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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 ^{1}H 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**), heterophylliin D (**11**), rugosin D (**12**), rugosin F (**13**), euprostin A (**14**), 1,2-di-*O*-galloyl-3-*O*-digalloyl-4,6-*O*-(*S*)-hexahydroxydiphenoy-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, Et_2O, 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 $C_{48}H_{32}O_{30}$. The ^{1}H 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 ^{1}H 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 ^{13}C 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 x 10^5), indicating the *S* configuration of both HHDP groups.[8]

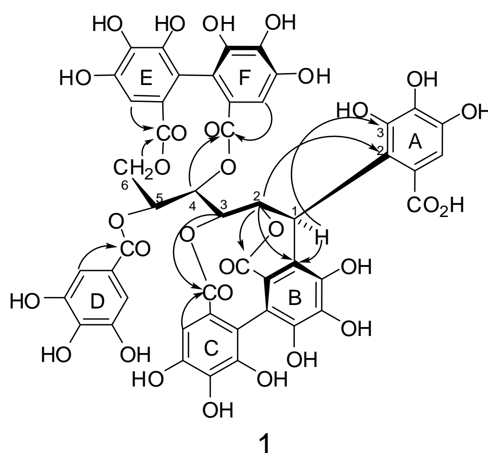

Figure 1. Structure of the new *C*-glucosidic ellagitannin **1**

Table 1. ^{1}H NMR spectral data for glucose protons of **1**-**5**, and **9** [acetone-d_6+D_2O, *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 $C_{48}H_{34}O_{31}$. The ^{1}H 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 $^4C_1$ conformation, and that a diphenoyl moiety of the triphenoyl group was at O-4/O-6 of the glucose core. The ^{13}C NMR spectrum of **2** indicated that the triphenoyl group was assignable to a tergalloyl group (see Experimental). The ^{1}H 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 ^{13}C 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 (DCl) to an acetone-d_6 solution of **2** on the ^{1}H 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 $C_{48}H_{32}O_{30}$. The ^{1}H 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 $^4C_1$ 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 ^{1}H 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 ^{13}C NMR spectrum of **3** to that of

2 showed upfield shifts in the following triphenoyl carbon signals: C-ring C-7" (δ 171.5 → 163.5), B-ring C-4' (δ 149.6 → 148.2), and B-ring C-6' (δ 150.0 → 145.1), in contrast to the downfield shifts of the carbon signals of B-ring C-1' (δ 115.9 → 120.8), B-ring C-3' (δ 107.9 → 112.4), and B-ring C-5' (δ 136.7 → 142.8). These changes in ^{13}C chemical shifts, coupled with the $[M-H]^-$ 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 (Δδ +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

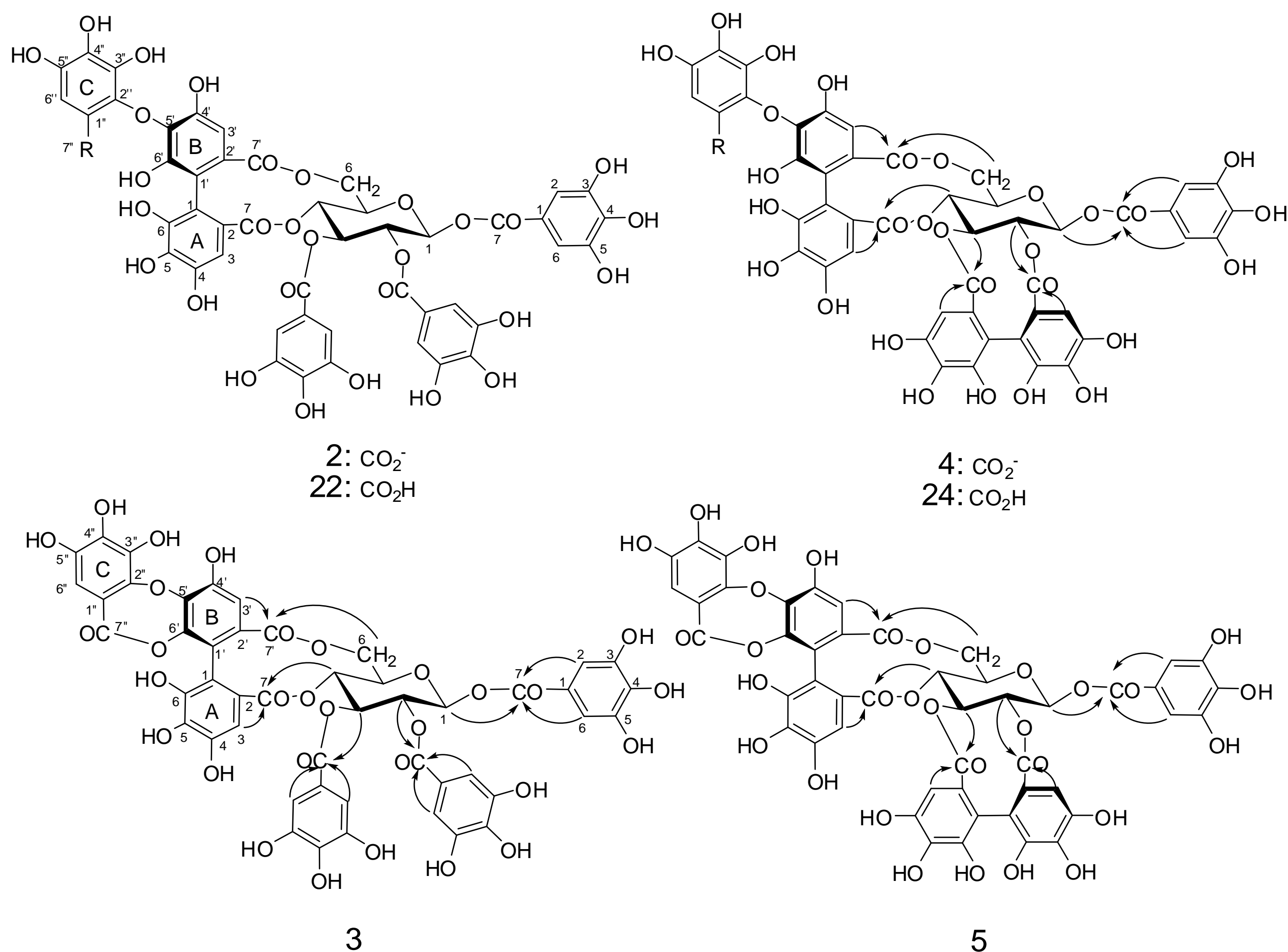

Figure 2. Structures of the monomeric hydrolysable tannins, **2**, **3**, **4**, **5**, **22**, and **24**

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 × 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.

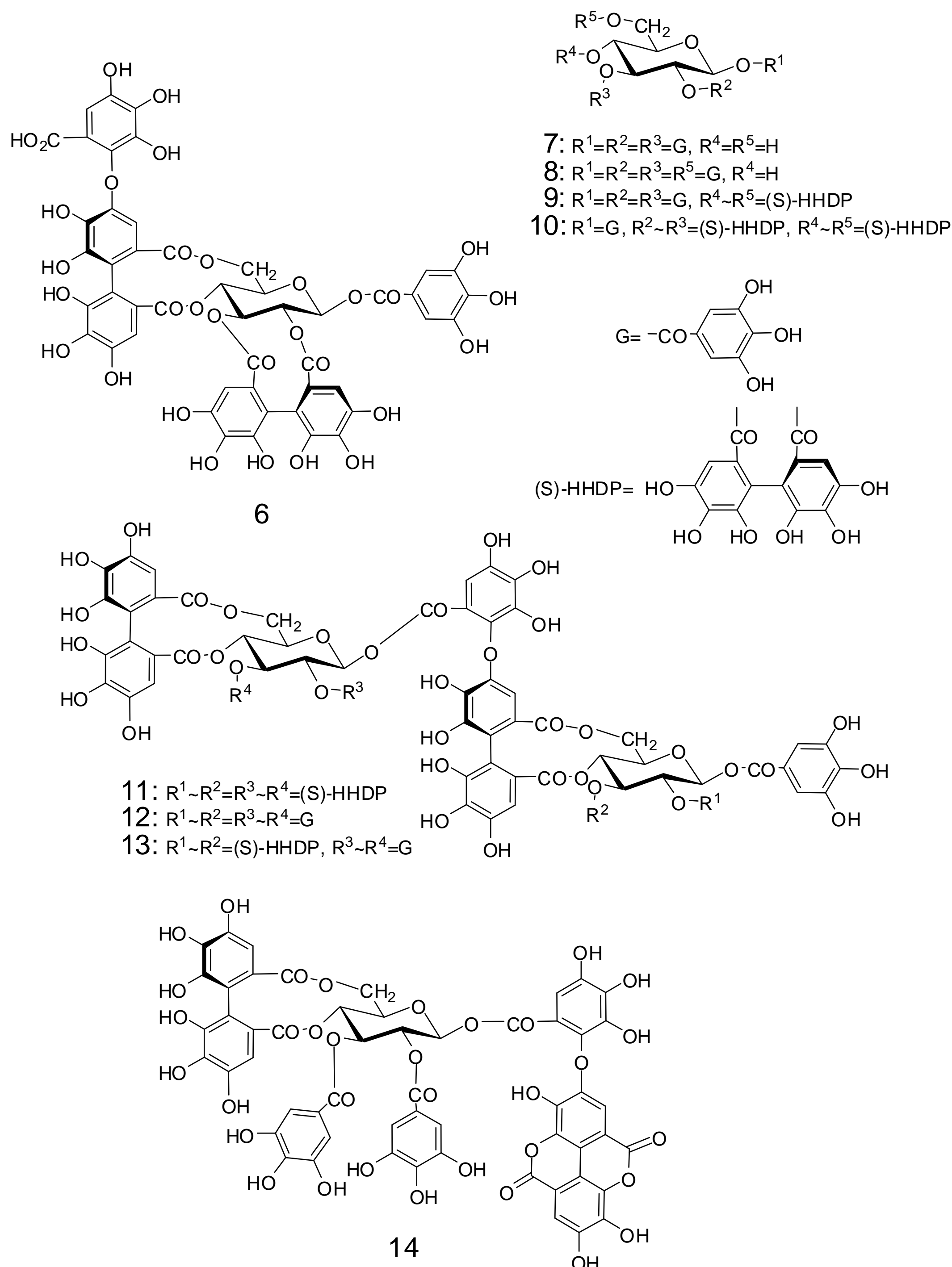

Figure 3. Structures of **6**–**14**

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 DCl to an

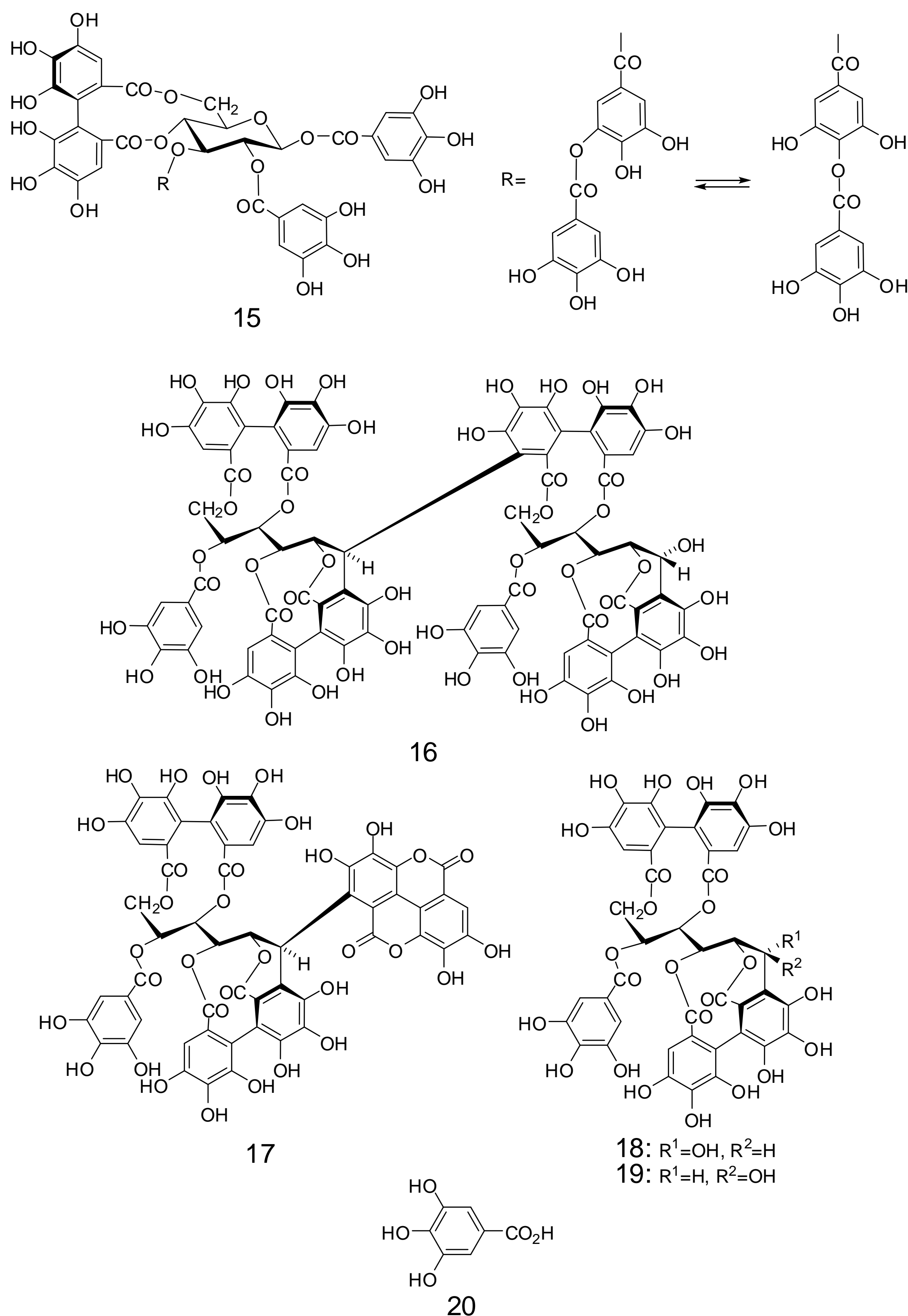

Figure 4. Structures of **15**–**20**

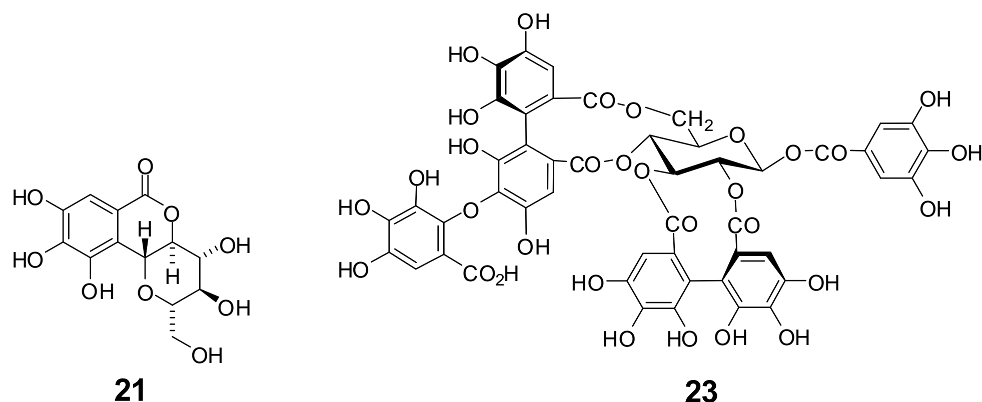

Figure 5. Structures of **21** and **23**

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 ^{1}H 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 desaltation 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 tergalloy 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 A[15]). 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 C[16] and δ 7.12 in prostratin C[17]). 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*)-hexahydroxydiphenoy-β-D-glucose (**15**),[22] alienanin B (**16**),[23,24] squarrosanin A (**17**),[6] and casuarinin (**18**).[4,14]

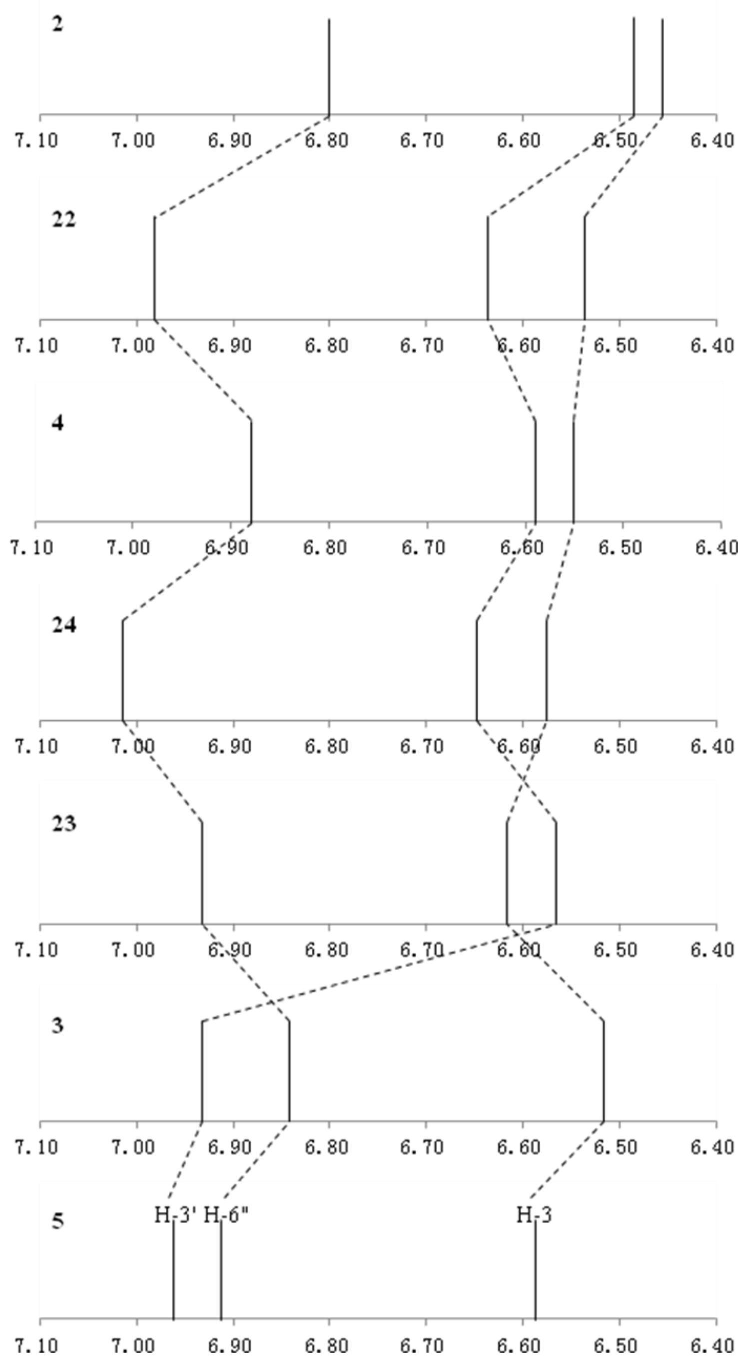

Figure 6. Comparison of the tergalloyl group or depsidone-forming tergalloyl group protons in the ^{1}H NMR spectra of **2**, **22**, **4**, **24**, **23**, **3**, and **5** (in acetone-d_6+D_2O)

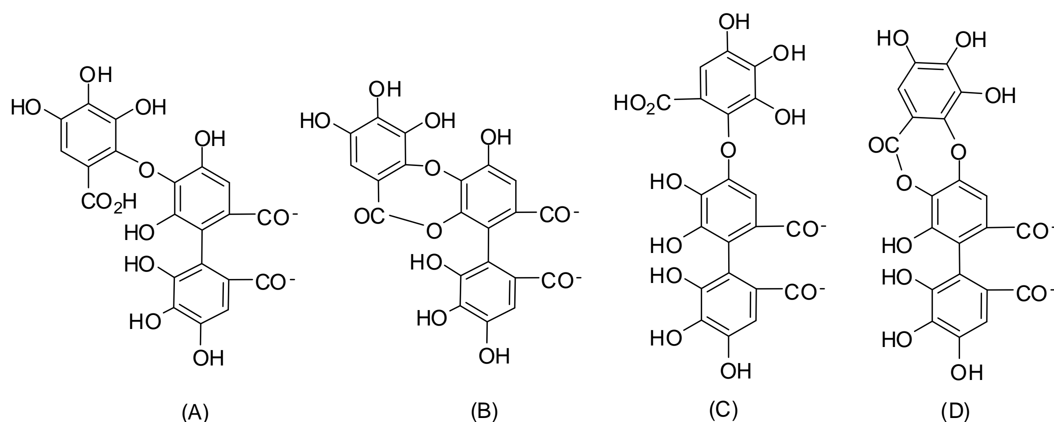

Figure 7. Structures of tergalloyl (A), depsidone-forming tergalloyl (B), valoneoyl (C), and depsidone-forming valoneoyl (D) groups

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]		
	C. albicans FH01	*C. tropicallis* NA01	*C. glabrata* TIMM1062
Amphotericin B	19	17	24
1,2,3,6-tetra-*O*-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 ^{1}H 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. × 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. × 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 ºC. Preparative reversed phase HPLC was performed on a YMC-Pack ODS A-324 column (10 i.d. × 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 ºC.

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 × 3), Et_2O (300 mL × 3), EtOAc (300 mL × 3), and *n*-BuOH (300 mL × 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. × 40 cm) (TP_1) with 70% EtOH → 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 → aq. MeOH → 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 → aq. MeOH (10% → 20% → 30% → 40%, v/v) → 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 → aq. MeOH (20% → 40% → 60%, v/v) → 100% MeOH → 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 C_{18} 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 H_2O-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), Et_2O (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), Et_2O (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) (TP_2) with 70% EtOH → 70% acetone. Fr. 165–210 (276.2 mg) from TP_2 was further subjected to MCI-gel CHP-20P (MC_1) using H_2O → aq. MeOH (20% → 40% → 60%, v/v) → 100% MeOH → 70% acetone. The Fr. 20% MeOH eluate from MC_1 afforded casuarinin (**18**) (19.7 mg). The Fr. 40% MeOH eluate from MC_1 was further subjected to column chromatography over MCI-gel CHP-20P with H_2O → 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 TP_2 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 H_2O → 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 H_2O → 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*)-hexahydroxydiphenoy-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 C_{18} cartridge with H_2O → 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 H_2O → 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° (*c* 1.0, MeOH). ESIMS *m/z*: 1087 $[M-H]^-$. HRESIMS *m/z*: 1087.0866 $[M-H]^-$ (calcd. for $C_{48}H_{32}O_{30}$ - H, 1087.0906). CD [θ] (nm, in MeOH): $[\theta]_{235}$ +1.4 × 10^5, $[\theta]_{262}$ -2.9 × 10^4, $[\theta]_{281}$ +2.4 × 10^4. ^{1}H 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). ^{1}H NMR (CD_3OD) 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). ^{13}C 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). ^{13}C NMR (CD_3OD) 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° (*c* 1.0, MeOH). ESIMS *m/z*: 1105 $[M-H]^-$. HRESIMS *m/z*: 1105.1027 $[M-H]^-$ (calcd. for $C_{48}H_{34}O_{31}$ - H, 1105.1011). CD [θ] (nm, in MeOH): $[\theta]_{239}$ +5.8 × 10^4, $[\theta]_{261}$ -1.3 × 10^4, $[\theta]_{286}$ +1.2 ×10^4. ^{1}H NMR δ: 7.10, 7.00, 6.93 (each 2H, s), 6.80, 6.49, 6.46 (each 1H, s), glucose protons (Table 1). ^{1}H NMR (acetone-d_6-D_2O + DCl) δ: 7.08, 6.99, 6.97 (each 2H, s), 6.91, 6.61, 6.46 (each 1H, s). ^{13}C 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° (*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 [θ] (nm, in MeOH): $[\theta]_{224}$ +4.9 × 10^4, $[\theta]_{258}$ -1.0 × 10^4, $[\theta]_{289}$ +1.9 × 10^4. ^{1}H 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). ^{1}H 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, 9.5Hz, 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° (*c* 0.6, MeOH). ESIMS *m/z*: 1103

$[M-H]^-$. CD [θ] (nm, in MeOH): $[\theta]_{238}$ +2.1 × 10^5, $[\theta]_{262}$ -6.0 × 10^4, $[\theta]_{286}$ +4.1 × 10^4. ^{1}H 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). ^{1}H NMR (acetone-d_6-D_2O + 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). ^{1}H NMR (CD_3OD) 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). ^{13}C 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"). ^{13}C NMR (CD_3OD) 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, $[\alpha]_D$ -13.6° (*c* 1.0, MeOH). ESIMS: *m/z* 1085 $[M-H]^-$. HRESIMS *m/z*: 1085.0741 $[M-H]^-$ (calcd. for $C_{48}H_{30}O_{30}$ - H, 1085.0749). CD (MeOH): $[\theta]_{237}$ +7.2 × 10^4, $[\theta]_{263}$ -2.7 × 10^4, $[\theta]_{288}$ +1.1 × 10^4, $[\theta]_{324}$ -3.2 × 10^3. ^{1}H 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). ^{13}C NMR (CD_3OD) 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 ºC 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 ^{1}H 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 ^{1}H 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 ºC 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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