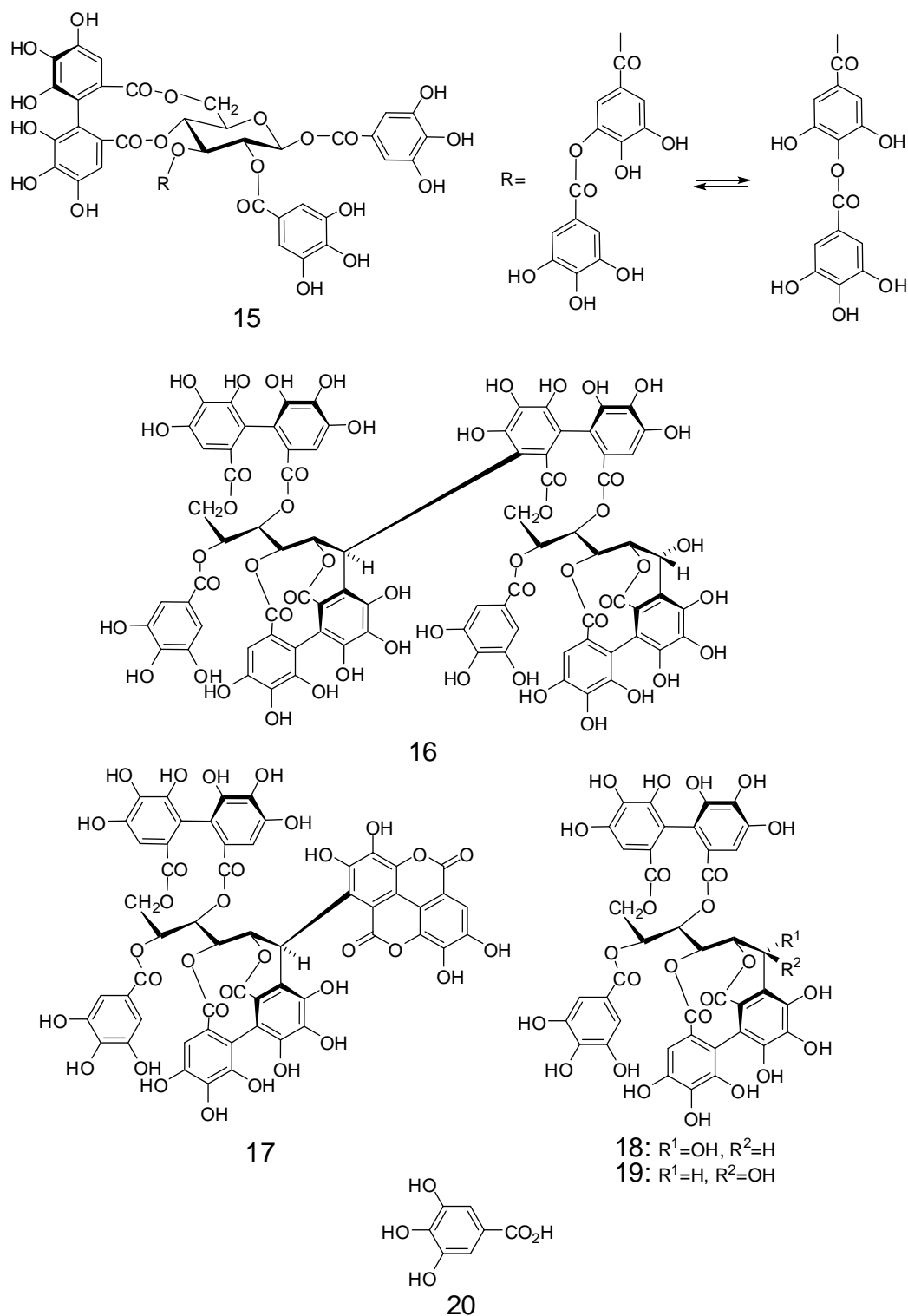


Figure 4. Structures of **15–20**

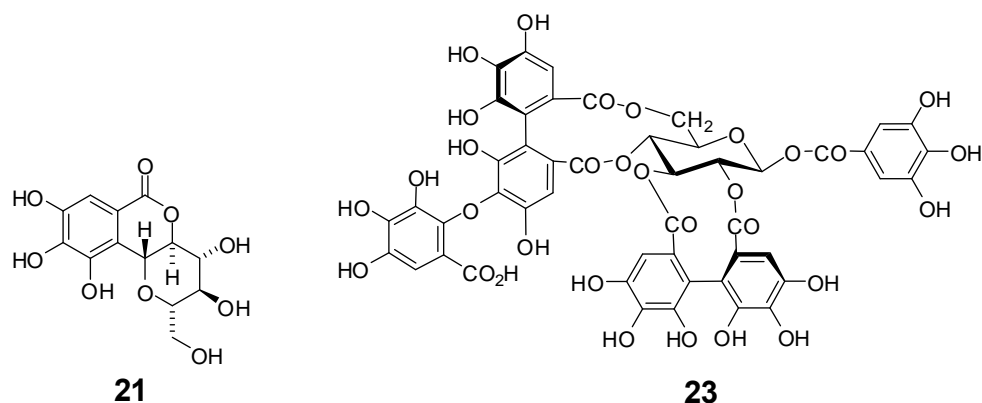


Figure 5. Structures of **21** and **23**

acetone- d_6 solution of **4** indicated that **4** is a salt form of **24** (Figure 2), as was the case with **2** and **22**. The orientation of the tergalloyl group in **4** was confirmed to be the same as that in **24** by HMBC correlation with **4**. The structural assignment for **4** was further supported by the formation of **4** from alunusnin A (**5**)^{13,14} and by cleavage of the depside linkage in **5** (see Experimental). Based on these findings, compound **4** was assigned to a salt in the carboxyl group in the tergalloyl residue in **24**.

As shown in Figure 6, respective comparisons of the ^1H NMR spectra of **2** and **4** to those of **22** and **24** showed upfield shifts of the tergalloyl group H-6'' signals, accompanied by salt formation of the free carboxyl group. As a result, the chemical shifts of the tergalloyl proton signals in **4** were apparently similar to those for **23**, although the assignments of the H-3 and H-3' signals in **23** were interchanged. This may cause confusion when identifying this type of tannin and strongly suggests the necessity for a desalting procedure to purify tannins. In contrast, the H-3' signals of the depsidone-forming tergalloyl group (Figure 7) of **3** and **5** showed remarkable downfield shifts relative to the corresponding signals of the tergalloyl group in **2** and **4**. Therefore, depsidone formation was indicative of this downfield shift [δ 6.93 (**3**) and 6.96 (**5**)] to show the pattern of two singlets (δ 6.84–6.96) and one singlet (δ 6.52–6.59) (for the depsidone form, **3**, **5** in Figure 6), from the pattern of one singlet (δ 6.80–7.01) and two singlets (δ 6.46–6.65) (for the carboxyl form, **2**, **4**, **22**, and **24** in Figure 6). Signals that appeared in the lowest chemical shifts were then compared to distinguish the tergalloyl from the valoneoyl group. Signals of the tergalloyl protons (H-6''; δ 6.98 in **22** and δ 7.01 in **24**) showed upfield shifts relative to the corresponding signals of the valoneoyl protons (H-6''; δ 7.10 in **6** and δ 7.14 in rugosin A¹⁵). Analogous differences were also observed in the comparison of the depsidone-forming tergalloyl groups (H-3'; δ 6.93 in **3** and δ 6.96 in **5**) and depsidone-forming valoneoyl groups (H-3'; δ 7.20 in praecoxin C¹⁶ and δ 7.12 in prostratin C¹⁷). These spectral features will facilitate identification of these types of tannins from other sources.

The remaining known compounds were identified as alunusnin A (**5**), rugosin C (**6**),¹⁵ 1,2,3-tri-*O*-galloyl- β -D-glucose (**7**),¹⁸ 1,2,3,6-tetra-*O*-galloyl- β -D-glucose (**8**),¹⁹ tellimagrandin II (**9**),^{4,10} casuarictin (**10**),⁴ heterophylliin D (**11**),²⁰ rugosin D (**12**),²¹ rugosin F (**13**),²¹ euprostin A (**14**),¹⁷ 1,2-di-*O*-galloyl-3-*O*-digalloyl-4,6-*O*-(*S*)-hexahydroxydiphenoyl- β -D-glucose (**15**),²² alienanin B (**16**),^{23,24} squarrosanin A (**17**),⁶ and casuarinin (**18**).^{4,14}

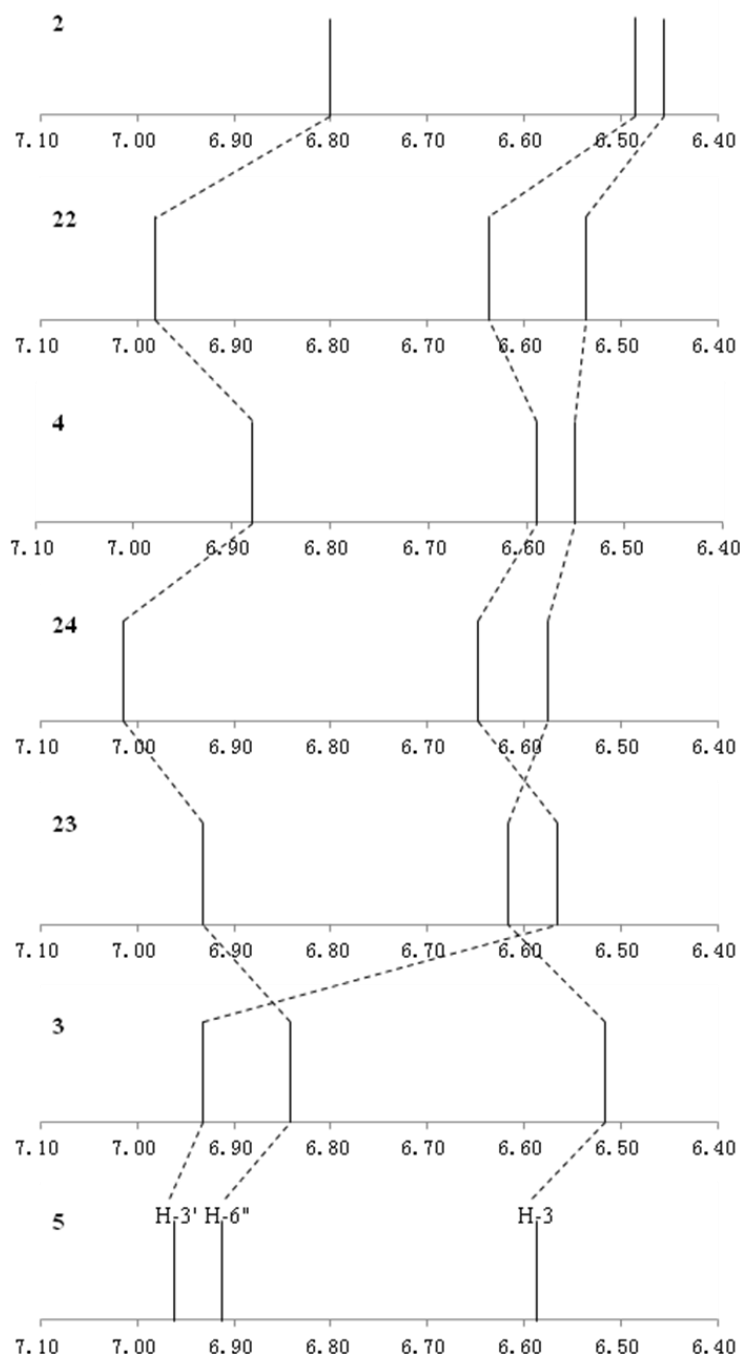


Figure 6. Comparison of the tergalloyl group or depsidone-forming tergalloyl group protons in the ¹H NMR spectra of **2**, **22**, **4**, **24**, **23**, **3**, and **5** (in acetone-*d*₆+D₂O)

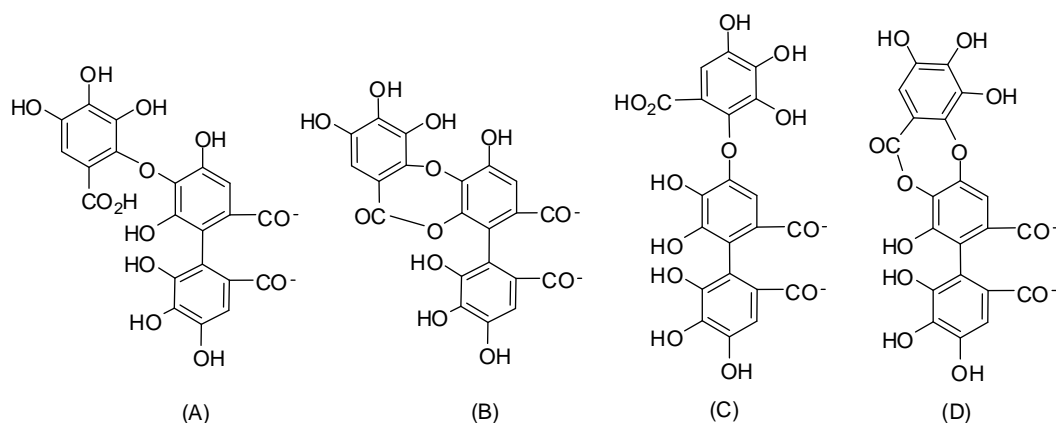


Figure 7. Structures of tergalloyl (A), depsidone-forming tergalloyl (B), valoneoyl (C), and depsidone-forming valoneoyl (D) groups

The preliminary results for the antifungal effects of four tannins, on the examination with those obtained from several sources (see Experimental), against three *Candida* strains are shown in Table 2. Although the antifungal activity of **9**, **12**, and **18** was lower than that of amphotericin B, used as a positive control, these compounds showed antifungal activities against all strains examined, but **8** had no activity. Further examination to find tannins with more potent effects on *Candida* species should be conducted.

Table 2. Inhibitory effects of tannins against *Candida* species

	Inhibition diameters (mm) ^a		
	<i>C. albicans</i>	<i>C. tropicalis</i>	<i>C. glabrata</i>
	FH01	NA01	TIMM1062
Amphotericin B	19	17	24
1,2,3,6-tetra- <i>O</i> -galloyl- β-D-glucose (8)	- ^b	-	-
Tellimagrandin II (9)	12	11	17
Rugosin D (12)	12	10	15
Casuarinin (18)	11	12	15

^a Filter paper disks of 8 mm in diameter were impregnated with 150 μg/disk of samples, and were incubated on the agar plates at 37 °C for 24 h.

^b no inhibition zone.

EXPERIMENTAL

General procedures. HRESIMS was performed using a Bruker MicroTOF-Q spectrophotometer in negative ion mode. ESIMS was performed using an API 4000 liquid chromatography-mass spectroscopy

system in negative ion mode. CD spectra were measured on a JASCO J-720 W spectrophotometer. NMR experiments were performed using a Varian INOVA AS 600 instrument (600 MHz for ^1H NMR and 151 MHz for ^{13}C NMR). The solvent was acetone- d_6 and D_2O (9:1, v/v), unless mentioned otherwise. Chemical shifts are given in δ (ppm) values relative to those of the solvent signal [acetone- d_6 (δ_{H} 2.04; δ_{C} 29.8), CD_3OD (δ_{H} 3.30; δ_{C} 49.0)] on the tetramethylsilane scale. Column chromatography was conducted on Toyopearl HW-40 (coarse grade; Tosoh, Tokyo, Japan), Sephadex LH-20 (Pharmacia Fine Chemicals, Upsala, Sweden), Diaion HP-20 (Mitsubishi Chemicals, Tokyo, Japan), and MCI-gel CHP-20P (Mitsubishi Chemicals, Tokyo, Japan). Normal phase HPLC was conducted on a YMC-Pack SIL A-003 column (4.6 i.d. \times 250 mm) developed with *n*-hexane-MeOH-tetrahydrofuran-formic acid (60:45:15:1) containing oxalic acid (500 mg/1.2 L; flow rate, 1.5 mL/min; 280 nm UV detection) at room temperature. Analytical reversed phase HPLC was performed on a YMC-Pack ODS A-302 column (4.6 i.d. \times 150 mm) with 0.01 M H_3PO_4 -0.01 M KH_2PO_4 - CH_3CN (42.5:42.5:15; flow rate, 1.0 mL/min; 280 nm UV detection) at 40 °C. Preparative reversed phase HPLC was performed on a YMC-Pack ODS A-324 column (10 i.d. \times 300 mm) developed with 0.01 M H_3PO_4 -0.01 M KH_2PO_4 - CH_3CN (2:2:1; flow rate, 2.0 mL/min; 280 nm UV detection) at 40 °C.

Plant material. Dried *S. aromaticum* flower buds were purchased from Tochimoto-tenkai-do (Osaka, Japan). The specimen was kept at the Medicinal Botanical Garden of Okayama University (No. 007605001).

Extraction and isolation. Plant material (68 g) was homogenized in H_2O -acetone (1:9, v/v, 3 L) and filtered. The filtrate was then concentrated to 300 mL and extracted with *n*-hexane (300 mL \times 3), Et_2O (300 mL \times 3), EtOAc (300 mL \times 3), and *n*-BuOH (300 mL \times 3), successively, to furnish the *n*-hexane (10.6 g), Et_2O (1.37 g), EtOAc (3.54 g), and *n*-BuOH (3.56 g) extracts, and a water-soluble portion (2.27 g). The EtOAc extract was subjected to chromatography on Toyopearl HW-40 (2.2 i.d. \times 40 cm) (TP_1) with 70% EtOH \rightarrow 70% acetone. The eluates were fractionated by monitoring either normal or reversed phase HPLC. Fr. 26–27 (41.6 mg) from TP_1 was further separated on MCI-gel CHP-20P with H_2O \rightarrow aq. MeOH \rightarrow 70% acetone, to yield 1,2,3-tri-*O*-galloyl- β -D-glucose (**7**) (6.4 mg) and 1,2,3,6-tetra-*O*-galloyl- β -D-glucose (**8**) (6.6 mg). Fr. 87–100 (132.6 mg) from TP_1 was applied to a Sep-Pak C_{18} cartridge with H_2O \rightarrow aq. MeOH (10% \rightarrow 20% \rightarrow 30% \rightarrow 40%, v/v) \rightarrow 100% MeOH to give tellimagrandin II (**9**) (49.2 mg). Fr. 121–165 (185.9 mg) from TP_1 was subjected to column chromatography on MCI-gel CHP-20P with H_2O \rightarrow aq. MeOH (20% \rightarrow 40% \rightarrow 60%, v/v) \rightarrow 100% MeOH \rightarrow 70% acetone, to give syzyginin A (**2**) (9.6 mg) and casuarictin (**10**) (15.2 mg). Fr. 183–195 (23.2 mg) from TP_1 was further

subjected to a Sep-Pak C₁₈ cartridge followed by preparative HPLC to yield platycaryanin A (**4**) (7.9 mg). In a separate experiment, another batch of cloves (500 g) was homogenized in H₂O-acetone (1:9, v/v, 15 L), and the filtered homogenate was concentrated in vacuo to 1.5 L and extracted with *n*-hexane (1.5 L × 3), Et₂O (1.5 L × 3), EtOAc (1.5 L × 3), and *n*-BuOH (1.5 L × 3), successively, to yield the *n*-hexane (93.2 g), Et₂O (15.1 g), EtOAc (25.7 g), and *n*-BuOH (66.0 g) extracts, and a water-soluble portion (23.9 g). A part (10 g) of the EtOAc extract was subjected to Toyopearl HW-40 (2.2 i.d. × 60 cm) (TP₂) with 70% EtOH → 70% acetone. Fr. 165–210 (276.2 mg) from TP₂ was further subjected to MCI-gel CHP-20P (MC₁) using H₂O → aq. MeOH (20% → 40% → 60%, v/v) → 100% MeOH → 70% acetone. The Fr. 20% MeOH eluate from MC₁ afforded casuarinin (**18**) (19.7 mg). The Fr. 40% MeOH eluate from MC₁ was further subjected to column chromatography over MCI-gel CHP-20P with H₂O → aq. MeOH (20% → 40% → 60%, v/v) → 100% MeOH → 70% acetone, followed by preparative HPLC to yield **2** (9.8 mg) and rugosin C (**6**) (5.8 mg). Fr. 70% acetone (306.6 mg) from TP₂ was separated on Toyopearl HW-40 (2.2 i.d. × 40 cm) [with 70% EtOH → 70% EtOH-70% acetone (9:1 → 8:2 → 7:3, v/v) → 70% acetone], MCI-gel CHP-20P [with H₂O → aq. MeOH (20% → 40% → 60%, v/v) → 100% MeOH → 70% acetone], Sephadex LH-20 (with 70% EtOH-70% acetone), successively, and further purification of the fractions by preparative HPLC gave bicornin (**3**) (2.2 mg), alunusnin A (**5**) (4.4 mg), heterophylliin D (**11**) (2.7 mg), rugosin D (**12**) (9.5 mg), and rugosin F (**13**) (15.8 mg). The *n*-BuOH extract (66.0 g) was subjected to Diaion HP-20 (5.5 i.d. × 25 cm) chromatography with H₂O → aq. MeOH (20% → 40% → 60%, v/v) → 100% MeOH → 70% acetone as eluants. The 40% MeOH eluate was applied to column chromatography over Toyopearl HW-40 (2.2 i.d. × 60 cm) (with 70% EtOH → 70% acetone), MCI-gel CHP-20P (with aq. MeOH → 70% acetone), Sephadex LH-20 (with 70% EtOH-70% acetone), and further purification of the fractions by preparative HPLC gave **6** (8.7 mg), euprostin A (**14**) (2.6 mg), 1,2-di-*O*-galloyl-3-*O*-digalloyl-4,6-*O*-(*S*)-hexahydroxydiphenoyl-β-*D*-glucose (**15**) (2.6 mg), and squarrosanin A (**17**) (1.6 mg). The 60% MeOH eluate (5.89 g) was purified by column chromatography on Toyopearl HW-40 (2.2 i.d. × 60 cm) with 70% EtOH → 70% acetone and a Sep-Pak C₁₈ cartridge with H₂O → aq. MeOH (20% → 40% → 60%, v/v) → 70% acetone, to give **13** (3.8 mg). The water-soluble portion (23.9 g) was applied to Diaion HP-20 (5.5 i.d. × 25 cm) chromatography with H₂O → aq. MeOH (20% → 40% → 60%, v/v) → 100% MeOH → 70% acetone as eluants. The 40% MeOH eluate (5.92 g) was further subjected to Toyopearl HW-40 (2.2 i.d. × 60 cm) with 70% EtOH → 70% acetone. Repeated chromatography of the 70% acetone fraction (249.3 mg) on Toyopearl HW-40 with 70% EtOH → 70% EtOH-70% acetone (9:1 → 8:2 → 7:3, v/v) → 70% acetone, followed by preparative HPLC of the fractions gave aromatinin A (**1**) (4.6 mg) and alienanin B (**16**) (2.6 mg). An additional 2 kg of cloves was also treated in an analogous way to afford **1** (9.8 mg), **3** (8.6 mg), and **5** (10.4 mg).

Aromatinin A (1): An off-white amorphous powder, $[\alpha]_D +92.0^\circ$ (c 1.0, MeOH). ESIMS m/z : 1087 [M-H]⁻. HRESIMS m/z : 1087.0866 [M-H]⁻ (calcd. for C₄₈H₃₂O₃₀ - H, 1087.0906). CD $[\theta]$ (nm, in MeOH): $[\theta]_{235} +1.4 \times 10^5$, $[\theta]_{262} -2.9 \times 10^4$, $[\theta]_{281} +2.4 \times 10^4$. ¹H NMR δ : 7.21 (2H, s), 7.18 (1H, s), 6.88 (1H, s), 6.544 (1H, s), 6.539 (1H, s), glucose protons (Table 1). ¹H NMR (CD₃OD) δ : 7.15 (2H, s), 7.04 (1H, s), 6.81 (1H, s), 6.48 (1H, s), 6.40 (1H, s), 5.70 (1H, d, J = 8 Hz, Glc H-4), 5.26 (1H, dd, J = 3.5, 8 Hz, Glc H-5), 5.22 (1H, br s, Glc H-1), 5.08 (1H, s, Glc H-3), 4.94 (1H, s, Glc H-2), 4.90 (1H, dd, J = 3.5, 13.5 Hz, Glc H-6), 4.09 (1H, d, J = 13.5 Hz, Glc H-6). ¹³C NMR δ : 41.3 (Glc C-1), 64.2 (Glc C-6), 71.4 (Glc C-5), 73.0 (Glc C-4), 75.3 (Glc C-3), 82.6 (Glc C-2), 105.9, 107.4, 108.8 (HHDP C, E, F-ring C-3), 110.2 (galloyl D-ring C-2, 6), 111.7 (galloyl A-ring C-6), 115.4, 115.5, 116.0, 116.9 (HHDP C-1), 120.5 (galloyl D-ring C-1), 121.8 (galloyl A-ring C-2), 123.0, 123.3, 125.1, 126.6 (HHDP C-2), 127.9 (HHDP B-ring C-3), 135.1, 136.1, 136.4, 137.5 (HHDP C-5), 137.6 (galloyl A-ring C-4), 139.4 (galloyl D-ring C-4), 142.7, 142.8, 143.8, 144.0, 144.2, 144.3, 145.0, 145.2 (HHDP C-4, 6), 145.6 (galloyl A-ring C-5), 145.9 (galloyl D-ring C-3, 5), 146.7 (galloyl A-ring C-3), 166.3 (galloyl D-ring C-7), 168.3 (HHDP E-ring C-7), 168.4 (galloyl A-ring C-7), 169.1 (HHDP F-ring C-7), 169.7 (HHDP B-ring C-7), 169.8 (HHDP C-ring C-7). ¹³C NMR (CD₃OD) δ : 42.5 (Glc C-1), 64.9 (Glc C-6), 72.1 (Glc C-5), 74.2 (Glc C-4), 76.6 (Glc C-3), 83.0 (Glc C-2), 105.8, 108.0, 109.3 (HHDP C, E, F-ring C-3), 110.6 (galloyl D-ring C-2, 6), 111.1 (galloyl A-ring C-6), 116.1 (HHDP B-ring C-1), 116.3 (HHDP F-ring C-1), 116.4 (HHDP E-ring C-1), 117.5 (HHDP C-ring C-1), 121.0 (galloyl D-ring C-1), 123.1, 123.8, 125.5, 127.0 (HHDP C-2), 128.2 (HHDP B-ring C-3), 130.8, 136.0, 137.2, 137.5, 137.7 (HHDP C-5), 139.3 (galloyl A-ring C-4), 140.3 (galloyl D-ring C-4), 144.0, 144.3, 144.9 (2C), 144.8, 145.4, 146.0, 146.04 (HHDP C-4, 6), 146.5 (galloyl A-ring C-5), 146.6 (galloyl D-ring C-3, 5), 147.5 (galloyl A-ring C-3), 167.4 (galloyl D-ring C-7), 169.2 (HHDP E-ring C-7), 170.0 (galloyl D-ring C-7), 170.4 (HHDP F-ring C-7), 171.3 (HHDP B-ring C-7, C-ring C-7).

Syzyginin A (2): An off-white amorphous powder, $[\alpha]_D +10.5^\circ$ (c 1.0, MeOH). ESIMS m/z : 1105 [M-H]⁻. HRESIMS m/z : 1105.1027 [M-H]⁻ (calcd. for C₄₈H₃₄O₃₁ - H, 1105.1011). CD $[\theta]$ (nm, in MeOH): $[\theta]_{239} +5.8 \times 10^4$, $[\theta]_{261} -1.3 \times 10^4$, $[\theta]_{286} +1.2 \times 10^4$. ¹H NMR δ : 7.10, 7.00, 6.93 (each 2H, s), 6.80, 6.49, 6.46 (each 1H, s), glucose protons (Table 1). ¹H NMR (acetone-*d*₆-D₂O + DCl) δ : 7.08, 6.99, 6.97 (each 2H, s), 6.91, 6.61, 6.46 (each 1H, s). ¹³C NMR δ : 63.3 (Glc C-6), 70.5 (Glc C-4), 71.8 (Glc C-2), 72.7 (Glc C-5), 73.1 (Glc C-3), 93.5 (Glc C-1), 107.9 (tergalloyl C-3'), 108.0 (tergalloyl C-3), 108.3 (tergalloyl C-6''), 109.9 (galloyl C-2', 6'), 110.0 (galloyl C-2'', 6''), 110.1 (galloyl C-2, 6), 115.9 (tergalloyl C-1'), 116.1 (tergalloyl C-1''), 116.6 (tergalloyl C-1), 119.2 (galloyl C-1''), 119.8 (galloyl C-1'), 119.9 (galloyl C-1), 124.7 (tergalloyl C-2), 131.4 (tergalloyl C-2'), 136.7 (tergalloyl C-5'), 137.1 (tergalloyl C-5), 139.3

(tergalloyl C-4''), 139.5 (galloyl C-4''), 139.8 (tergalloyl C-2'', galloyl C-4'), 139.9 (tergalloyl C-3'', galloyl C-4), 142.2 (tergalloyl C-5''), 144.5 (tergalloyl C-6), 145.1 (tergalloyl C-4), 145.7 (galloyl C-3'', 5''), 145.9 (galloyl C-3', 5'), 146.1 (galloyl C-3, 5), 149.6 (tergalloyl C-4'), 150.0 (tergalloyl C-6'), 165.2 (galloyl C-7), 166.1 (galloyl C-7'), 166.6 (galloyl C-7''), 168.0 (tergalloyl C-7), 168.1 (tergalloyl C-7'), 171.5 (tergalloyl C-7'').

Bicornin (3): An off-white amorphous powder, $[\alpha]_D -11.2^\circ$ (c 0.7, MeOH). ESIMS m/z : 1087 $[M-H]^-$. HRESIMS m/z : 1087.0906 $[M-H]^-$ (calcd. for $C_{48}H_{32}O_{30} - H$, 1087.0906). CD $[\theta]$ (nm, in MeOH): $[\theta]_{224} +4.9 \times 10^4$, $[\theta]_{258} -1.0 \times 10^4$, $[\theta]_{289} +1.9 \times 10^4$. 1H NMR δ : 7.06 (2H, s), 6.97 (2H, s), 6.95 (2H, s), 6.93 (1H, s), 6.84 (1H, s), 6.52 (1H, s), glucose protons (Table 1). 1H NMR (CD_3OD) δ : 7.04 (2H, s), 6.95 (2H, s), 6.93 (2H, s), 6.90 (1H, s), 6.87 (1H, s), 6.49 (1H, s), 6.12 (1H, d, $J = 8$ Hz, Glc H-1), 5.77 (1H, t, $J = 9.5$ Hz, Glc H-3), 5.54 (1H, dd, $J = 8, 9.5$ Hz, Glc H-2), 5.32 (1H, dd, $J = 6, 13$ Hz, Glc H-6), 5.30 (1H, t, $J = 9.5$ Hz, Glc H-4), 4.45 (1H, dd, $J = 6, 9.5$ Hz, Glc H-5), 3.98 (1H, d, $J = 13$ Hz, Glc H-6). ^{13}C NMR δ : 63.9 (Glc C-6), 70.8 (Glc C-4), 71.8 (Glc C-2), 72.6 (Glc C-5), 73.2 (Glc C-3), 93.5 (Glc C-1), 106.9 (tergalloyl C-3), 109.7 (tergalloyl C-6''), 110.0 (galloyl C-2', 6'), 110.10 (galloyl C-2'', 6''), 110.13 (galloyl C-2, 6), 112.3 (tergalloyl C-1''), 112.4 (tergalloyl C-3'), 113.9 (tergalloyl C-1), 119.2 (galloyl C-1), 119.8 (galloyl C-1'), 119.9 (galloyl C-1''), 120.8 (tergalloyl C-1'), 124.7 (tergalloyl C-2), 130.4 (tergalloyl C-2'), 132.1 (tergalloyl C-3''), 136.1 (tergalloyl C-5), 136.4 (galloyl C-4''), 139.3 (galloyl C-4'), 139.5 (galloyl C-4), 139.9 (tergalloyl C-4''), 142.8 (tergalloyl C-5'), 143.4 (tergalloyl C-2''), 143.9 (tergalloyl C-5''), 145.1 (tergalloyl C-6'), 145.2 (tergalloyl C-6), 145.8 (galloyl C-3'', 5''), 145.90 (galloyl C-3', 5'), 145.92 (galloyl C-3, 5), 146.1 (tergalloyl C-4), 148.2 (tergalloyl C-4'), 163.5 (tergalloyl C-7''), 165.2 (galloyl C-7), 166.1 (galloyl C-7'), 166.7 (galloyl C-7''), 167.2 (tergalloyl C-7'), 167.8 (tergalloyl C-7). ^{13}C NMR (CD_3OD) δ : 64.4 (Glc C-6), 71.2 (Glc C-4), 72.5 (Glc C-2), 73.3 (Glc C-5), 73.9 (Glc C-3), 94.1 (Glc C-1), 107.2 (tergalloyl C-3), 110.1 (tergalloyl C-6''), 110.4 (galloyl C-2', 6'), 110.5 (galloyl C-2'', 6''), 110.6 (galloyl C-2, 6), 112.3 (tergalloyl C-1''), 113.0 (tergalloyl C-3'), 114.5 (tergalloyl C-1), 119.7 (galloyl C-1), 120.3 (galloyl C-1'), 120.4 (galloyl C-1''), 121.3 (tergalloyl C-1'), 124.9 (tergalloyl C-2), 132.5 (tergalloyl C-2'), 137.0 (tergalloyl C-3''), 137.4 (tergalloyl C-5), 140.1 (galloyl C-4''), 140.3 (galloyl C-4'), 140.7 (galloyl C-4), 141.6 (tergalloyl C-4''), 143.4 (tergalloyl C-5'), 144.2 (tergalloyl C-2''), 144.5 (tergalloyl C-5''), 145.5 (tergalloyl C-6'), 145.6 (tergalloyl C-6), 146.3 (galloyl C-3'', 5''), 146.4 (galloyl C-3', 5'), 146.5 (galloyl C-3, 5), 146.6 (tergalloyl C-4), 148.9 (tergalloyl C-4'), 165.5 (tergalloyl C-7''), 166.1 (galloyl C-7), 166.9 (galloyl C-7'), 167.5 (galloyl C-7''), 168.2 (tergalloyl C-7'), 169.1 (tergalloyl C-7).

Platycaryanin A (4): An off-white amorphous powder, $[\alpha]_D -10.6^\circ$ (c 0.6, MeOH). ESIMS m/z : 1103

[M-H]⁻. CD [θ] (nm, in MeOH): [θ]₂₃₈ +2.1 × 10⁵, [θ]₂₆₂ -6.0 × 10⁴, [θ]₂₈₆ +4.1 × 10⁴. ¹H NMR δ: 7.15 (2H, s), 6.88 (1H, s), 6.59 (1H, s), 6.55 (1H, s), 6.44 (1H, s), 6.36 (1H, s), glucose protons (Table 1). ¹H NMR (acetone-*d*₆-D₂O + DCl) δ: 7.16 (2H, s), 6.95 (1H, s), 6.62 (1H, s), 6.56 (1H, s), 6.45 (1H, s), 6.39 (1H, s). ¹H NMR (CD₃OD) δ: 7.11 (2H, s), 6.80 (1H, s), 6.57 (1H, s), 6.54 (1H, s), 6.43 (1H, s), 6.41 (1H, s), 6.14 (1H, d, *J* = 8.5 Hz, Glc H-1), 5.46 (1H, t, *J* = 9.5 Hz, Glc H-3), 5.33 (1H, dd, *J* = 6.5, 13.2 Hz, Glc H-6), 5.22 (1H, t, *J* = 9.5 Hz, Glc H-4), 5.20 (1H, dd, *J* = 8.5, 9.5 Hz, Glc H-2), 4.37 (1H, dd, *J* = 6.5, 9.5 Hz, Glc H-5), 3.92 (1H, d, *J* = 13.2 Hz, Glc H-6). ¹³C NMR δ: 63.3 (Glc C-6), 69.0 (Glc C-4), 73.2 (Glc C-5), 75.9 (Glc C-2), 77.0 (Glc C-3), 92.1 (Glc C-1), 107.1 (HHDP C-3'), 107.2 (HHDP C-3), 107.7 (tergalloyl C-3, 3'), 108.3 (tergalloyl C-6''), 110.1 (galloyl C-2, 6), 114.3 (HHDP C-1'), 115.0 (HHDP C-1), 116.6 (tergalloyl C-1'), 116.9 (tergalloyl C-1), 119.4 (galloyl C-1), 124.7 (HHDP C-2), 125.7 (HHDP C-2'), 126.0 (tergalloyl C-2), 131.5 (tergalloyl C-2'), 136.1 (HHDP C-5'), 136.5 (HHDP C-5), 136.8 (tergalloyl C-5'), 137.2 (tergalloyl C-5), 139.1 (tergalloyl C-4''), 139.6 (tergalloyl C-2''), 140.0 (tergalloyl C-3'', galloyl C-4), 142.2 (tergalloyl C-5''), 144.36 (tergalloyl C-6), 144.4 (HHDP C-6'), 144.7 (HHDP C-6), 145.07 (tergalloyl C-4), 145.09 (HHDP C-4, 4'), 146.2 (galloyl C-3, 5), 149.7 (tergalloyl C-4', 6'), 165.2 (galloyl C-7), 168.1 (tergalloyl C-7), 168.2 (tergalloyl C-7'), 168.8 (HHDP C-7), 169.4 (HHDP C-7'), 171.7 (tergalloyl C-7''). ¹³C NMR (CD₃OD) δ: 64.0 (Glc C-6), 69.6 (Glc C-4), 74.0 (Glc C-5), 76.4 (Glc C-2), 77.7 (Glc C-3), 92.8 (Glc C-1), 107.7 (HHDP C-3, 3'), 108.1 (tergalloyl C-3), 108.4 (tergalloyl C-6''), 108.9 (tergalloyl C-3'), 110.5 (galloyl C-2, 6), 114.9 (HHDP C-1'), 115.6 (HHDP C-1), 116.3 (tergalloyl C-1'), 117.2 (tergalloyl C-1), 119.8 (galloyl C-1), 125.1 (HHDP C-2), 126.0 (HHDP C-2'), 126.3 (tergalloyl C-2), 131.6 (tergalloyl C-2'), 137.3 (HHDP C-5'), 137.5 (HHDP C-5), 137.8 (tergalloyl C-5'), 138.0 (tergalloyl C-5), 139.6 (tergalloyl C-4''), 140.2 (tergalloyl C-2''), 140.8 (tergalloyl C-3'', galloyl C-4), 142.8 (tergalloyl C-5''), 144.8 (tergalloyl C-6), 144.9 (HHDP C-6), 145.0 (HHDP C-6'), 145.8 (tergalloyl C-4), 145.9 (HHDP C-4'), 146.0 (HHDP C-4), 146.7 (galloyl C-3, 5), 150.1 (tergalloyl C-6'), 150.4 (tergalloyl C-4'), 166.1 (galloyl C-7), 169.0 (tergalloyl C-7), 169.2 (tergalloyl C-7'), 169.9 (HHDP C-7), 170.7 (HHDP C-7'), 173.5 (tergalloyl C-7'').

Alunusnin A (5): An off-white amorphous powder, [α]_D -13.6° (*c* 1.0, MeOH). ESIMS: *m/z* 1085 [M-H]⁻. HRESIMS *m/z*: 1085.0741 [M-H]⁻ (calcd. for C₄₈H₃₀O₃₀ - H, 1085.0749). CD (MeOH): [θ]₂₃₇ +7.2 × 10⁴, [θ]₂₆₃ -2.7 × 10⁴, [θ]₂₈₈ +1.1 × 10⁴, [θ]₃₂₄ -3.2 × 10³. ¹H NMR δ: 7.15 (2H, s), 6.96 (1H, s), 6.91 (1H, s), 6.59 (1H, s), 6.45 (1H, s), 6.40 (1H, s), glucose protons (Table 1). ¹³C NMR (CD₃OD) δ: 63.8 (Glc C-6), 69.1 (Glc C-4), 73.0 (Glc C-5), 75.9 (Glc C-2), 76.9 (Glc C-3), 92.1 (Glc C-1), 106.6 (tergalloyl C-3), 107.1 (HHDP C-3), 107.2 (HHDP C-3'), 109.7 (tergalloyl C-6''), 110.1 (galloyl C-2, 6), 112.3 (tergalloyl C-1''), 112.5 (tergalloyl C-3'), 113.9 (tergalloyl C-1), 114.4 (HHDP C-1'), 114.9 (HHDP C-1), 119.3

(galloyl C-1), 120.8 (tergalloyl C-1'), 124.6 (tergalloyl C-2), 125.7 (HHDP C-2), 125.9 (HHDP C-2'), 132.0 (tergalloyl C-2'), 136.18 (tergalloyl C-5), 136.2 (HHDP C-5'), 136.5 (HHDP C-5), 140.0 (galloyl C-4), 140.5 (tergalloyl C-4''), 142.8 (tergalloyl C-5'), 143.5, 144.0 (tergalloyl C-5''), 144.39 (HHDP C-6'), 144.41 (HHDP C-6), 145.07 (HHDP C-4'), 145.09 (HHDP C-4), 145.2 (tergalloyl C-6'), 145.9 (tergalloyl C-4), 146.1 (galloyl C-3, 5), 148.2 (tergalloyl-4'), 163.7 (tergalloyl C-7''), 165.2 (galloyl C-7), 167.2 (tergalloyl C-3'), 168.0 (tergalloyl C-3), 168.7 (HHDP C-7), 169.5 (HHDP C-7').

Cleavage of the depside linkage in 3 and 5:¹⁶ A solution of **3** (1.3 mg) in 0.03 M KH_2PO_4 - Na_2HPO_4 buffer (pH 5.8, 1 mL) was maintained at 37 °C for 10 h. The solution was acidified with 10% HCl (0.2 mL) and then extracted with EtOAc. Removing the organic layer solvent gave **2** (1 mg). Compound **5** (1 mg) was similarly treated to yield **4**. The identities of **2** and **4** were also confirmed by ^1H NMR and HPLC.

Transformation of 18 and 20 into 1:²⁵ A mixture of **18** (1.5 mg), **20** (3 mg), and *p*-toluenesulfonic acid (1.5 mg) in dioxane (300 μL) was heated in a boiling-water bath for 5 h. After evaporation of the solvent, the residue was purified by preparative HPLC to yield **1** (0.8 mg). The identity of **1** was also confirmed by ^1H NMR and HPLC.

Antifungal effects on *Candida* species:¹ The method used was described in ref. 1. Briefly, a fungal suspension in nutrient broth was inoculated onto the surface of a Sabouraud agar plate. Each sterile paper disk (8 mm in diameter) was impregnated with 10 μL of sample solution (15 mg/mL) and was placed onto the agar plates. The diameter (in mm) of the growth inhibition zones was measured after incubation at 37 °C for 24 h. Tannins used in this study were those obtained from *Camptotheca acuminata* (**8**, **9**),²⁶ *Rosa rugosa* (**12**),²¹ and *Casuarina stricta* (**18**).⁴

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